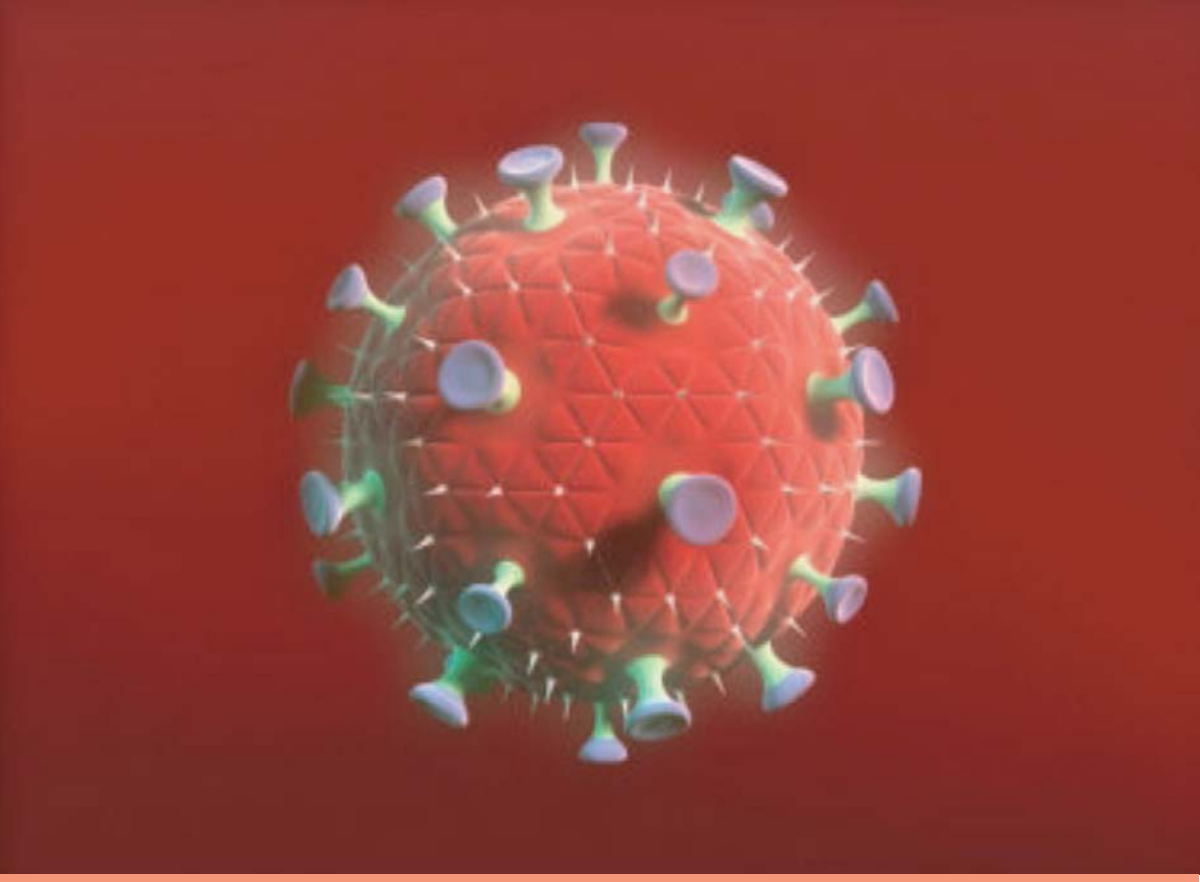
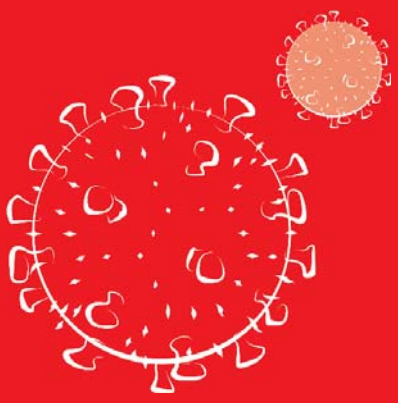


South African Edition

2008

Medical Management of HIV Infection



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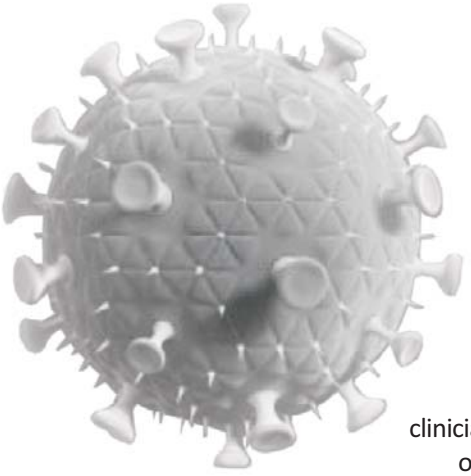

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Medical Management of HIV Infection

2008 South African Edition

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Some of the information contained in this book may cite the use of a particular drug in a dosage, for an indication, or in a manner other than recommended or FDA-approved. Therefore, the manufacturers' package inserts should be consulted for complete prescribing information.

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Note

This book is provided as a resource for physicians and other health care professionals in providing care and treatment to patients with HIV/AIDS. Every possible effort is made to ensure the accuracy and reliability of material presented in this book; however, recommendations for care and treatment change rapidly, and opinion can be controversial. Therefore, physicians and other healthcare professionals are encouraged to consult other sources and confirm the information contained within this book. The author, reviewers, and production staff will not be held liable for errors, omissions, or inaccuracies in information or for any perceived harm to users of this book. It is up to the individual physician or other health care professional to use his/her best medical judgment in determining appropriate patient care or treatment because no single reference or service can take the place of medical training, education, and experience.

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This book is available online at **http://www.bartletthiv.org**.

Additional sources of information include the websites of the Johns Hopkins University Division of Infectious Diseases:

The Johns Hopkins AIDS Service: **http://www.hopkins-hivguide.org**

The Hopkins Antibiotic-Guide: **http://www.hopkins-abxguide.org**

The Johns Hopkins Center for Tuberculosis Research: **http://www.hopkins-tb.org**

Contents

continued

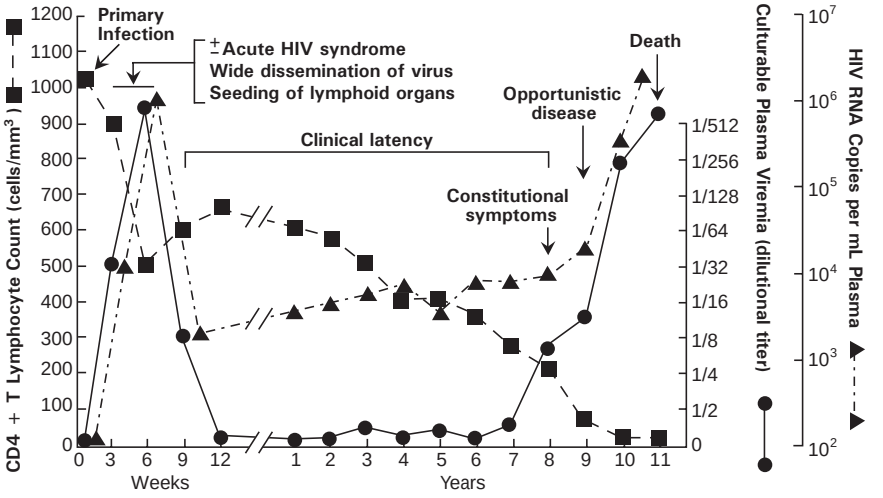
Contents, *continued*

1 | Natural History and Classification

Stages

The natural history of untreated HIV infection is divided into the following stages:

Viral transmission —(2-3 wks)→ Acute retroviral syndrome —(2-3 wks)→ Recovery + seroconversion —(2-4 wks)→ Asymptomatic chronic HIV infection —(Avg. 8 yrs)→ Symptomatic HIV infection/AIDS —(Avg. 1.3 yrs)→ Death



■ FIGURE 1-1: **Natural history of HIV infection in an average patient without antiretroviral therapy from the time of HIV transmission to death at 10-11 years.** The initial event is the acute retroviral syndrome (Table 1-1), which is accompanied by a precipitous decline in CD4 cell counts (closed squares) and high concentrations of HIV RNA in plasma (closed triangles). Clinical recovery is accompanied by a reduction in plasma viremia, reflecting development of cytotoxic T-cell (CTL) response. The CD4 cell count decreases are due to HIV-induced cell death (*J Exp Med* 2001;194:1277). This may be due to a high state of CD8 and CD4 cell stimulation producing "T cell exhaustion" and cell death (Papagno L, *PLoS Biol* 2004;2:E20). The slope of the CD4 cell decline depends on the viral load; in one study the median rate of decline was 4%/year for each $\log_{10}$ HIV RNA/mL (*J Infect Dis* 2002;185:905). The slope increases in late stage disease. HIV RNA concentrations in plasma show an initial "burst" during acute infection and then decline to a "set point" as a result of seroconversion and immune response. With continued infection, HIV RNA levels gradually increase (*J Infect Dis* 1999;180:1018). Late-stage disease is characterized by a CD4 count <200 cells/mm^3 and the development of opportunistic infections, selected tumors, wasting, and neurologic complications (Table 1-1).. In an untreated patient, the median survival after the CD4 count has fallen to <200 cells/mm^3 is 3.7 years; the median CD4 count at the time of the first AIDS-defining complication is 60-70 cells/mm^3; the median survival after an AIDS-defining complication is 1.3 years. (Figure reprinted with permission from *Ann Intern Med* 1996;124:654).

■ TABLE 1-1: **Correlation of Complications With CD4 Cell Counts (see *Arch Intern Med* 1995;155:1537)**

CD4 Cell Count*	Infectious Complications	Noninfectious† Complications
>500/mm³	■ Acute retroviral syndrome ■ Candidal vaginitis	■ Persistent generalized lymphadenopathy (PGL) ■ Guillain-Barré syndrome ■ Myopathy ■ Aseptic meningitis
200-500/mm³	■ Pneumococcal and other bacterial pneumonia ■ Pulmonary tuberculosis ■ Herpes zoster ■ Oropharyngeal candidiasis (thrush) ■ Cryptosporidiosis, self-limited ■ Kaposi's sarcoma ■ Oral hairy leukoplakia	■ Cervical and anal dysplasia ■ Cervical and anal cancer ■ B-cell lymphoma ■ Anemia ■ Mononeuronal multiplex ■ Idiopathic thrombocytopenic purpura ■ Hodgkin's lymphoma ■ Lymphocytic interstitial pneumonitis
<200/mm³	■ *Pneumocystis* pneumonia‡ ■ Disseminated histoplasmosis and coccidioidomycosis ■ Miliary/extrapulmonary TB ■ Progressive multifocal leuko-encephalopathy (PML)	■ Wasting ■ Peripheral neuropathy ■ HIV-associated dementia ■ Cardiomyopathy ■ Vacuolar myelopathy ■ Progressive polyradiculopathy ■ Non-Hodgkin's lymphoma
<100/mm³	■ Disseminated herpes simplex ■ Toxoplasmosis ■ Cryptococcosis ■ Cryptosporidiosis, chronic ■ Microsporidiosis ■ Candidal esophagitis	
<50/mm³	■ Disseminated cytomegalovirus (CMV) ■ Disseminated *Mycobacterium avium* complex	■ Primary central nervous system lymphoma (PCNSL)

* Most complications occur with increasing frequency at lower CD4 cell counts.

† Some conditions listed as "noninfectious" are associated with transmissible microbes. Examples include lymphoma (Epstein-Barr virus [EBV]) and anal and cervical cancers (human papillomavirus [HPV]).

‡ Preferred name is now *P. jiroveci* pneumonia; PCP is the accepted abbreviation. See p. 49.

The WHO clinical staging has been adopted in South Africa as both a stagy tool and a epidemiological tool. This revision published in 2005 requires documentation of HIV positive status by antibody positivity or detection of the virus.

Revised WHO Clinical Staging of HIV/AIDS

For Adults and Adolescents

(Interim African Region version for person aged 15 years or more with positive HIV antibody test or other laboratory evidence of HIV infec¬tion.)

Primary HIV infection
Asymtomatic
Acute retroviral syndrome
Clinical stage 1
Asymtomatic
Persistent generalized lymphadenopathy(PGL)
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (RTIs, sinusitus, bronchitis,otitis media, pharyngitis)
Herpes zoster
Angular chelitis
Recurrent oral ulcerations
Papular pruritic eruptions
Seborrheaic dermatitis
Fungal nail infections of fingers
Clinical stage 3
Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigation
Severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhea for longer than one month
Unexplained persistent fever (Intermittent or constant for longer that one month)
Oral candidiasis
Oral hair leukoplakia
Pulmonary tuberculosis (TB) diagnosed in last two years
Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis, periodontitis

Revised WHO clinical staging of HIV/AIDS for adults and Adolescents

Clinical stage 3 (continue)
Conditions where confirmatory diagnostic testing is necessary
Unexplained anaemia (<8 g/dl, and or neutroperia (<500mm3) and or thrombocytopenia (<50 000 mm3) for more than one month
All clinical events or conditions are described in the Annexes. The UN defines dolescents as persons aged 10 -19 years but in the present documents, the category of adults and adolescents comprises people aged 15 years and over for surveillance purposes.
Clinical stage 4
Asymtomatic
Persistent generalized lymphadenopathy(PGL)
Clinical stage 2
Conditions where a presumptive diagnosis can be made on the basis of clinical signs of simple investigation, HIV wasting syndrome, Pnuemocysitis pneumonia
Recurrent severe or radiological pneumonia
Chronic herpes simplex infection (orolabial, genital anorectal of more than one month duration)
Oesophageal candidiasis, Extrapulmonary TB, Kaposi's sarcoma
Central nervous system (CNS) toxoplasmosis
HIV encephalopathy
Conditions where confirmatory diagnostic testing is necessary
Extrapulmonary cryptocosis including meningitis
Disseminated non-tubercolous mycobacteria infection
Progressive multifocal leukoencephalophathy (PML)
Cancida of trachea, bronchi or lungs
Cryptosporidiosis
Isosporiasis
Visceral herpes simplex infection
Cytomegalovirus (CMV) infection (retinis or of an organ other than liver, spleen or lymph nodes)
Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, peniciliosis)
Recurrent non-typhoidal salmonella septicaemia
Lymphoma (cerebral or B cel non-Hodgkin)
Invasive cervical carcinoma
Visceral leishmaniasis

http://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf

The AIDS Surveillance Case definition for Adolescents and Audits in table 1-3 below is more appropriate for the developed world.

It combines both clinical and laboratory parameters. Laboratory access is not always available.

In this staging method, TB of any form both pulmonary and extra-pulmonary is considered to be AIDS defining.

Primary HIV Infection

DIAGNOSIS: HIV RNA >10,000 c/mL + indeterminate or negative HIV serology or recent seroconversion (*Ann Intern Med* 2001;134:25). An alternative is the "detuned" serologic test which is less sensitive than standard serology and consequently negative for an average of 170 days post-infection (*J Acquir Immune Defic Syndr* 2003;33:625). For mass screening, the recommendation is to pool seronegative specimens for PCR testing, with PCR testing of individual samples from any batch that tests positive (*N Engl J Med* 2005;352:1873). In counseling and testing sites in North Carolina, use of this method found that acute infections accounted for 4% to 10% of all newly detected HIV infections (*N Engl J Med* 2005;352:1873; *J Acquir Immune Defic Syndr* 2006;42:75).

■ TABLE 1-2: **Primary HIV Infection: Signs and Symptoms (Department of Health and Human Services [DHHS] Guidelines [*Ann Intern Med* 2002;137:381])**

Fever – 96%	Myalgias – 54%	Hepatosplenomegaly – 14%
Adenopathy – 74%	Diarrhea – 32%	Weight loss – 13%
Pharyngitis – 70%	Headache – 32%	Thrush – 12%
Rash* – 70%	Nausea & vomiting – 27%	Neurologic symptoms† – 12%

* Erythematous maculopapular rash on face and trunk, sometimes extremities, including palms & soles. Some have mucocutaneous ulceration involving mouth, esophagus, or genitals.

† Aseptic meningitis, meningoencephalitis, peripheral neuropathy, facial palsy, Guillain-Barré syndrome, brachial neuritis, cognitive impairment, or psychosis.

■ TABLE 1-3: **AIDS Surveillance Case Definition for Adolescents and Adults: 1993**

	Clinical Categories		
	A	**B**	**C***
CD4 Cell Categories	**Asymptomatic, or PGL, or Acute HIV Infection**	**Symptomatic† (not A or C)**	**AIDS Indicator Condition (1987)**
>500/mm^3 (≥29%)	A1	B1	C1
200 to 499/mm^3 (14% to 28%)	A2	B2	C2
<200/mm^3 (<14%)	A3	B3	C3

* All patients in categories A3, B3, and C1-3 are defined as having AIDS based on the presence of an AIDS-indicator condition (Table 1-4) and/or a CD4 cell count <200/mm^3.

(continued)

† Symptomatic conditions not included in Category C that are a) attributed to HIV infection or indicative of a defect in cell-mediated immunity or b) considered to have a clinical course or management that is complicated by HIV infection. Examples of B conditions include, but are not limited to, bacillary angiomatosis; thrush; vulvovaginal candidiasis that is persistent, frequent, or poorly responsive to therapy; cervical dysplasia (moderate or severe); cervical carcinoma *in situ*; constitutional symptoms such as fever (38.5°C) or diarrhea >1 month; oral hairy leukoplakia; herpes zoster involving two episodes or >1 dermatome; idiopathic thrombocytopenic purpura (ITP); listeriosis; pelvic inflammatory disease (PID), especially if complicated by a tubo-ovarian abscess; and peripheral neuropathy.

■ TABLE 1-4: **Indicator Conditions in Case Definition of AIDS (Adults) – 1997***

Candidiasis of esophagus, trachea, bronchi, or lungs – 3,846 (16%)
Cervical cancer, invasive† ‡ – 144 (0.6%)
Coccidioidomycosis, extrapulmonary† – 74 (0.3%)
Cryptococcosis, extrapulmonary – 1,168 (5%)
Cryptosporidiosis with diarrhea >1 month – 314 (1.3%)
CMV of any organ other than liver, spleen, or lymph nodes; eye – 1,638 (7%)
Herpes simplex with mucocutaneous ulcer >1 month or bronchitis, pneumonitis, esophagitis – 1,250 (5%)
Histoplasmosis, extrapulmonary† – 208 (0.9%)
HIV-associated dementia†: Disabling cognitive and/or other dysfunction interfering with occupation or activities of daily living – 1,196 (5%)
HIV-associated wasting†: Involuntary weight loss >10% of baseline plus chronic diarrhea (2 loose stools/day ≥30 days) or chronic weakness and documented enigmatic fever ≥30 days – 4,212 (18%)
Isosporiasis with diarrhea >1 month† – 22 (0.1%)
Kaposi's sarcoma in patient under 60 yrs (or over 60 yrs)† – 1,500 (7%)
Lymphoma, Burkitt's – 162 (0.7%), immunoblastic – 518 (2.3%), primary CNS – 170 (0.7%)
Mycobacterium avium complex or *M. kansasii* – disseminated or extrapulmonary disease – 1,124 (5%)
Mycobacterium tuberculosis, pulmonary – 1,621 (7%), extrapulmonary – 491 (2%)
Pneumocystis pneumonia – 9,145 (38%)
Pneumonia, recurrent-bacterial (2 episodes in 12 months)† ‡ – 1,347 (5%)
Progressive multifocal leukoencephalopathy – 213 (1%)
Salmonella septicemia (nontyphoid), recurrent† – 68 (0.3%)
Toxoplasmosis of internal organ – 1,073 (4%)

* Indicates frequency as the AIDS-indicator condition among 23,527 reported cases in adults for 1997. The AIDS diagnosis was based on CD4 count in an additional 36,643 or 61% of the 60,161 total cases. Numbers indicate sum of definitive and presumptive diagnoses for stated condition. The number in parentheses is the percentage of all patients reported with an AIDS-defining diagnosis; these do not total 100% because some had a dual diagnosis.

† Requires positive HIV serology.

‡ Added in the revised case definition, 1993.

2 | Laboratory Tests

Laboratory tests recommended for initial evaluation and follow-up of all patients are summarized in Table 2-8.

HIV Types and Subtypes

HIV infection is established by detecting antibodies to the virus, viral antigens, viral RNA/DNA, or by culture (*Lancet* 1996;348:176). The standard test is serology for antibody detection. Two HIV types are HIV-1 and HIV-2, which show 40% to 60% amino acid homology. HIV-1 accounts for nearly all cases except a minority of strains that originate in West Africa. HIV-1 is divided into subtypes designated A through K (collectively referred to as "M subtypes") and O.

■ TABLE 2-1: **HIV-1 Subtype Distribution *(J Acquir Immune Defic Syndr 2002;29:184)***

Predominant Subtypes	Regions
A*	E. Africa, Central Asia, East Europe, Russia
B*	N. America, Western Europe, Mideast, E. Asia, Latin America
C*	S. Africa, E. Africa, China, India, S. Asia, Brazil
D*	E. Africa
G-K	Central Africa
CRF01_AE*	Southeast Asia
CRF02_AG*	West and West Central Africa, Spain, Russia

*Predominant subtypes in the world; C accounts for 50% and B for 12%

HIV-2 (See www.cdc.gov/hiv/pubs/facts/hiv2.htm)

HIV-2 is another human retrovirus that causes immune deficiency due to depletion of CD4 cells. It is found primarily in West Africa.*

CLINICAL FEATURES OF HIV-2: Compared with HIV-1, HIV-2 is less transmissible, and is associated with a lower VL, leading to slower rates of both CD4 cell decline and clinical progression.

* Endemic areas in West Africa – Benin, Burkina Faso, Cape Verde, Cote d'Ivoire, Gambia, Ghana, Guinea Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, São Tome, Senegal, Sierra Leone, and Togo; other African countries – Angola and Mozambique (*MMWR* 1992;4[RR-12]:1).

HIV Serology

INDICATIONS:

- The test should be considered a routine component of health care for persons 13 to 64 years of age and should be obtained in common care settings such as emergency rooms, primary care clinics, hospital admissions, birth control clinics, and STD clinics.
- Currently an opt-in strategy has been employed in South Africa. Cosent for testing must be obtained. However an opt-out strategy where consent is implied has been adopted in some countries both low- and middle-income countries including Botswana, Kenya, Malawi, Uganda and Zambia. Patients can refuse testing as for any other procedure.

  After opt-in testing started in Botswana, the percentage of all HIV-infected women delivering in the regional hospital who knew their HIV status increased from 47% to 78% and the percentage receiving PMTCT interventions increased from 29% to 56%. (JAIDS 2007, 45:1)

  However testing should remain confidential and counseling both pre and post should be offered.
- Patients with positive tests should be referred for HIV care.
- HIV status should be tested annually.
- Test results should be delivered like any other test result.
- Prevention counseling is encouraged but not required.

Standard Test

The standard test laboratory based test in South Africa is an Enzyme Linked Immunosorbent Assay (ELISA)

ACCURACY: Standard serologic assays (ELISA and WB or immuno-fluorescent assay) show sensitivity in patients with established disease (>3 months after transmission) of 99.5% (CI 98-99.9%) and a specificity of 99.994% (*N Engl J Med* 2005;352:570; *JAMA* 1991;266: 2861; *Am J Med* 2000;109:568). If an ELISA is positive, it should be confirmed with a second test also an ELISA or less commonly a Western Blot or IFA. This is to exclude any technical errors.

FALSE NEGATIVE RESULTS: These are most commonly due to technical and clerical errors. False negative results are usually due to testing in the "window period."

- **Window period:** The time delay from infection to positive ELISA averages 10 to 14 days with newer test reagents (*Clin Infect Dis* 1997;25:101; *Am J Med* 2000;109:568). Some do not seroconvert for 3 to 4 weeks, but virtually all patients seroconvert within 6 months (*Am J Med* 2000;109:568).

- **Seroreversion:** Rare patients serorevert in late-stage disease (*JAMA* 1993;269:2786; *Ann Intern Med* 1988;108:785).
- **"Atypical host response"** accounts for rare cases and is largely unexplained (*AIDS* 1995;9:95; *MMWR* 1996;45:181; *Clin Infect Dis* 1997;25:98).
- **Agammaglobulinemia** (*N Engl J Med* 2005;353:1074)
- **Type N or O strains or HIV-2:** Standard serologic tests detect M subtypes (subtypes A-K) of HIV-1, and some detect both HIV-1 and -2. EIA screening tests may fail to detect the O and N subtypes (*Lancet* 1994;343:1393;).

FALSE POSITIVE RESULTS: The frequency of false positive HIV serology (both ELISA and WB) was reported to range from 0.0004% to 0.0007% (*JAMA* 1998;280:1080; *Arch Intern Med* 2003;163:1857; *Arch Intern Med* 2000;160:2386) Important clues to possible false positive tests are undetectable viral load and normal CD4 count (*Arch Intern Med* 2003;163:1857). The serologic test should be repeated in patients without other laboratory evidence of infection. Causes of false-positive results include:

- These are most commonly due to technical and clerical errors.
- **Autoantibodies:** A single case was reported in which a false-positive serology was ascribed to autoantibodies (*N Engl J Med* 1993;328:1281), but a subsequent report indicated that this patient did have HIV infection as verified by positive cultures (*N Engl J Med* 1994;331:881). this test in available in South Africa but is more expensive and less sensitive.
- **HIV vaccines:** HIV vaccines are the most common cause of false positive HIV serology. In an analysis of 266 healthy volunteers in HIV vaccine studies, 68% had positive EIA tests, and 0% to 44% had positive WB, depending on the antigen used in the vaccine (*Ann Intern Med* 1994;121:584).
- **Factitious HIV infection:** This refers to patients who report a history of a positive test that is erroneous, due to either misunderstanding or an intent to deceive (*Ann Intern Med* 1994;121:763). It is important to confirm anonymous tests and to repeat laboratory reports that cannot be verified, using either repeat serology or viral load testing. Note that 2% to 9% of VL tests are falsely positive, usually with low viral titers (*Ann Intern Med* 1999;130:37).
- **Influenza vaccination**: Any brand of influenza vaccine may cause false positive screening results for HIV-1, presumably due to homology in their envelope proteins (*Am J Epidemiol* 1995;141:1089; *N Engl J Med* 2006;354:1422; *Cell* 1997;89:263).

INDETERMINATE RESULTS: Causes of indeterminate results include:

- **Serologic tests in the process of seroconversion**; anti-p24 is usually the first antibody to appear.
- **Late-stage HIV infection**, usually with loss of core antibody.
- **Cross-reacting nonspecific antibodies**, as seen with collagen-vascular disease, autoimmune diseases, lymphoma, liver disease, injection drug use, multiple sclerosis, parity, or recent immunization.
- **Infection with O strain or HIV-2**
- **HIV vaccine recipients** (see above)
- **Technical or clerical error**

FREQUENCY OF TESTING: The frequency is arbitrary, but most suggest annual testing (*MMWR* 2002;51:736; *MMWR* 2002;57[RR-6]:7).

Alternative HIV Serologic Tests

IMMUNOFLUORESCENCE ASSAY (IFA): This is another method to detect HIV antibodies using patient serum reacted with HIV infected cells. A fluorochrome is used as the indicator method.

RAPID TESTS: This strategy has been adopted in many settings in South Africa. Some of the reasons for this include the cost and the rapid turn around time. Mobile clinics can provide an effective and efficient way of getting testing to many individuals. Two different rapid tests should be used to confirm a diagnosis of HIV infection.

SALIVA TEST: *OraSure* (OraSure Technologies, Inc.; Bethlehem, Pa; 800-672-7873; www.orasure.com) is an FDA-approved device for collecting saliva and concentrating IgG for application of EIA tests for HIV antibody.

Viral Detection

Other methods to establish HIV infection include techniques to detect DNA (HIV-1 DNA PCR) or RNA (HIV-1 RNA by bDNA or RT-PCR . HIV-1 DNA PCR is the most sensitive and can detect 1 to 10 copies of HIV proviral DNA. None of these tests is considered to be more accurate than routine serology, but some may be useful in patients with confusing serologic test results, and for HIV detection when routine serologic tests are likely to be misleading, as in patients with agammaglobulinemia, acute retroviral infection, neonatal HIV infection, and patients in the window period following viral exposure. In most cases, confirmation of positive serology is accomplished simply by repeat serology.

■ TABLE 2-2: **Tests for HIV-1**

Assay	Sensitivity	Comments
Routine serology	99.7%	Readily available and inexpensive. Sensitivity >99.7% and specificity >99.9% (*MMWR* 1990;39:380; *N Engl J Med* 1988;319:961; *JAMA* 1991;266:2861).
Rapid test	99.6%	Results are available in 20 min. Advantages with CLIA-waived tests (*OraQuick* and *Uni-Gold* Recombigen) are that the test requires no lab equipment, results are available in ≤20 minutes, and interpretation may be done by the provider. Negative tests are a definitive negative; positive tests must be confirmed with another test.
Salivary test (*OraSure* Test System)	99.6%	Salivary collection device to collect IgG for EIA and WB. Advantage is avoidance of phlebotomy. Sensitivity and specificity are comparable with standard serology (*JAMA* 1997;227:254).
DNA PCR assay	>99%	Qualitative DNA PCR is used to detect cell-associated proviral DNA, including HIV reservoirs in peripheral CD4 cells in patients responding to HAART with a sensitivity of about 5 copies/10^6 cells (*J Virol Methods* 2005;124:157). This is not considered sufficiently accurate for diagnosis without confirmation and is not FDA approved (*Ann Intern Med* 1996;124:803), although it is occasionally used with disputed or indeterminate serologic tests.

(Continued)

■ TABLE 2-2: **Tests for HIV-1** ***(Continued)***

Assay	Sensitivity	Comments
HIV RNA PCR	95% to 98%	False positive tests in 2% to 9%, usually at low titer (<10,000 c/mL). Sensitivity depends on viral load, threshold of assay, and status of antiretroviral therapy. Sensitivity approaches 100% with acute HIV infection; specificity is 97%, but nearly 100% with viral load >10,000 c/mL.
p24 antigen	30% to 90%	Sometimes used as an alternative to HIV RNA test to detect acute HIV infection due to reduced cost. Specificity is 100%, but sensitivity is about 90% – less than quantitative HIV RNA tests (*Ann Intern Med* 2001;134:25). Another use is as a lower-cost alternative to VL testing in resource-limited countries (*J Clin Micro* 2005;43:506).

Quantitative Plasma HIV RNA (Viral Load)

TECHNIQUES

- **HIV RNA PCR** (*Amplicor HIV-1 Monitor Test* version 1.5).
- **Branched chain DNA or bDNA** (*Versant HIV-1 RNA 3.0 Assay).*
- **Nucleic acid sequence-based amplification (NABSA)** or *NucliSens* HIV-1 QT (bioMérieux).

REPRODUCIBILITY: Commercially available assays vary based on the lower level of detection and dynamic ranges, (*J Clin Microbiol* 1996;34:3016; *J Med Virol* 1996;50:293; *J Clin Microbiol* 1996;34:1058; *J Clin Microbiol* 1998;36:3392).

SEX DIFFERENCE: There appears to be a modest difference in viral load, averaging 0.23 $\log_{10}$ c/mL (about 2-fold) lower in women compared with men according to a meta-analysis of 12 reports (*J Acquir Immune Defic Syndr* 2002;31:11). However, these differences disappear at CD4 counts <300 cells/mm^3 and are therefore unlikely to affect treatment decisions (*J Acquir Immune Defic Syndr* 2000;24:218; *J Infect Dis* 1999;180:666; *Clin Infect Dis* 2002;35:313; *Lancet* 1998;352:1510; *N Engl J Med* 2001;344:720).

COST: R650-800.

INDICATIONS: Quantitative HIV RNA is useful for diagnosing acute HIV infection, for predicting probability of transmission, predicting the rate of progression in chronically infected patients, making decisions about the need for antiretroviral therapy, and for therapeutic monitoring (*Ann Intern Med* 1995;122:573; *N Engl J Med* 1996;334:426; *J Infect Dis* 1997;175:247; *J Infect Dis* 2002;185:905).

- **Acute HIV infection:** Plasma HIV RNA is commonly used to diagnose the acute retroviral syndrome prior to seroconversion

(*N Engl J Med* 2005;352:1873). Most studies show high levels of virus (10^5 to 10^6 c/mL). Note that 2% to 9% of persons without HIV infection have false-positive results, virtually always with low HIV RNA titers (<10,000 c/mL) (*Ann Intern Med* 1999;130:37; *J Clin Microbiol* 2000;38:2837; *Ann Intern Med* 2001;134:25).

- **Prognosis:** Viral load correlates with the rate of CD4 decline (CD4 slope; *J Infect Dis* 2002;185:908), but this association is not nearly as strong as once thought (*JAMA* 2006;296:1523). The most comprehensive study to assess the association between viral load and natural history is the analysis of stored sera from the Multicenter AIDS Cohort Study (MACS), which showed a strong association between "set point" and rate of progression that was independent of the baseline CD4 count (*Ann Intern Med* 1995;122:573; *Science* 1996;272:1167; *J Infect Dis* 1996;174:696; *J Infect Dis* 1996;174:704; *AIDS* 1999;13:1305; *N Engl J Med* 2001;349,720; *AIDS* 2002;16:2455; *Lancet* 2003;362:679; *J Acquir Immun Defic Syndr* 2005;38:289). This has changed in the HAART era, when outcome is determined by therapy regardless of the baseline VL (*AIDS* 2006;20:1197; *Clin Infect Dis* 2006;42:136; *J Infect Dis* 2004;190:280).
- **Risk of opportunistic infection:** The viral load appears to predict opportunistic infections independently of CD4 count when counts are <200 cells/mm^3 (*JAMA* 1996;276:105; *AIDS* 1999;13:341; *AIDS* 1999;13:1035; *J Acquir Immune Defic Syndr* 2001;27:44). The only prospective study examining this association was ACTG 722, which showed that the failure to decrease viral load by $\geq$1 $\log_{10}$ c/mL in patients with a baseline CD4 count of <150 cells/mm^3 increased the risk of an opportunistic infection 15-fold (*J Acquir Immune Defic Syndr* 2002;30:154). A retrospective review of over 12,000 patients showed that CD4 counts are the best predictors of progression to an AIDS-defining complication (*Lancet* 2002;360:119), but the VL predicts the rate of CD4 decline (*J Infect Dis* 2002;185:908).
- **Probability of transmission:** The probability of HIV transmission with nearly any type of exposure is directly correlated with viral load (*N Engl J Med* 2000;342:921; *J Acquir Immune Defic Syndr* 1996;12:427; *J Acquir Immune Defic Syndr* 1998;17:42; *J Acquir Immune Defic Syndr* 1999;21:120; *J Infect Dis* 2002;185:428; *Lancet* 2001;357:1149; *AIDS* 2001;15:621; *Clin Infect Dis* 2002;34:391; *J Infect Dis* 2005;191:1403; *AIDS* 2006;20:895).
- **Therapeutic monitoring:** Following initiation of therapy, there is a rapid initial decline in HIV RNA level over 1 to 4 weeks (alpha slope), reflecting activity against free plasma HIV virions and HIV in acutely infected CD4 cells. This is followed by a second decline (beta slope) that is longer in duration (months) and more modest in degree (see quantitation, below, under "Frequency and therapeutic monitoring"). The beta slope reflects activity against HIV-infected macrophages

and HIV released from other compartments, especially those trapped in follicular dendritic cells of lymph follicles. The maximum antiviral effect is expected by 4 to 6 months. HIV RNA levels are accepted as the most important barometer of therapeutic response, although CD4 count best predicts clinical progression (*N Engl J Med* 1996;335:1091; *Ann Intern Med* 1996;124:984; *J Infect Dis* 2002;185:178). The most important long-term benefit of achieving a VL <50 c/mL is that clonal sequence analyses show no viral evolution with resistance mutations at that level (*J Infect Dis* 2004;189:1452; *J Infect Dis* 2004;189:1444). The implication is that there is no viral replication and little likelihood of developing resistance.

- **Unexpectedly low viral load:** A minority of patients are chronic nonprogressors, with low VLs and persistently high CD4 cell counts. Another even more uncommon group are the "elite suppressors," who have persistent VL <50 c/mL without treatment (*J Exp Med* 2006;203:1357).
- **Reservoirs:** HIV resides in some anatomical sites that may be differentially affected by antiretroviral drugs and may be the source of archived strains resistant to these drugs. The major sources are the latent CD4 cells; others are the CNS and genital tract (*AIDS* 2002;16:39; *J Clin Microbiol* 2000;38:1414).

RECOMMENDATIONS:

- **Quality assurance:** Assays on individual patients should preferably be obtained at times of clinical stability, at least 4 weeks after immunizations or intercurrent infections, and with use of the same lab and same technology over time.
- **Frequency and therapeutic monitoring:** If possible a baseline viral load should be done. Ideally it should be repeated 6 weeks when a log drop should be achieved. Thereafter this test should be done every six months. If the viral load becomes detectable, i.e. above 1000-5000 copies/ml, increased adherence counseling must be done. A repeat viral load should be done within 4-6 weeks. If it remains detectable, a regimen switch is recommended.

■ TABLE 2-3: **Comparison of FDA-approved Assay Methods for Viral Load**

	Roche	Bayer	bioMérieux
Trade name	*Amplicor HIV Monitor* 1.5	*Versant* HIV-1 RNA 3.0	*NucliSens* HIV-1 QT
Technique	RT-PCR	bDNA	NASBA
Comparison of results	Results with the RT-PCR assay are similar to bDNA (*Versant*) results using version 2.0 or 3.0.	Results with are comparable with RT-PCR (*Amplicor*) assays.	Results appear comparable with RT-PCR and bDNA assays, but supporting data are less robust.
Advantages/ disadvantages	■ Fewer false-positives in patients without HIV infection compared with lo DNA.	■ Less technician time. ■ Good dynamic range, but higher threshold for undetectable virus.	■ May be used with tissue or body fluids such as genital secretions. ■ Greatest dynamic range.
Dynamic range	■ Standard: (*Amplicor* 1.5) 400 to 750,000 c/mL ■ Ultrasensitive: (*Ultra-Direct* 1.5) 50 to 100,000 c/mL	bDNA Version 3.0: 75 to 500,000 c/mL*	*NucliSens* HIV-1 QT: 176-3,500,000 c/mL depending on volume
Subtype amplified	■ Version 1.5: A to G	A to G	A to G
Specimen volume	■ *Amplicor*: 0.2 mL ■ Ultrasensitive: 0.5 mL	1 mL	10 µL to 2 mL
Tubes	EDTA (lavender top)	EDTA (lavender top)	EDTA, heparin, whole blood, any body fluid, PBMC, semen, tissue, etc.
Requirement	Separate plasma <6 hours and freeze prior to shipping at -20°C or -70°C.	Separate plasma <4 hours and freeze prior to shipping at -20°C or -70°C.	Separate serum or plasma <4 hours and freeze prior to shipping at -20°C or -70°C.

- **Factors not measured by viral load tests:** Immune function, CD4 regenerative reserve, susceptibility to antivirals, infectivity, viral fitness, syncytial vs nonsyncytial inducing forms, and viral load in compartments other than blood (e.g., lymph nodes, CNS, GI tract, and genital secretions).
- **Factors that increase viral load**
  - Failing antiretroviral therapy due to inadequate potency, inadequate drug levels, nonadherence, and resistance.
  - Switch from non-syncitium virus (R5-tropic) to syncitium-inducing virus (X4-tropic).

- Progressive disease.
- HIV superinfection (*J Infect Dis* 2005;192:438).
- Active infections; active TB increases viral load 5- to 160-fold (*J Immunol* 1996;157:1271); pneumococcal pneumonia increases viral load 3- to 5-fold.
- Immunizations such as influenza and *Pneumovax* (*Blood* 1995; 86:1082; *N Engl J Med* 1996;335:817; *N Engl J Med* 1996;334: 1222). Increases are modest and last (2 to 4 weeks).

- **Relative merit of tests:** The *Versant* version 3.0 assay has good reproducibility for viral load levels of 75 to 500,000 c/mL. The linear range for *Amplicor* is 50 to 100,000 c/mL for the ultrasensitive test. It should not be used in patients expected to have higher viral loads (*J Clin Microbiol* 2000;38:2837). The *NucliSens* assay has a broad dynamic range (176 to 3,500,000 c/mL) and can be used for HIV quantification on blood or on various body fluids or tissue such as seminal fluid, CSF, breast milk, saliva, and vaginal fluid (*J Clin Microbiol* 2000;38:1414).

CD4 Cell Count

This is a standard test to assess prognosis for progression to AIDS or death, to formulate the differential diagnosis in a symptomatic patient, and to make therapeutic decisions regarding antiviral treatment and prophylaxis for opportunistic pathogens. It is the most reliable indicator of prognosis (*Ann Intern Med* 1997;126:946; *Lancet* 2002;360:119; *Lancet* 2003;362:679). CD8 cell counts have not been found to predict outcome (*N Engl J Med* 1990;322:166), but a prolonged time from HIV seroconversion to inversion of the CD4/CD8 ratio predicts slow progression (*J Acquir Immune Defic Syndr* 2006;42:620). HIV-specific CD8 cells (CD38 cells) are important for controlling HIV levels but cannot be routinely measured (*Science* 1999;283:857; *J Acquir Immune Defic Syndr* 2002;29:346).

Technique: The standard method for determining CD4 count uses flow cytometers and hematology analyzers that are expensive, require fresh blood (<18 hours old), and generally cost R130 to R160. There is great need for rapid, simple, and affordable CD4 tests in resource-limited countries.

A novel method for Cd4 measurement was developed by Prof Debbie Glencross of the University of Witwatersrand. Traditionally, CD4 cells are referenced to total lymphocytes, a sub-population of the total white cells, which is notoriously unreliable and generally poorly quality controlled. Several steps are recommended in an attempt to quality control the identification of lymphocytes by flow cytometry, adding significant extra cost to the conventional test.

By simplifying the strategy and referencing the test to all white blood cells, the need for extra steps and extra costs falls away that is required with the traditional CD4 testing.

The result is the PLG CD4 assay which is much cheaper (more than 75% cheaper) because it needs only one quality control step, whereas up to 5 parameters are required in the conventional CD4 test.

Due to the nature of the previous method of CD4 testing, blood samples would have to be analyzed within 24 hours for an adequate result. Now, with the new test, samples can be analyzed up to five days after collection. This means that people in remote areas have access to a CD4 service as long as their samples can be transported to a central testing facility that does PLG CD4 testing.

Normal Values: Normal values for most laboratories are a mean of 800 to 1050 cells/mm^3, with a range representing two standard deviations of approximately 500 to 1400 cells/mm^3 (*Ann Intern Med* 1993;119:55).

Frequency of Testing: CD4 count should be measured at baseline. Frequency of testing to add CD4 count should be repeated at least every 6 months in both patients on and not yet on treatment. The test should be repeated when results are inconsistent with prior trends. Frequency will vary with individual circumstances. In the absence of therapy, the average rate of CD4 decline is 4% per year for each $\log_{10}$ HIV RNA c/mL (*J Infect Dis* 2002;185:905).

Reproducibility: Both clinicians and patients must be aware of the variability in CD4 test results, especially if they will be used to make clinical decisions, such as initiation of antiretroviral therapy or opportunistic infection prophylaxis. The 95% confidence range for a true count of 200 cells/mm^3, for example, is 118-337 cells/mm^3 (*J Acquir Immune Defic Syndr* 1993;6:537). Results that are inconsistent with prior trends should be repeated. A 30% change in the absolute count or a 3% change in CD4 percentage is considered significant.

Factors that Influence CD4 Cell Counts: Factors include analytical variation, seasonal and diurnal variations, some intercurrent illnesses, and corticosteroids. Substantial analytical variations, which account for the wide range in normal values (usually about 500 to 1400 cells/mm^3), reflect the fact that the CD4 cell count is the product of three variables: the white blood cell count, percent lymphocytes, and the CD4 percentage. There are also seasonal changes (*Clin Exp Immunol* 1991;86:349) and diurnal changes, with the lowest levels at 12:30 PM and peak values at 8:30 PM (*J Acquir Immune Defic Syndr* 1990;3:144);

these variations do not clearly correspond to the circadian rhythm of corticosteroids. Modest decreases in the CD4 cell count have been noted with some acute infections and with major surgery. Corticosteroid administration may have a profound effect, with decreases from 900 cells/mm^3 to less than 300 cells/mm^3 during acute administration; chronic administration has a less pronounced effect (*Clin Immunol Immunopathol* 1983;28:101). Acute changes are probably due to a redistribution of leukocytes between the peripheral circulation and the marrow, spleen, and lymph nodes (*Clin Exp Immunol* 1990;80:460).

Deceptively high CD4 counts may occur with splenectomy. Splenectomy results in a prompt, sustained increase in CD4 count. The CD4 percentage more accurately reflects immunocompetence (*Clin Infect Dis* 1995;20:768; *Arch Surg* 1998;133:25).

The following have minimal effect on the CD4 cell count: gender, age in adults, risk category, psychological stress, physical stress, and pregnancy (*Ann Intern Med* 1993;119:55).

CD4 Count Percentage: The CD4 cell percentage is sometimes used because it reduces the variation to a single measurement (*J Acquir Immune Defic Syndr* 1989;2:114). Data from a large observational database suggested that the CD4 count is the most useful predictor of the risk for development of opportunistic infections (*J Acquir Immune Defic Syndr* 2004;36:1028). More recent analyses based on cohort studies suggest that the CD4 percentage may be better for predicting disease progression with a CD4 count >350/mm^3 (*J Infect Dis* 2005;192:950), but the absolute count may be preferred for levels below the 350/mm^3 threshold (*J Infect Dis* 2005;192:945; *J Acquir Immune Defic Syndr* 2004;36:1028). Corresponding CD4 cell counts and percentages are provided in the table below.

■ TABLE 2-4: **Approximate CD4/CD4% Equivalents**

CD4 Cell Count	% CD4
>500/mm^3	>29%
200 to 500/mm^3	14% to 28%
<200/mm^3	<14%

Response to HAART: The CD4 count typically increases ≥50 cells/mm^3 at 4 to 8 weeks after viral suppression with HAART and then increases an additional 50-100 cells/mm^3/year thereafter (*JAMA* 2002;288:222; *J Infect Dis* 2002;185:471; *AIDS* 2001;15:735). Factors that correlate with good response include high baseline VL and low baseline CD4 count (*J Infect Dis* 2004;190:1860). Despite good virological response, there may be an initial delay in CD4 response that cannot be explained (*JAMA* 2002;288:222). The CD4 response gener-

ally correlates with viral load suppression, but discordant results are common in both directions (*Antivir Ther* 1999;4(Suppl 3):7; *J Infect Dis* 2001;183:1328). Nevertheless, population-based studies show the most important factor in CD4 response to HAART is the duration of virologic control (*J Infect Dis* 2004;190:148). The CD4 count usually declines rapidly, up to 100-150 cells/mm^3 in 3 to 4 months, when therapy is discontinued (*Clin Infect Dis* 2001;33:344; *Clin Infect Dis* 2001;32:1231; *N Engl J Med* 2003;349:837). This decrease may be seen with or without antecedent viral suppression and is ascribed either to reduced replication capacity due to resistant mutations (*N Engl J Med* 2003;349:837) or to loss of partial antiviral activity despite resistance (*J Infect Dis* 2005;192:1537).

Total Lymphocyte Count (TLC): The TLC is sometimes used as a surrogate for CD4 count in resource-limited areas (*JAMA* 1993;269:622; *Am J Med Sci* 1992;304:79). TLC of <1200/mm^3 combined with clinical symptoms is recommended as a surrogate for a CD4 count of <200 cells/mm^3 as an indication for antiretroviral therapy in the DHHS guidelines (*Scaling Up Antiretroviral Therapy in Resource Limited Settings*, WHO, 2006). The addition of a hemoglobin ≤12 g/dL improves the sensitivity of detecting CD4 counts <200/mm^3 when the TLC is 1200-2000/mm^3 (*AIDS* 2003;17:1311).

CD4 Repertoire: Progressive immunodeficiency in HIV infection is associated with both quantitative and qualitative changes in CD4 cells. The two major categories of CD4 cells are naïve cells and memory cells. In early life, all cells are naïve and express the isoform of CD45RA$^+$. Memory cells (CD45RA$^-$) represent the component of the T-cell repertoire that has been activated by exposure to antigens. These are the CD4 cells with specificity for most opportunistic infections, such as *P. jiroveci*, cytomegalovirus, and *Toxoplasma gondii*. It is the depletion of these cells that accounts for the inability to respond to recall antigens, a defect noted relatively early in the course of HIV infection. Studies of HIV-infected patients show a preferential decline in naïve cells. With HAART, there is a three-phase component to the CD4 rebound. The initial increase is due primarily to redistribution of CD4 cells from lymphatic sites. The second phase is characterized by an influx of CD4 memory cells with reduced T-cell activation and improved response to recall antigens. In the third phase there is an increase in naïve cells following at least 12 weeks of HAART (*Nat Med* 1997;5:533; *Science* 1997;277:112). By 6 months the CD4 repertoire is diverse. The competence of these cells is evidenced by favorable control of selected chronic infections such as cryptosporidiosis, microsporidiosis, and molluscum contagiosum, the ability to discontinue maintenance therapy for disseminated MAC and CMV, and the ability to safely discontinue primary prophylaxis for PCP and MAC in responders. Nevertheless, some patients with immune

reconstitution have deficits in CTL responses to specific antigens that may result in PCP or relapses in CMV retinitis despite CD4 counts >300 cells/mm^3 (*J Infect Dis* 2001;183:1285).

Idiopathic CD4 Lymphocytopenia (ICL): ICL is a syndrome characterized by a low CD4 cell count that is unexplained by HIV infection or other medical conditions. Case definition criteria include: 1) CD4 less than 300 cells/mm^3 or a CD4 percent less than 20% on 2 or more measurements; 2) lack of laboratory evidence of HIV infection; and 3) absence of alternative explanation for the CD4 cell lymphocytopenia including Sjögren syndrome, sarcoid, radiation, atopic dermatitis, collagen vascular disease, steroid therapy, or lymphoma (*N Engl J Med* 1993;328:373). Transient, unexplained decreases in CD4 cells may occur in healthy persons (*Chest* 1994;105:1335; *Eur J Med* 1993;2:509; *Am J Med Sci* 1996;312:240). One study of 430 HIV negative TB patients showed 62 (14%) had ICL (*J Infect Dis* 2000;41:167). (Dr. T.J. Spira, personal communication).

Resistance Testing (see *N Engl J Med* 2004;350:1023)

In South Africa, there is little transmitted resistance. Resistance develops as a result of inadequate drug levels. This may be due to non-adherence, incorrect doses, or drug-drug interactions.

- Resistance assays measure only dominant species at the time the test is performed; resistant variants that account for <20% of the total viral population in blood and strains in "sequestered havens" (CNS, latent CD4 cells, genital tract, etc.) are not detected.
- There must be a viral load of ≥500 to 1,000 c/mL to perform the test.
- Genotypic assays may be difficult to interpret because multiple mutations are required for drug resistance for antiretroviral agents other than 3TC and non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- Phenotypic assays are easier to interpret because they are more like antibacterial sensitivity results. However, they often use arbitrary thresholds to define susceptibility, particularly for some RTV-boosted regimens, and they are also less sensitive at detecting emerging resistance.

As a result of these limitations, the following conclusions can be drawn:

- **Resistance testing most reliably identifies drugs that should be avoided** but is less reliable at detecting the drugs that are most likely to be active.
- **Testing is most reliable for indicating activity of drugs (or class of drugs) the patient is taking or has recently taken,** because discontinuation of therapy eventually results in the reemergence and proliferation of wild-type virus. The time required for reappearance of

wild-type virus after discontinuation of antiretrovirals appears to be at least 4 weeks, though this varies among drugs. Reversion of 184V within 20 days has been reported (*J Infect Dis* 2005;192:1537).

- **Interpretation of results in patients who have received prior antiretroviral agents is difficult**, due to failure to detect "archived strains" or "minority species." Thus, prior drug history and outcome of prior resistance tests are important considerations in regimen selection. This was shown in ACTG 398, in which EFV-experienced patients failed EFV therapy despite baseline resistance tests showing NNRTI susceptibility. Single genome sequencing revealed resistance in minority species (*Antivir Ther* 2003;8:S150).
- **A viral load of 500 to 1,000 c/mL is usually required.**
- **There is a preference for genotypic resistance testing,** at least for baseline testing and early virologic failures. This is based on better clinical trial results and lower cost. The relative merits of the available assays are discussed below ("Test Methods").
- **Expert interpretation improves results.**

Indications for Resistance Testing in South Africa

Currently there is no provision for individual patient monitoring on Comprehensive HIV and AIDS Care, Management Treatment program of South Africa (CCMT). Sentinel sites have been established to monitor the emergence of resistance strains. In the public sector, resistances testing is available at the cost of R 3500.

EVALUATION: A meta-analysis of published reports and conference presentations through February 2001 compared virologic results at 3 to 6 months after using resistance testing vs clinician decision or standard of care (SOC) for salvage regimens (*HIV Clin Trials* 2002;3:1). For genotypic analysis, there was a modest but statistically significant benefit with genotypic testing. Results were significantly better with expert interpretation of the resistance assay. There was no significant benefit with phenotypic resistance testing compared with SOC (although the analyses were done prior to currently accepted thresholds to define resistance). Viral suppression at 6 months after regimen change based on aggregate data for genotypic analysis vs SOC was as follows: genotype 168/432 (39%) vs SOC 115/400 (29%). Many studies showed only short-term benefit (*AIDS* 2002;16:369). Possibly the most important studies of the value of resistance testing with therapeutic failure was TORO-1 and TORO-2 (*N Engl J Med* 2003; 348:2175 and 2293). These studies showed a strong correlation between the number of active drugs in the background regimen (by genotype or phenotype analysis) and virologic response.

IAS-USA guidelines state 1) there is at least short-term benefit with both phenotypic and genotypic testing, but it is hard to demonstrate; 2) evidence of benefit is strongest for genotypic testing; and 3) expert

interpretation notably improves results (*Clin Infect Dis* 2003;17:37).

The currently available tests are standardized for clade B strains; utility for the other clades is not known (*Scand J Infect Dis* 2003;35[Suppl 106]:75).

- **Pregnancy:** Some guidelines recommend routine resistance tests for pregnant women, although the rationale, beyond the indications cited above, is unclear.

Test Methods: There are two types of tests, genotypic and phenotypic assays. These are compared in Table 2-5, p. 24 (*J Antimicrob Chemother* 2004;53:555).

GENOTYPIC ASSAYS: Genotype analysis identifies mutations associated with phenotypic resistance. Testing may be performed using commercial kits or "home brews." There is 98% concordance when two commercial kits are tested by the same laboratory (*Antivir Ther* 2000;5 suppl 4:60; *Antivir Ther* 2000; suppl 3:53). Another study found a 0.3% frequency of false positive results and a 6.4% frequency of false negative results (*Antivir Ther* 2001;6 suppl 1:1). Assays vary in cost, number of mutations tested, and method of reporting and interpreting results. The methodology involves: 1) amplification of the reverse transcriptase (RT) and protease (Pr) gene, by RT PCR. 2) DNA sequencing of amplicons generated for the dominant species (mutations are limited to those present in >20% of plasma virions). 3) Reporting of mutations for each gene using a letter-number-letter standard, in which the first letter indicates the amino acid at the designated codon with wild-type virus, the number is the codon position, and the second letter indicates the amino acid substituted in the mutation. Thus, the RT mutation K103N indicates that asparagine (N) has replaced lysine (K) on codon 103. Table 2-5 (p. 24) shows the amino acids and corresponding letter codes used to describe mutations in genotype analyses. Interpretation is based on judgement using lists of drug resistance mutations or computerized rules-based algorithms. Updated information on resistance testing can be obtained at http://www.iasusa.org or http://hivdb.stanford.edu.

PHENOTYPIC ASSAYS: Phenotype analysis measures the ability of HIV to replicate at different concentrations of tested drugs. It is available from three commercial labs, which show generally good concordance when compared (*Antivir Ther* 2001;6 suppl 1:129; *Antivir Ther* 2000;5[suppl 3]:49). The test involves insertion of the RT and protease genes from the patient's strain into a backbone laboratory clone by cloning or recombination. Replication is monitored at various drug concentrations and compared with a reference wild-type virus. This assay is comparable with conventional *in vitro* tests of antimicrobial sensitivity, in which the microbe is grown in serial dilutions of antiviral agents.

Results are reported as the IC_{50} for the test strain relative to that of a reference or wild-type strain. The interpretation was previously based on interassay variation of control, but current interpretations use either biologic thresholds based on the normal distribution of wild-type virus from untreated patients or, for a growing number of drugs, clinical thresholds based on data from clinical trials.

VIRTUAL PHENOTYPE: This is a prediction of the phenotype of the test strain based on genotypic analysis. The mutational pattern of the test strain is compared with results of phenotypic assay using strains showing similar mutations from a databank of >55,000 HIV isolates. Lack of sufficient paired genotype and phenotype assays in the database preclude results in about 20% (*Antivir Therapy* 2003;8:S103).

RELATIVE MERITS: Genotypic resistance tests are generally preferred for baseline (pretreatment) testing and with early failures. Arguments for this approach are that genotypes are easy to interpret at this stage and more sensitive for detecting wild-type/mutant mixtures which may be present in treatment-naïve patients, and that clinical trial data show better outcomes in this setting when compared to the standard of care (GART [*AIDS* 2000;14:F83], VIRADAPT [*Lancet* 1999;353:2195]; HAVANA [*AIDS* 2002;16:209]) or when compared to phenotypic testing (REALVIRFEN [*Antivir Ther* 2003;8:577]; NARVAL [*Antivir Ther* 2003;8:427]). Genotypic testing is also less expensive and appears cost-effective when used for first or second regimen failures *(Ann Intern Med* 2001;134:440; *J Acquir Immune Defic Syndr* 2000;24:227). Phenotype resistance may be preferred or may supplement genotypic test results in patients with more extensive resistance after multiple regimen failures (CERT [*Clin Infect Dis* 2004;38:723] and TORO [*N Engl J Med* 2003;348:2175]). Phenotypes provide quantitative results, allowing comparison of relative susceptibility and resistance. They assess interactions among mutations, and may be preferable for the assessment of susceptibility to new drugs for which genotype correlates of resistance have not been completely determined.

■ TABLE 2-5: **Comparison of Genotypic and Phenotypic Assays**

Genotypic Assays	
Advantages	**Disadvantages**
■ Less expensive (R3500/test). ■ Short turn-around of 1 to 2 weeks. ■ Well standardized. ■ Good reproducibility. ■ Possibility of virtual phenotype.* ■ More sensitive for detection of emerging resistance (mixtures). ■ Favored in comparative studies with failure of first or second regimens.	■ Detect resistance only in dominant species (>20%). ■ Interpretation requires expertise. ■ Technician experience influences results. ■ Algorithms may be incomplete, especially for new drugs. ■ May show discrepancy with phenotype. ■ Require VL >500-1000 c/mL. ■ Limited data on non-clade B virus.
Phenotypic Assays	
■ Interpretation more straightforward and familiar. ■ Assess total effect, including mutational interactions. ■ Do not require data on genotypic correlates of resistance (advantageous with newer agents). ■ Reproducibility is good. ■ Advantage over genotype when there are multiple mutations. ■ Provide quantitative assessment of susceptibility.	■ More expensive (usually R5000 – R7000). High cost may affect reimbursement. ■ Report takes longer than genotypic assay. ■ Clinically determined thresholds not available for all drugs, and not all PI thresholds account for ritonavir boosting. ■ Detect resistance only to single drug, not combinations. ■ Detect resistance only in dominant species (>20%). ■ Require VL >500-1000 c/mL.

**Virtual phenotype* is rapid, easily done, and less expensive than phenotypic assays; disadvantages are inability to perform when database is inadequate.

■ TABLE 2-6: **Letter Designations for Amino Acids***

A	Alanine	**I**	Isoleucine	**R**	Arginine
C	Cytosine	**K**	Lysine	**S**	Serine
D	Aspartic acid	**L**	Leucine	**T**	Threonine
E	Glutamic acid	**M**	Methionine	**V**	Valine
F	Phenylalanine	**N**	Asparagine	**W**	Tryptophan
G	Glycine	**P**	Proline	**Y**	Tyrosine
H	Histidine	**Q**	Glutamine		

* Single-letter codes are used in describing genotypes.

■ TABLE 2-7: **Resistance Mutations Adapted From IAS-USA (*Top HIV Med* 2006:14:125-130). Updated at http://www.iasusa.org and Stanford University HIV Drug Resistance Database http://hivdb.stanford.edu)**

Drug	Mutations selected	Comments
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
AZT	41L, 67N, 70R, 210W, 215Y/F, 219Q/E	Thymidine analog mutations (TAMs): reduce susceptibility to all NRTIs. TAMs infrequently coexist with 65R. Most frequent TAMs are 41L, 210W, 215Y, which have greatest impact on NRTI susceptibility. 67N, 70R, 219Q/E also decrease susceptibility, but to lesser degree. 184V, 65R, 74V increase AZT susceptibility. TAMs cause hypersusceptibility to NNRTIs. 44D and 118I further decrease susceptibility when present with TAMs.
d4T	41L, 67N, 70R, 210W, 215Y/F, 219Q/E, 75T/M/A	Most d4T resistance due to TAMs (see AZT). 75T/M/A are d4T-specific mutations, but are uncommon.
3TC	65R, 184V/I	184V/I: high-level 3TC resistance, with increase in activity of AZT, d4T, and TDF, but effect can be overcome by TAMs. Reduces susceptibility to ddI, ABC, though not clinically significant with 184V/I alone. 44D and 118I not selected by 3TC, but they confer moderate 3TC resistance.
FTC	65R, M184V/I	Similar or identical to 3TC.
ddI	65R, 74V	TAMs confer ddI resistance. 74V or 65R mutations alone or combined with 184V/I associated with ddI resistance and cross-resistance to ABC (74V, 65R) and TDF (65R).
ABC	65R, 74V, 115F, 184V	Resistance depends on number of TAMs and TAM-pathway. 184V/I alone does not confer clinically significant resistance but further decreases susceptibility in combination with TAMs or ABC mutations.
TDF	65R, 70E	Reduced activity with 65R or with 3 TAMs that include 41L and 210W. 184V/I increases TDF activity, partially compensating for 65R or TAMs. 70E uncommon, but reduces TDF susceptibility.
Multi-nucleoside resistance: Q151M compex	151M plus 62V, 75I, 77L, 116Y	Uncommon with 3TC- or FTC-containing regimens. Occurs with or without TAMs. When 151M "complex" present, confers high-level resistance to AZT, d4T, ABC, ddI, intermediate resistance to TDF, and low-level resistance to 3TC, FTC.
Multi-nucleoside resistance: T69 insertion	69ins	Uncommon with 3TC- or FTC-containing regimens. Usually occurs with TAMs, conferring high-level resistance to all NRTIs including TDF.

■ TABLE 2-7: **Resistance Mutations *(Continued)***

Drug	Mutations selected	Comments
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
Multi-nucleoside resistance: multiple TAMs	41L, 67N, 70R, 210W, 215Y/F, 219Q/E	Most common cause of multinucleoside resistance. Only AZT and d4T select for TAMs. 44D and 118I further decrease NRTI susceptibility.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
NVP	100I, 103N, 106A/M, 108I, 181C/I, 188C/L/H, 190A	181C is favored mutation with NVP unless combined with AZT, in which case 103N favored. 103N, 106M, 188L/C cause high-level NVP resistance. 188H causes low-level NVP resistance.
EFV	100I, 103N, 106M, 108I, 181I/C, 188L, 190S/A, 225H	103N is favored mutation with EFV, causing high-level NNRTI resistance. 188L and 106M also cause high-level EFV resistance. Although 181C (and some other NNRTI mutations) cause only low-level EFV resistance phenotypically, other NNRTI mutations may be present in sub-populations.

Drug	Major mutations	Minor mutations	Comments
Protease Inhibitors (PIs)			
IDV/r	46I/L, 82A/F/T, 84V	10I/R/V, 20M/R, 24I, 32I, 35I, 54V, 71V/T, 73S/A, 77I, 90M	At least 3 mutations required for resistance to unboosted IDV (>4-fold decrease in susceptibility).
NFV	30N, 90M	10F/I, 36I, 46I/L, 71V/T, 77I, 82A/F/T/S, 84V, 88D/S	30N most common mutation, causing no PI cross-resistance. 90M occurs in some (especially non-B subtypes), causing greater PI cross-resistance.
SQV/r	48V, 90M	10I/R/V, 24I, 54L/V, 62V, 71V/T, 73S, 77I, 82A/F/T/S, 84V	90M is typically first mutation, then 48V. 48V unique to SQV, but 90M causes PI cross-resistance. Evidence for decreased selection of PI mutations with SQV/r than SQV in PI-naïve patients.
LPV/r	32I, 47V/A, 82A/F/T/S	10F/I/R/V, 20M/R, 24I, 33F, 46I/L, 50V, 53L, 54V/L/A/M/T/S, 63P, 71V/T, 73S, 84V, 90M	Most PI-naïve patients failing LPV/r as first PI have no PI mutations. 47A confers intermediate-to-high level LPV resistance.

(continued)

■ TABLE 2-7: **Resistance Mutations *(Continued)***

Drug	Major mutations	Minor mutations	Comments
Protease Inhibitors (PIs) *(continued)*			
DRV/r	50V, 54M/L, 76V, 84V	11I, 32I, 33F, 47V, 50V, 73S, 89V	Reduced response withincreasing DRV mutations, with poor response with 3.
ATV or ATV/r	50L, 84V, 88S	10I/F/V/C, 16E, 20R/M/I/T/V, 24I, 32I, 33I/F/V, 36I/L/V, 46I/L, 48V, 53L/Y, 54L/V/M/T/A, 60E, 62V, 64I/M/V, 71V/I/T/L, 73C/S/T/A, 82A/T/F/I, 85V, 90M, 93L/M	50L causes no PI cross-resistance, and possible hypersusceptibility to other PIs. Reduced *in vivo* activity associated with 3 of the following: 10F/V/I, 16E, 33F/I/V, 46I/L, 60E, 84V, 85V

* The distinction between primary and secondary mutations has been eliminated for NRTIs NNRTIs by the IAS-USA Expert Committee; this distinction has been retained for PIs, but with the terms "major" or "minor."

† **Major mutations** develop first or are associated with decreased drug binding or reduced viral activity; these effect phenotype resistance.

‡ **Minor mutations** appear later and, by themselves, do not significantly change phenotype resistance.

Screening Laboratory Tests

The usual screening battery advocated for patients with established HIV infection is summarized, pp. 38-39 (Primary Care Southern African HIV Clinicians Society).

Full Blood Count: The FBC is important, because anemia, leukopenia, lymphopenia and thrombocytopenia are common due to HIV per se or to medications (*J Acquir Immune Defic Syndr* 1994;7:1134; *J Acquir Immune Defic Syndr* 2001;28:221). Repeat at 3- to 6-month intervals and more frequently in patients with symptoms (headache, fatigue), those receiving marrow-suppressing drugs such as AZT, and in those with marginal or low counts.

■ TABLE 2-8: **Routine Laboratory Tests**

Test	Cost*	Frequency and Comment
Serologic Tests		
Hep B surface antigen or core antibody	R220	Screen for chronic hepatitis B. Conside HBV DNA in HBsAg negatives with abnormal transaminases.
HIV	R108	Repeat test for patients with positive test results and inadequate confirmation.
Syphilis – VDRL or RPR**	R27	Repeat annually in sexually active patients. Confirm positives with FTA-ABS.
Chemistry		
Liver function tests and Urea and Electrolytes	LFT R332, UTE R171	Includes LFTs and renal function. Repeat annually or more frequently in patients with abnormal results and with administration of hepatotoxic or nephrotoxic drugs.
Lipogram and glucose (fasting)	R208	Therapeutic monitoring recommended for patients receiving antiretroviral regimens that include a PI or NNRTI. Test at baseline and at 3 to 6 months with subsequent measurements annually or more frequently based on initial results and risks.**
Hematology		
Full blood count (FBC)	R128	Repeat at 3 to 6 months, more frequently for low values and with marrow-toxic drugs.
CD4 cell count and %**	R162	Repeat every 3 to 6 months and repeat for discordant results, including those results with results that are inconsistent with prior trends. Routine testing when counts are <50 cells/mm^3 is of minimal use except for monitoring response to antiretroviral therapy.

(Continued)

■ TABLE 2-8: **Routine Laboratory Tests *(Continued)***

Test Test	Cost*	Frequency and Comment
Other		
Chest x-ray	R220	May be routine or restricted to those with past pulmonary disease, chronic pulmonary disease or a positive PPD*
PAP smear**	R120	Repeat at 6 months and then annually if results are normal. Results reported as "inadequate" should be repeated. Refer to a gynecologist for results showing atypia or greater on the Bethesda scale (see pp. 41-43).
PPD skin test**	R8.00	The use of PPD is limited in South Africa as approximately 60% of South Africa as PPD positive. A negative PPD may indicate lack of exposure to TB or overwhelming TB. A positive PPD may be used to start Intermittent Prophylaxis for TB (IPT) in the absence of active TB (more to follow)

*Common charges are based on survey of five laboratories.
** Recommendations of Primary Care Guidelines of IDSA (*Clin Infect Dis* 2004;39:609).

Serum Chemistry Panel: This panel is advocated in the initial evaluation of HIV infection due to high rates of hepatitis (*J Infect Dis* 2002;186:231), to help stage the disease, and to obtain baseline values in patients who are likely to have multisystem disease due to HIV or its treatment. (*J Acquir Immune Defic Syndr* 1994;7:1134).

■ TABLE 2-9: **Liver functions tests (LFTs and Urea and Electrolytes)**

Test	Tube to be used	Special instructions
Full blood count	Purple top 5ml	Refrigerate if kept overnight
CD4+ count and percentage	Purple top 5ml	Do not refrigerate

CXR, (chest X-ray) pap smear and PPD should also be considered.

CXR If possible a CXR should be done at baseline. However if this facility is not easily accessed, then a baseline CXR should be considered in patient with evidence of pulmonary disease. This is strongly recommended in those with Cd4+ below 100

Syphilis Serology (*MMWR* 2006;55[RR-1]:22): Screen with a nontreponemal test (VDRL or RPR) at baseline and annually thereafter in sexually active patients due to high rates of co-infection. Up to 6% of patients with HIV infection have biologic false-positive (BFP) screening tests. Risk factors for biologic false-positive results include injection drug use, pregnancy, and HIV infection (*Clin Infect Dis* 1994;19:1040; *J Infect Dis* 1992;165:1124; *J Acquir Immune Defic Syndr* 1994;7:1134; *Am J Med* 1995;99:55).

Chest X-Ray: The frequency of lung disease with HIV infection is high even in the HAART era (*Am Rev Respir Crit Care Med* 2001;164:21; *Chest* 2001;120:1888).

The authors argued that in resource-limited areas, x-rays could be limited to those with symptoms.

PPD Testing: The recommendation for the Southern African HIV Clinicians society is that a PPD of > 5mm should be considered for TB prophylaxis(*SAMJ* 2000: 90 59-4). This should be done at baseline.

Pap Smear: While the Department of Health recommends the all women with no symptoms of cervical cancer are offered at least three smears starting at the age of thirty, this is not sufficient for HIV infected women. Most guidelines recommend a pap at baseline and every six months thereafter.

■ TABLE 2-10: **Recommendations for Intervention Based on Results of Pap Smear (*MMWR* 2002;51[RR-6]:58; *JAMA* 1989;262:931; *JAMA* 2002;287:2114)**

Results	Management
Severe inflammation	Evaluate for infection; repeat Pap smear, preferably within 2 to 3 months.
Atypia, atypical squamous cells of undetermined significance (ASCUS) ■ ASC-US (undetermined significance) ■ ASC-H (cannot exclude HSIL). ASC-H is intermediate between ASC-US and HSIL	Consider HPV testing: If high risk type (16, 18, 31, 33, or 35) – colposcopy. Alternative without HPV testing is follow-up. Follow-up Pap without colposcopy every 4 to 6 months x 2 years until three are negative; if second report of ASCUS, perform colposcopy.
Low-grade squamous intraepithelial lesion (LSIL)	Colposcopy ± biopsy or follow with Pap smear every 4 to 6 months, as above, with colposcopy and biopsy if repeat smears are abnormal.*
High-grade squamous intraepithelial lesion (HSIL) (carcinoma *in situ*)	Referral for colposcopy ± biopsy.
Invasive carcinoma	Colposcopy with biopsy or conization; treat with surgery or radiation.

* Most gynecologists recommend evaluation with any abnormality due to the high prevalence of underlying SIL.

METHOD: The cervix is scraped circumflexually using an Ayer spatula or a curved brush; a sample from the posterior fornix or the "vaginal pool" may also be included. The endocervical sample is taken with a saline-moistened cotton-tipped applicator or straight ectocervical brush that is rolled on a slide and immediately fixed in ethyl ether plus 95% ethyl alcohol or 95% ethyl alcohol alone. The yield is 7-fold higher with the brush specimen. The following are important steps in obtaining an adequate sample:

- Collect Pap prior to bimanual exam.
- Avoid contaminating sample with lubricant.
- Obtain Pap before samples for STD testing.
- Carefully remove large amounts of vaginal discharge (if present) with large swab before obtaining Pap smear.
- Obtain ectocervical sample before endocervical sample.
- Defer Pap smear if patient is bleeding heavily (small amounts of blood will not interfere with cytologic sampling).
- Apply collected material to slide uniformly, with no clumping. Fix rapidly to avoid air drying. If spray fixatives are used, the spray should be held at least 10 inches away from the slide to prevent disruption of cells by propellant.

When performing speculum examination, if an ulcerative or exophytic lesion suspicious for invasive cancer is noted, the patient should be referred for possible biopsy.

ANAL PAP SMEAR FOR SIL AND CARCINOMA IN MSM

More recent studies suggest this risk applies to all men with HIV, leading some to recommend routine anal cytology regardless of a history of receptive anal intercourse, especially those with a low CD4 count (*Ann Intern Med* 2003;183:453). Abnormal anal Paps should lead to referral for high-resolution anoscopy and biopsy (*Clin Infect Dis* 2004;38:1490). HAART is also important due to its profound impact on survival (*Dis Colon Rectum* 2004;47:1305).

Hepatitis B Serology: All HBV seronegative patients with HIV should receive the standard 3-dose HBV vaccine series. The standard screening test is anti-HBc or anti-HBs (*MMWR* 2002;51RR-6:63). For patients with prior vaccination the appropriate test is anti-HBs, but the titer wanes with time and many patients have protection despite negative serology several years after vaccination, presumably due to cell-mediated immunity (*Ann Intern Med* 2005;142:333). The test is highly sensitive for detecting antiHBs, although occasionally a patient will have HBV mutations that cause false negative results (*J Med Virol* 2006;51:556).

The prevalence of Hep B surface antigenaemia (hep B Sag) ranges between 5-10% in the HIV infected population.

It is estimated that over 50% of South Africans have been infected by the virus and at least 3 million people are chronic hepatitis B carriers. (http://www.savic.ac.za/disease) South Africa, all babies born in or after April 1995 receive hepatitis B vaccine, as part of routine childhood immunization at 6, 10, and 14 weeks of life.

Screening for Chronic HBV Infection: All patients should be tested for chronic HBV infection with HBsAg. Those with unexplained liver disease and negative HBsAg should be evaluated for chronic HBV infection with HBV DNA. Prevalence of chronic HBV is 0.2-1.0% in the general population and 6-7% for MSM, IDUs and hemophilia patients.

Chronic carriers of HBsAg should be evaluated with LFTs, HBeAg and HBV DNA to determine the replicative status and possible indication for liver biopsy and/or therapy. Management of HBV co-infection is complicated in patients with HIV due to the frequent use of antivirals with anti-HBV activity including 3TC, FTC, and TDF.

Adverse Drug Reaction Monitoring

Adverse drug reactions attributed to antiretroviral agents include diabetes mellitus, blood lipid changes associated with risks for coronary artery disease and stroke, lactic acidosis/steatosis attributed to nucleoside analogs, peripheral neuropathy, and hepatic toxicity (see Table 4-8). (http://www.mccza.com/main.asp)

3 Disease Prevention: Prophylactic Antimicrobial Agents and Vaccines

Recommendations for the prevention of HIV related and AIDS related opportunistic infections as per the Southern Journal of HIV Medicine (2002,1(17-20)

Strongly Recommended as Standard of Care

Pneumocystis jiroveci (P. carinii)

NOTE: The newer name from Stringer et al is *P. jiroveci* (*Emerg Infect Dis* 2002;8:891), but the term PCP (*Pneumocystis jiroveci* Pneumonia) continues to be used.

Primary prophylaxis refers the use of a medication to prevent an infections ever occurring. Secondary prophylaxis refers to the use of a medication to prevent a recurrence.

RISK: CD4 count <200/mm^3, prior PCP or HIV-associated thrush, or unexplained fever x 2 weeks.

Some experts advocate the use TMX-SMX in all patients with Cd4+ counts less than 350/mm^3
(http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf)

PREFERRED REGIMEN: TMP-SMX 1 DS/day or 1 SS/day (AI)

ALTERNATIVE REGIMENS

- TMP-SMX 1 DS 3x/week (BI)
- Dapsone 100 mg/day or 50 mg PO bid (BI)
- Aerosolized pentamidine 300 mg/month by *Respirgard II* nebulizer using 6 mL diluent delivered at 6L/min from a 50 psi compressed air source until reservoir is dry (usually 45 min), with or without albuterol (2 whiffs) to reduce cough and bronchospasm (BI)
- Atovaquone 1500 mg PO qd with meals (*N Engl J Med* 1998;339: 1889) (BI)
- While the last two options are available in South Africa, the cost prevents their use.

RISK: The risk of PCP without prophylaxis is 60% to 70% per year in those with prior PCP and 40% to 50% per year for those with a CD4 count <100/mm^3. The mortality for patients hospitalized and treated for PCP is 15% to 20%. PCP prophylaxis reduces the risk of PCP 9-fold, and patients who get PCP despite prophylaxis have a lower mortality rate (*Am J Respir Crit Care Med* 1997;155:60). The major reasons for PCP prophylaxis failure are CD4 count <50/mm^3 and non-

compliance (*JAMA* 1995;273:1197; *Arch Intern Med* 1996;156:177). TMP-SMX has established efficacy for reducing the incidence of bacterial infections and toxoplasmosis. This drug is active against *Nocardia*, *Legionella*, most *Salmonella*, most methicillin-sensitive *S. aureus*, community-acquired MRSA (USA 300 strains), many gram-negative bacilli, most *H. influenzae*, and about 70% of *S. pneumoniae*. No other PCP prophylaxis regimen has this spectrum of activity.

ADVERSE REACTIONS: Adverse reactions sufficiently severe to require discontinuation of the drug are noted in 25% to 50% with TMP-SMX, 25% to 40% with dapsone (*N Engl J Med* 1995:332:693). Patients who have a non-life-threatening reaction to TMP-SMX should continue this drug if it can be tolerated. Those who have had such a reaction in the past should be rechallenged, possibly using desensitization (see pp. 317-318).

IMMUNE RECONSTITUTION: Patients whose CD4 count increases to >200/mm^3 x ≥3 months may safely discontinue primary PCP prophylaxis (AI) (*N Engl J Med* 1999;340:1301; *Lancet* 1999;353:1293; *Lancet* 1999;353:201; *J Infect Dis* 2000;181:1635) and secondary prophylaxis (BII) (*N Engl J Med* 2001;344:159; *N Engl J Med* 2001; 344:168). Prophylaxis should be restarted if the CD4 count falls to <200/mm^3 (AIII).

TRANSMISSION RISK: Some authorities recommend avoidance of "high-intensity exposure," meaning that a patient with PCP should not room with a vulnerable patient (*N Engl J Med* 2000;342:1416; *Am J Respir Crit Care Med* 2000;162:167; *Emerg Infect Dis* 2004;10:1713). Recent reports do not support this recommendation (*JAMA* 2001;286:2450).

M. tuberculosis

RISK (*MMWR* 1998;47:[RR-20]): Positive PPD (≥5 mm induration) without prior prophylaxis or treatment (AI), recent TB contact (AII). The rate of active TB in those with a positive PPD is magnified 7- to 80-fold by HIV co-infection (*Lancet* 2000;356:470; *MMWR* 2000;49[RR-6]). It also appears that active TB accelerates the rate of HIV progression (*J Acquir Immune Defic Syndr* 1998;19:361; *BMJ* 1995;311:1468; *J Infect Dis* 2004;190:869). HIV-positive persons who are close contacts of active TB cases should be evaluated to exclude active disease and should receive treatment for latent TB infection regardless of PPD results. Active TB must be excluded before starting Intermittent Prophylaxis therapy (IPT) for TB. Careful adherence to the treatment schedule is necessary to prevent the development of resistance. Prophylaxis should therefore only be given to patients who can be relied upon to take their medication correctly.

Health care workers who are HIV positive should also be offered IPT.

EFFICACY OF PROPHYLAXIS: The Cochrane Library review for TB prophylaxis in patients with AIDS showed an odds ratio (OR) for active TB of 0.38 in those with a positive PPD based on 11 trials including 8,130 patients. Efficacy was similar for different drug regimens (*Cochrane Database Syst Rev* 2004, D000171.

PREFERRED REGIMEN FOR COMPLIANT PATIENT LIKELY TO COMPLETE 9-MONTH COURSE (*MMWR* 2000;49[RR-6]; *MMWR* 2001;50:773)

- INH 300 mg + pyridoxine 50 mg PO daily
- INH 900 mg + pyridoxine 100 mg PO 2x/week

PREFERRED REGIMEN FOR PATIENT UNLIKELY TO COMPLETE 9-MONTH INH COURSE WITHOUT CONCURRENT PI OR NNRTI

- Rifampin 600 mg qd + pyrazinamide (PZA) 15-20 mg/kg qd x 2 months (AI)

PREGNANCY: INH regimens

M. avium complex

RISK: CD4 count <50/mm^3. The incidence of MAC with a CD4 <50/mm^3 and no HAART or prophylaxis is 20-40% (*J Infect Dis* 1997;176:126; *Clin Infect Dis* 1993;17:7).

Primary prophylaxis is not recommended. Treatment and secondary prophylaxis are closely linked.

PREFERRED: Clarithromycin 500 mg PO bid (AI) or azithromycin 1200 mg PO weekly (AI). Note:

ALTERNATIVE: Rifabutin 300 mg/day PO (BI) or azithromycin 1200 mg/week plus rifabutin 300 mg/day (CI) (see rifabutin dose adjustment for use with PIs or NNRTIs). Use caution when rifabutin is combined with clarithromycin due to drug interactions resulting in reduced levels of clarithromycin (*J Infect Dis* 2000;181:1289).

IMMUNE RECONSTITUTION: It is safe to discontinue primary and secondary MAC prophylaxis with immune reconstitution at a CD4+ count of above 200.mm^3.

Vaccines

■ TABLE 3-1: **Vaccine Recommendations for Patients with HIV**

Vaccine	HIV
Hepatitis B	Recommended
Influenza	Recommended
Meningococcal vaccine	Use if indicated
Pneumococcal vaccine	Recommended when CD4 >200/mm^3
Yellow fever vaccine	Recommended when traveling to endemic areas.

S. pneumoniae

RISK: All patients with HIV infection. Risk for invasive pneumococcal infection is 50- to 100-fold greater than in the general population (*Ann Intern Med* 2000;132:182; *J Infect Dis* 1996;173:857; *J Acquir Immune Defic Syndr* 2001;27:35; *AM J Respir Crit Care Med* 2000;162:2063).

PREFERRED: *Pneumovax* 0.5 mL IM x 1 (CD4 count >200/mm^3 – BII; CD4 count <200/mm^3 – CIII).

REVACCINATE: When CD4 count increases to >200/mm^3 if initial immunization was given with CD4 count <200/mm^3 (CIII) (*MMWR* 1999;[RR-10]:16). Revaccination is recommended at 3- to 5-year intervals (*N Engl J Med* 2000;342:1416), though there is no evidence of efficacy for revaccination.

ALTERNATIVE: The 7 valent protein-conjugated pneumococcal vaccine approved by the FDA in March 2000 is recommended only for children. Use of this vaccine in adults shows no advantage over *Pneumovax* in terms of antibody levels (*Vaccine* 2001;20:545).

Hepatitis B

RISK: Negative anti-HBc or anti-HBs screening test.

PREFERRED: *Recombivax HB* 10 ug IM x 3 (at 0, 1, and 6 mos) (BII) or *Engerix-B* 20 µg IM x 3 (BII).

Influenza

RISK: All patients annually.

PREFERRED: Influenza vaccine 0.5 mL IM each year March to April (BIII). A trial in 2002-2003 showed a good humoral immune response even with low CD4 counts (*J Acquir Immune Defic Syndr* 2005;39:167). A

review of 6 published reports showed vaccine effectiveness rates of 27-78% (*BMC Infect Dis* 2006;11:138).

4 | Antiretroviral Therapy

Recommendations for Antiretroviral Therapy

These are based on the Southern African HIV Clinicians Society (SAHIVSC) (http://www.sahivsoc.org/index.php/guideline/index/2/9), the Department of Health, (http://www.info.gov.za/issues/hiv/careplan.htm) and the WHO guidelines (http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf)

Goals of Therapy

CLINICAL GOALS: Prolongation of life and improvement in quality of life.

VIROLOGIC GOALS: Greatest possible reduction in viral load (preferably to <50 c/mL) for as long as possible to halt disease progression and prevent or delay progression.

IMMUNOLOGIC GOALS: Immune reconstitution that is both quantitative (CD4 cell count in normal range) and qualitative (pathogen-specific immune response).

THERAPEUTIC GOALS: Rational sequencing of drugs in a fashion that achieves clinical, virologic, and immunologic goals while maintaining treatment options, limit drug toxicity and facilitate adherence.

EPIDEMIOLOGIC GOALS: Reduce HIV transmission

Indications for Therapy

■ TABLE 4-1: **SAHIVSC guidelines**

Symptomatic Patient	Treatment
Presence of severe HIV-related symptoms (WHO clinical stage 3 or 4) *	ART treatment recommended
Asymptomatic Patient	**Treatment**
CD4+ count <200	ART treatment recommended
CD4+ count 200 - 350	ART treatment should be considered on an individual basis **
CD4+ count >350	Defer treatment

DEPARTMENT OF HEALTH OF SOUTH AFRICA

CD4< 200 and symptomatic irrespective of stage. And/or WHO stage 4 irrespective of stage And Patient prepared and ready to take ARV adherently

Recommendations are based on CD4 cell count, symptoms, and viral load. It is assumed that the patient is ready and willing to start therapy and understands the critical importance of adherence.

RECOMMENDATION FOR ANTIRETROVIRAL THERAPY

These are based on the Southern African HIV Clinicians Society (SAHIVSC) (http://www.sahivsoc.org/index.php/guideline/index/2/9), the Department of Health, (http://www.info.gov.za/issues/hiv/careplan.htm) and the WHO guidelines (http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf)

WHO GUIDELINES

■ TABLE 4-2: **First line regimen- WHO**

First line regimen	
First line regimen	AZT or D4T, 3TC and NVP or EFV
	<200/mm^{3}TNF,3TC and NVP or EFV
	AZT,3TC and NVP or EFV
B	AZT or D4T 3TC and TNF or ABC

DEPARTMENT OF HEALTH GUIDELINES (DOH, SOUTH AFRICA)

Two ART regimens are recommended in the South African public sector. Patients failing both regimens are referred to ART specialists for individual evaluation. New developments in ART will determine options for salvage therapy. Substitution of drugs for toxicities can be made. Drug swaps can be made for toxicity, between regimens.

■ TABLE 4-3: **Regimen DOH guidelines**

Regimen	Drugs	Indications
Regimen 1a	d4T/3TC/EFV	Men and women who are not of child-bearing potential or using injectable contraception plus condoms
Regimen 1b	d4T/3TC/NVP	Women who are unable to guarantee reliable contraception whilst on therapy
Regimen 2	AZT/ddI and lopinavir-ritonavir	For patients virologically failing Regimen 1 despite demonstrating adherence

Initial Regimen

REGIMEN SELECTION: Preferred regimens for initial therapy are summarized according to guidelines for WHO (Table 4-2) and DOH (Table 4-3)

■ TABLE 4-4: Advantages and Disadvantages of Antiretroviral Agents and Combinations for Initial Therapy

Agents	Advantages	Disadvantages
2 NRTIs + 1 PI or RTV-boosted PI*		
Atazanavir + ritonavir	■ Low pill burden ■ Once daily dosing ■ Minimal or no effect on lipids or insulin resistance ■ Fewer GI side effects ■ ATV may be given without RTV unless given with TDF or EFV ■ Minimal PI resistance with initial failure	■ Food requirement ■ Hyperbilirubinemia/jaundice ■ Reduced ATV AUC when given with TDF or EFV (use ATV/r 300/100 qd) ■ Potential for QTc prolongation ■ Absorption dependent on acidic pH (PPIs, antacids and H2 blockers contraindicated) ■ No studies in pregnancy
Indinavir + ritonavir*	■ Long term experience documenting sustained benefit ■ RTV boosting eliminates food effect ■ Alternative agent in pregnancy	■ Nephrolithiasis, skin/hair side effects ■ IDV/RTV 400/400 bid – Poor GI tolerance 800/100 bid – Increased nephrolithiasis
2 NRTIs + 1 PI or RTV-boosted PI*		
Lopinavir + ritonavir	■ Co-formulation ■ High potency documented ■ Comparable potency with viral load >100,000 c/mL ■ Minimal PI resistance with initial failure ■ Durable potency established ■ Once daily therapy FDA approved for treatment-naïve patients ■ Can combine with EFV for nuke sparing (ACTG 5142) ■ Advocated by DHHS guidelines in pregnancy	■ Nausea, diarrhea ■ More viral failures than EFV-based HAART (ACTG 5142) ■ PI class toxicity-lipodystrophy ■ Requires RTV
Nelfinavir	■ Generally well tolerated ■ No PI cross-resistance with D30N ■ Extensive experience establishing favorable pharmokinetics and safety in pregnancy	■ Diarrhea ■ PI class toxicity – lipodystrophy ■ Reduced potency compared with boosted PIs (main disadvantage) ■ Decreased efficacy with viral load >100,000 c/mL and/or low CD4 ■ Fatty food requirement ■ PI cross-resistance with L90M ■ Poor boosting with RTV ■ BID dosing required
Saquinavir (Invirase) + ritonavir*	■ Extensive experience ■ Preliminary 24-wk data from Gemini trial showing possible equivalence to LPV/r	■ Poor GI tolerability ■ PI class toxicity – lipodystrophy ■ Requires RTV ■ Most published data is with *Fortovase* formulation which is no longer available

■ TABLE 4-4: **Advantages and Disadvantages of Antiretroviral Agents and Combinations *(Continued)***

Agents	Advantages	Disadvantages
2 NRTI + NNRTI		
Efavirenz	■ High potency documented ■ Comparable potency with viral load >100,000 c/mL ■ Coformulated with TDF/FTC ■ One tab per day ■ May use with rifampin ■ Durable potency established ■ Unbeaten in clinical trials	■ Neuropsychiatric toxicity and rash ■ Contraindicated in pregnancy and with pregnancy potential ■ Single mutation confers class resistance ■ Methadone interaction ■ Reduces PI levels
Nevirapine	■ Low pill burden ■ No food effect ■ Minimal lipid changes ■ Comparable efficacy to EPV ■ Least expensive "third drug"	■ Hepatotoxicity including lethal hepatic necrosis especially with pre-treatment CD4 counts >250 (F) or >400 (M) ■ High rate of rash, including life-threatening hypersensitivity ■ Single mutation confers class resistance ■ Methadone interaction ■ Reduces PI levels ■ Less clinical trial data than with EFV
3 NRTIs		
AZT/3TC/ABC	■ Extensive experience ■ Low pill burden ■ Preserves PI and NNRTI options ■ Minimal drug interactions ■ Coformulated	■ Reduced potency at all VL levels compared to EFV-based HAART ■ ABC hypersensitivity reactions ■ AZT effects (see below) ■ Requires bid dosing
2 NRTIs (as component of HAART regimen)		
AZT/3TC or AZT/FTC	■ Extensive experience ■ Low pill burden ■ Co-formulated (AZT/3TC) ■ No food effect ■ M184V slows AZT resistance and increases AZT activity	■ AZT toxicity: Anemia, neutropenia, GI intolerance ■ TAMs and NRTI cross-resistance with prolonged failure ■ Mitochondrial toxicity (AZT) including lipoatrophy and lactic acidosis ■ Requires bid dosing
TDF/FTC or TDF/3TC	■ Once daily regimen ■ Both effective against HBV ■ Well tolerated ■ Low pill burden (l/d) ■ Avoids TAMs ■ Coformulated (TDF/FTC and TDF/FTC/EFV) ■ Low potential for mitochondrial toxicity ■ Efficacy >AZT/3TC (*N Engl J Med* 2006;354:251) ■ 184V increases TDF activity ■ Low potential for mitochondrial toxicity	■ Risk of ABC and ddI cross-resistance after failure (K65R) ■ TDF interaction to decrease levels of ATV (use ATV/r) ■ Potential for nephrotoxicity

■ TABLE 4-4: Advantages and Disadvantages of Antiretroviral Agents and Combinations *(Continued)*

Agents	Advantages	Disadvantages
2 NRTIs (as component of HAART regimen)		
ABC/3TC or ABC/FTC	■ No food effect ■ Once daily regimen ■ Low pill burden (l/d) ■ Well tolerated ■ Avoids TAMs ■ Avoids thymidine analogues ■ Coformulated (ABC/3TC) ■ Low potential for mitochondrial toxicity	■ ABC hypersensitivity reaction ■ Risk of ddI cross-resistance (L74V) or TDF and ddI cross-resistance (K65R)
ddI/3TC or ddI/FTC	■ Once daily regimen ■ Avoid TAMs	■ Minimal data ■ ddI toxicity: Pancreatitis, neuropathy, GI intolerance, mitochondrial toxicity ■ Food effect (ddI) ■ Risk of K65R with ABC and TDF cross-resistance
d4T/3TC or d4T/FTC	■ Good short-term tolerability ■ No food effect ■ M184V (3TC) slows d4T resistance	■ d4T toxicity: Neuropathy, lipoatrophy, hyperlipemia, ascending paralysis (rare), lactic acidosis ■ TAMs and cross-resistance with prolonged failure ■ Requires bid dosing
ddI/d4T (not recommended)	■ Extensive prior experience ■ Low pill burden	■ Contraindicated in pregnancy ■ ddI/d4T toxicity: Lactic acidosis, peripheral neuropathy, pancreatitis, lipoatrophy, and hyperlipidemia ■ Food effect (ddI) ■ May increase risk of TAMs and multi-nucleoside resistance mutations ■ Requires bid dosing
TDF/ddI (not recommended)	■ Once daily regimen	■ High rates of viral failure with 3rd NRTI or with NNRTI ■ Reduced CD4 response without dose adjustment ■ Drug interaction requiring reduced dose of ddI ■ Possible increased risk of pancreatitis and lactic acidosis

*All PIs except ATV are associated with class adverse reactions (hyperlipidemia, insulin resistance, fat redistribution).

All PIs preserve the NNRTI option.

All PIs, except nelfinavir, are boosted to give better pharmacokinetics.

■ TABLE 4-5: **Once-Daily Drugs and Pill Burden**

Once-daily antiretrovirals			
Class	**Agent**	**Class**	**Agent**
NRTI	ddI 400mg ABC 600 mg TDF 300 mg 3TC 300 mg FTC 200 mg	NNRTI	EFV 600 mg
		PI	ATV 400 mg ATV/r 300/100 mg FPV/r 1400/200 mg LPV/r 800/200 mg* SQV/r 2000/100 mg†

*LPV/r qd is not FDA -approved for salvage

†SQV/r is not FDA-approved for qd dosing.

PILL BURDEN (number of pills required each day)
D4T, 3TC and NVP (Triomune) – 2
EFV/3TC/ABC* – 2
NVP + (TDF/FTC or 3TC/ABC)* – 3
ATV/r + (TDF/FTC or 3TC/ABC)* – 3
LPV/r + (TDF/FTC or 3TC/ABC)* – 5
FPV/r + (TDF/FTC or 3TC/ABC)* – 5
SQV/r + (TDF/FTC or 3TC/ABC)* – 7

*For combinations using AZT/3TC, add 1 pill to number shown above

Factors That Influence Probability of Prolonged Viral Suppression

REGIMEN POTENCY: A review of the literature and conference presentations of clinical trials of treatment-naïve patients from 1994 through July 2006 covered 53 trials and 14,264 participants. Results showed the percentage of patients who achieved a VL <50 c/mL at 48 weeks increased with time: before 1998, 41%; 1999-2000, 50%; 2001-2, 56%; and 2003-4, 64%. The results (by drug class) are summarized in Table 4-6 (*AIDS* 2006;20:251).

■ TABLE 4-6: **Potency of Antiviral Classes in Achieving an HIV Viral Load <50 c/mL at 48 Weeks (*AIDS* 2006;20:251)**

Class	VL <50	CD4 Increase
NNRTI	64%*	+173
PI/r	64%*	+200*
3 NRTIs	54%	+161
PI (unboosted)	43%	+179

*Significantly better ($P<0.05$)

■ TABLE 4-7: **96-Week Results for EFV + 2 NRTIs vs. LPV/r + 2 NRTIs (XVI Int AIDS conference, Toronto, Aug. 2006; Abstr. THLB 0204)**

	EFV n = 250	LPV/r n = 250
VL <50 c/mL	89%*	77%
CD4 count (median)	+240	+285*
Grade 3-4 toxicity	18%	19%
Resistance (failures)		
NNRTI mutations	48%	4%*
Major PI mutations	0	0

ADHERENCE: The report most often quoted is by Paterson et al (*Ann Intern Med* 2000;133:21) from a trial with NFV-based HAART. This study showed consumption of >95% of prescribed doses was required to achieve an 80% probability of VL <400 c/mL at 24 weeks; with 90-95% adherence the probability of VL <400 c/mL dropped to 50%. Multiple studies have confirmed the importance of adherence (*AIDS* 2001;15:2109; *Clin Infect Dis* 2001;33:386; *Clin Infect Dis* 2002;34:115; *AIDS* 2004;35:S35). However, more recent work has shown that adherence requirements vary depending on the regimen, so the oft-quoted "95% rule" applies to unboosted PI-based HAART, but not to NNRTI- or boosted PI-based HAART (*AIDS* 2006;20:223; *Clin Infect Dis* 2006;43:939). The difference is based on potency and pharmacokinetics. For example, the half-life of NFV is 5-6 hours; for EFV it is 36-100 hours. Thus, in a prospective study of unboosted PI regimens vs. EFV-based HAART showed that suppressing VL to <400 c/mL required 95%-100% adherence with PI-based HAART but only 54%-100% adherence with EFV-based HAART (*Clin Infect Dis* 2006;43:939).

- **Adherence and resistance:** Poor adherence predicts virologic failure but not necessarily resistance.
- **Guidance for improved adherence:**
  1. Common strategies and observations
     - Establish patient readiness before initiating treatment.
     - Use a standardized approach to assess adherence.
     - Use the entire health care team to reinforce adherence messages
     - Health care professionals are poor predictors of who will adhere.
     - Patients will usually over-report their adherence.
     - Adherence may decrease with time, becoming significantly worse at 6-12 mos than it is initially (*Topics HIV Med* 2003;11:185).
     - Patients need to understand that the regimen most likely to succeed is the first one, although "rescue" regimens are becoming more effective.

- Address obvious issues of convenience: pill burden, frequency of daily administrations, food or fasting requirements, tolerance, pill size.

The most important and prevalent factors that have been reported to negatively affect adherence in sub-Saharan Africa are cost, not disclosing HIV status to a loved one or fear of being stigmatized, alcohol abuse, and difficulty in following complex drug regimens. Studies report that the majority of patients receiving ART have disclosed their HIV status to family or friends and that those who have not appear to do worse with therapy. Such patients are likely to have frequent treatment interruptions due to the fact that tablets must be hidden and therefore not taken in the presence of others. Encouraging voluntary HIV status disclosure in a community with access to ART may result in improved uptake of voluntary counseling and testing, help decrease the stigma, and improve adherence. *(JAMA 2006; 296(6))*

PRIOR EXPOSURE TO ANTIRETROVIRAL AGENTS: Multiple studies demonstrate an inverse correlation between response and the extent of prior antiretroviral therapy as determined by number of agents, number of classes, and duration of treatment. This applies especially to patients who initiated therapy prior to the HAART era (1996-7). In the Swiss Cohort study for example, the probability of achieving a viral load <500 c/mL with HAART therapy was 91% in treatment-naïve patients compared with 75% in treatment-experienced patients (*Lancet* 1999;353:863). Among patients who achieved undetectable viral loads, the probability of maintaining a viral load <500 c/mL at 2 years was 80% for treatment-naïve patients compared with 62% for treatment-experienced patients. The conclusion of many authorities is that the initial regimen is the most important regimen because it is associated with the greatest probability of achieving prolonged viral suppression (*J Acquir Immune Defic Syndr* 2000;24:115). Nevertheless, the substantial influx of new drugs since 2003 has changed this. The standard goal of treatment for most patients is VL <50 c/mL, even with multiple regimens and 3-class resistance.

VIRAL LOAD NADIR: Multiple studies demonstrate that the viral load nadir predicts the durability of response (*AIDS* 2002;16:1521; *JAMA* 1998;279:930; *Lancet* 2001;358:1760; *J Acquir Immune Defic Syndr* 2002;30:167; *AIDS* 1998;12:F9). An analysis of 22 cohorts with 9323 patients started on an initial HAART regimen, the most important predictor of mortality or development of an AIDS-defining event was the VL and CD4 count 6 months after starting (*Lancet* 2003;362:22).

RAPIDITY OF VIRAL LOAD RESPONSE: The trajectory of the viral load response predicts the nadir plasma HIV RNA level and consequently the durability of HIV response. One large review showed the median time to a VL <50 c/mL in treatment-naïve patients was 13.5 weeks (*Int*

*Significantly better in the comparison of EFV vs LPV/r ($P<0.05$)

J Sex Transm Dis AIDS 2006;17:522). To achieve an optimal and durable virologic response, treatment-naïve patients treated with HAART should respond as follows:

- Decrease 0.7-1.0 $\log_{10}$ c/mL at 1 week (*Lancet* 2001;358:1760; *J Acquir Immune Defic Syndr* 2002;30:167)
- Decrease 1.5-2.0 $\log_{10}$ c/mL to <5,000 c/mL at 4 weeks (*AIDS* 1999;13:1873; *J Acquir Immune Defic Syndr* 2000;25:36). One review of 656 treatment-naïve patients given HAART showed a VL reduction to <1000 c/mL by week 4 predicted with an 82%-95% probability of VL <50 c/mL at week 24 (*J Acquir Immune Defic Syndr* 2004;37:1155).
- Decrease to <500 c/mL at 8 to 16 weeks and <50 c/mL at 16 to 24 weeks (*Ann Intern Med* 2001;135:954; *J Acquir Immune Defic Syndr* 2000;24:433)

Failure to achieve these goals suggests lack of antiretroviral potency, non-adherence, resistance or inadequate drug levels due to drug interactions, poor absorption, etc.

When to Modify Therapy

DEFINING TREATMENT FAILURE

- **Virologic failure:** The goal of therapy is a sustained VL level <50 c/mL, according to 2006 guidelines of IAS-USA (*JAMA* 2006;296:827), the 2006 U.S. DHHS (http://AIDSinfo.nih.gov) and the British HIV Association (http://www.bhiva.org/guidelines/2006/hiv/hivfs06.html).
  - *Blips:* Blips are defined as a transient VL >50 c/mL preceded and followed by measurements <50 c/mL without a change in treatment. One study that measured VL every 2-3 days for 3-4 mos found that blips were common (9/10 patients), low-level (median of 79 c/mL), transient (isolated events), unrelated to clinical events (illness, vaccination, etc.), inconsistent (noted in only one of duplicate samples), and appeared to represent a statistical variation around the mean HIV level below 50 c/mL (*JAMA* 2005;293:817). Levels >200 c/mL or sustained VL >50 c/mL usually indicate virologic failure.
  - *Frequency of virologic failure:* In an analysis of 12 reports with 1,197 patients in the U.S., 62% failed to achieve the goal of VL <50 c/mL by 24 wks (*Clin Infect Dis* 2004;38:614). A review of 14,264 treatment-naïve patients in clinical trials between 1994 and 2004 found that 45% failed to achieve a VL <50 c/mL at 48 weeks, but this improved to 36% in 2003-04 (*AIDS* 2006;20:2051).
  - *Rationale for the 50 c/mL threshold:* Sequence analysis of HIV clones from patients with sustained VL <50 c/mL show no sequence evolution with emergence of resistance mutations (*JAMA* 2005;293:817; *J Infect Dis* 2004;189:1444; *J Infect Dis*

2004;189:1452). A similar analysis in patients with persistent low-level viremia (50-400 c/mL) showed acquisition of resistance mutations in 9/21 patients at a median follow-up of 11 mos (*Clin Infect Dis* 2004;39:1030). These observations suggest that a VL <50 c/mL indicates an absence of viral replication; virus present below that cutoff appears to reflect release from the latent CD4 cell pool. However, VL consistently >50 c/mL indicates viral replication and sequence evolution with resistance mutations.

- **Immunologic failure:** This is arbitrarily defined as failure of the CD4 count to increase 25-50/mm^3 in the first year of HAART (DHHS, http://AIDSinfo.nih.gov, Oct. 10, 2006). The CD4 response correlates with viral suppression; the increase has a biphasic pattern, increasing by 50-120 cells/mm^3 during the first 3 months, thereafter increasing by 2-7 cells/mm^3/month (*J Infect Dis* 2006;94:29; *JAMA* 2002;288:222; *J Infect Dis* 2002;185:471; *JAMA* 2004;292:1911). As expected, the response correlates with the duration of HIV suppression. Using virologic failure as the reference, a review of 596 patients followed for a median of 2.5 yrs showed annual increase of 5.2 cells/mm^3/yr for each 10% cumulative time spent with viral suppression to <400/mm^3 (*J Infect Dis* 2004;190:1860). Despite the seemingly logical association supported by these studies, a more recent study indicates that HIV viral load accounts for only 5% of the CD4 cell decline (*JAMA* 2006;296:1498). The other factors are not known.

  Although this correlation is consistent in population-based studies, individual variation is great and discordant changes in both directions are relatively common (*J Infect Dis* 2001;183:1328; *Clin Infect Dis* 2002;35:1005). One study indicated that CD4 and CD8 cell activation at baseline correlated negatively with CD4 response (*J Infect Dis* 2006;194:29). The problem is that there are no strategies with established merit to deal with the discordance, e.g., the patient with viral suppression and a blunted CD4 response. Many patients appear to have a ceiling in the CD4 response of about 200-300/mm^3. This implies that CD4 rebound may be limited to 300-400/mm^3 when treatment is initiated at levels <200/mm^3 (Keruly J, 13th CROI, Denver, 2006, Abstr. 529).

- **Clinical failure:** This is defined as the occurrence or re-occurrence of an AIDS-defining opportunistic complication after 3 mos of HAART. Immune reconstitution syndrome does not qualify as a clinical failure and should be excluded.

- **Monitoring for adverse drug reactions (Table 4-8):**

■ TABLE 4-8: **Monitoring for Adverse Drug Reactions (ADRs) (*Clin Infect Dis* 2006;43:645)**

Adverse Reactions		
Toxicity and risks	**Routine tests**	**Comment**
Peripheral neuropathy : D4T, ddI and very occasionally 3TC	None.	Ascending sensory neuropathy, glove and stocking but usually involves feet, painful.
Lactic acidosis; d4T AZT, ddI	None	■ Serum lactate only with symptoms and with high risk groups receiving NRTIs: pregnancy, history of lactic acidosis.
Hyperlipidemia (*Clin Infect Dis* 2002;34:838); d4T, PIs (except ATV), EFV >NVP	Fasting total, LDL, HDL cholesterol and triglycerides at baseline, then at 3-6 months, then at least annually (fasting preferred, but non-fasting can be useful)	■ Treat according to Framingham risks and National Cholesterol Education Program (NCEP) guidelines ■ Associated with PIs, especially RTV (dose dependent). Also associated with d4T among NRTIs and EFV among NNRTIs. ■ Consider switch to non-PI-based regimen or ATV.
Insulin Resistance: Most PIs (except ATV) ATV/r – slight	FBS at baseline + every 3 to 6 months (IAS-USA) or at 1-3 mo, then q 3-4 mo (DHHS)	■ Associated with most PIs (not ATV). ■ Treat hyperglycemia, preferably with insulin sensitizing agents, or switch to non-PI-containing or ATV-containing regimen.
Fat accumulation and lipoatrophy d4T, AZT (lipoatrophy), PIs (possible fat accumulation)	No screening test Lipoatrophy: exam and self report Fat accumulation exam and self report; waist-hip ratio	■ Cosmetic issue; patient perception is usually most important. ■ Best monitoring: Waist-hip ratio. ■ No established treatment, but drug switches (PI- to non-PI-based regimens for fat accumulation, d4T or AZT to TDF or ABC switches for lipoatrophy) may be helpful.
Hepatitis NVP (hepatic necrosis), EFV, NVP, all PIs (transaminitis) d4T, AZT, ddI (steatosis)	■ Regular monitoring of ALT/AST q 3-4 mo (all PI and NNRTI regimens) ■ NVP and TPV: Monitor more closely for hepatotoxicity (see comments)	■ NVP: DHHS and FDA recommendations: ALT/AST at baseline, 2, 4, 8, 12, 16 wks, then q 3 mo. ■ TPV/r monitoring in patients at risk for hepatitis.

■ **VL response:** The standard goal is viral suppression with the specific targets to decrease VL ≥1 $\log_{10}$ c/mL (90%) within 1-4 weeks and viral load <50 c/mL by 24 weeks. Studies show that <5% of all AIDS-defining complications occur in patients with a viral load of <5,000 c/mL, suggesting that thresholds that define virologic failure and clinical failure may be different (*AIDS* 1999;13:1035; *AIDS* 1999;13:341; *J Acquir Immune Defic Syndr* 2001;27:44; *J Acquir*

Immune Defic Syndr 2002;30:154). However, long-term studies show that virologic failure will eventually lead to clinical and immunologic failure (*J Infect Dis* 2004;190:280), and studies of HIV show no sequence evolution with new resistance mutations over a 1-yr period when the VL is maintained at <50 c/mL (*J Infect Dis* 2004;189:1444; *J Infect Dis* 2004;189:1452).

- **CD4 Response:** (See Immunologic failure)

CAUSE OF VIROLOGIC FAILURE: Inadequate virologic response is ascribed to (1) resistance or (2) failure of the drugs to reach the virus (inadequate adherence, altered metabolism, drug interaction).

GUIDELINES FOR CHANGING THERAPY

TABLE 4-8a: WHO Recommendations for Treatment Failure (WHO Guidelines 2006)

- **Definition of clinical failure:** New or recurrent stage IV condition. Exceptions are lymph node or pleural TB, candida esophagitis, and recurrent bacterial pneumonia; must rule out IRIS.
- **Definition of CD4 cell count failure:** Fall to baseline level; 50% fall from treatment peak; or levels persistently <100/mm^3
- **Definition of virologic failure:** VL >10,000 c/mL, because this level is associated with clinical progression and rapid CD4 decline. (There is concern that this high level of viremia, if sustained and used as a threshold to change therapy, may promote resistance.)
- **Criteria to change therapy**

  Clinical disease progression: Events occurring >6 months after starting ARV because events in the first 6 months often represent IRIS. New or recurrent events in the first 6 months meriting change in AIDS-defining conditions (WHO clinical stage IV) and Consider changing therapy for these WHO clinical stage III conditions: weight loss >10%, unexplained diarrhea or fever >1 month, OHL, severe bacterial infection or bedridden >50% of days in past month.

TABLE 4-8b: CD4 and Viral Load Criteria

	WHO staging (see footnote Table 4-10a)			
Criteria	**1**	**2**	**3**	**4**
CD4 (see criteria above)	No change CD4 – 3 mo	No change CD4 – 3 mo	Consider change	Change
CD4 (above) + VL >10,000 after 6 mo	Consider change	Consider change	Change	Change

■ TABLE 4-9: **Recommended Initial and Second-line Regimens (WHO, 2006)**

Initial regimen	Second line
(NVP or EFV) + one of the 3 nucleoside pairs listed below	PI/r including LPV/r*, ATV/r, FPV/r, IDV/r, SQV/r (NFV* can be considered but is less potent)
(AZT or d4T) + 3TC†	ddI/ABC or TDF/ABC or TDF/3TC (±AZT)‡
TDF + 3TC†	ddI/ABC or ddI/3TC (±AZT)‡
ABC + 3TC†	ddI/3TC (±AZT)‡ or TDF/3TC (±AZT)‡
(AZT or d4T) + 3TC† + (TDF or ABC)	EFV + ddI

* NFV and meltrex formulation of LPV/r do not require refrigeration.

† 3TC and FTC are considered interchangeable.

‡ Consider continuing 3TC to reduce viral fitness, provide residual antiviral activity and preserve the M184V mutation to increase sensitivity of AZT or TDF. AZT may delay K65R mutation.

GUIDELINES FOR CHANGING ANTIRETROVIRAL REGIMEN

■ **Assessing failure:**

- □ *Adherence:* Address issues of access, depression, tolerability, convenience (food effect, pill burden, multiple dosing regimens), substance abuse, patient comprehension, dementia
- □ *Convenience*

  Once-daily regimen (see Table 4-5)

  Low pill burden: coformulation of EFV/TDF/FTC (*Atripla*) permits a single pill once a day with a potent regimen. NVP, ATV, LPV/r, FPV-based HAART can be given with a daily burden of 2-5 pills.

  Food effect: see below
- □ *Tolerability*

  GI intolerance is most common. Treatment may be symptomatic with anti-emetic, antidiarrheal agent, or fiber supplement; administration with food often improves tolerability, but this is not possible with ddI or unboosted IDV.
- □ *Pharmacokinetic issues*

  Food effect: fasting requirements – ddI, unboosted IDV, and possibly EFV (first 2-3 wks); Food requirement – ATV, TPV/r, NFV, and SQV.

- *Drug interactions* – Avoid TDF or EFV with unboosted ATV, d4T/AZT, TDF/ddI (unless ddI is dose reduced).
- *Resistance:* resistance testing may require expertise for reliable interpretation. These tests are most accurate for evaluating resistance to drug classes being taken at the time the test is performed or within 4 wks of the test. Transmitted mutations persist longer than acquired mutations; the duration of persistence depends somewhat on the effect of the mutation on replication capacity. For example, mutations at codon 215 on the RT gene persist, whereas the M184V mutation quickly reverts to wild-type. Genotype resistance assays do not reliably detect minority species (<20%) and consequently are more useful in determining which agents are unlikely to be effective than to determine which drugs are likely to be effective. To assess minority strains, consider prior resistance test results and treatment history, including duration of therapy in presence of virologic failure and agent-specific genetic barriers to resistance (high barrier with most boosted PIs and thymidine analogs; low barrier with 3TC, FTC, and NNRTIs).

  The sensitivity of resistance testing after ART is discontinued depends on the time off treatment and the drug evaluated (*Antimicrob Agents Chemother* 2004;48:644). Wild-type virus may re-emerge as early as 4 weeks after discontinuation, so 4 weeks is the anticipated minimal duration of resistance test validity. Nevertheless, some mutations such as K103N may persist 9 to 12 months or longer (*J Clin Lab Anal* 2002;16:76), possibly because this mutation does not alter replication capacity (*J Med Virol* 2003;69:1). The M184V mutation more strongly influences replication capacity (*AAC* 2003;47:3377) and usually cannot be detected 5-20 wks after discontinuation (*AAC* 2002;46:2255; *Antimicrob Agents Chemother* 2004;48:644).

- **Guidance for changes based on intolerance**
  - Changes due to side effects or toxicity can be made with single agent substitution, provided the patient has an appropriate virologic response to the original regimen.
  - Changes for class adverse reactions (see pp. 102-115)

STRATEGIES FOR VIROLOGIC FAILURE

In general, the probability of success with a second regimen is nearly as great as with the first, but with subsequent regimens it has traditionally been increasingly difficult to achieve viral suppression. Recent drug development may be changing this: in recent salvage trials, a substantial proportion of patients achieved full virologic suppression despite extensive drug resistance.

- **First regimen failure:** In most cases the usual regimen change after virologic failure to the initial regimen is to switch from an NNRTI-based to a PI-based HAART regimen or from a PI-based regimen to either another PI- or an NNRTI-based regimen. In each instance the second regimen should include ≥2 nucleosides, and all components are selected on the basis of resistance tests performed on treatment or within 4 weeks of changing or stopping treatment (DHHS Guidelines, Oct. 10, 2006; IAS-USA 2006 Guidelines; *JAMA* 2006;296:827).

- **3TC and FTC resistance:** With virologic failure, the first RT resistance mutation to appear with most regimens containing 3TC of FTC is often 184V. This results in high-level resistance to 3TC and FTC, residual antiviral activity, and resultant increase in activity of AZT, d4T, and TDF. For this reason it is common practice to continue 3TC or FTC despite resistance, but in such cases these drugs should not be counted as active components of an antiviral regimen.

- **Virologic failure without resistance mutations:** If the test was performed on therapy, the usual cause is failure of the drug to reach the target, usually due to inadequate adherence but sometimes due to drug interactions, noncompliance with food requirements, etc. This is most common with boosted-PI-based HAART.

- **Limited prior exposure with VL 1000 c/mL:** Consider intensified or new regimen. With intensification, virologic goals should be reached within 2 to 3 weeks (*Antimicrob Agents Chemother* 2002;46:3907). When VL >1000 c/mL, drug selection should be based on resistance test results.

- **Limited prior exposure with resistance to one drug:** Consider single drug substitution based on resistance test results.

- **PI-based regimen with virologic failure**
  - Patients failing boosted PI-based regimens frequently have **no resistance mutations**, in which case the cause of failure is usually non-adherence. Options are 1) continue the regimen after encouraging adherence and repeat the VL test after 2-4 wks, 2) use alternative PIs, 3) change to NNRTI-based HAART (but only if no NRTI or NNRTI resistance is suspected), or 4) intensify the NRTI backbone or change NRTIs based on genotypic resistance tests.
  - With PI resistance mutations, the options are dictated largely by **resistance test results**, combined with any available historic data on drug exposures and prior resistance tests. Options are:
    1. NNRTI-based HAART, though this can be risky in patients with possible sNNRTI resistance.

2. Double-boosted PI, such as LPV/r/SQV or LPV/r/ATV, for which pharmacokinetic data indicate effective plasma levels of both PIs (*AIDS* 2004;18:503). There are very limited clinical data to support the utility of dual-boosted-PI therapy.
3. Combinations of a PI and NNRTI, especially in patients with few or no NRTI options and no prior exposure to NNRTIs. It is emphasized that EFV and NVP reduce exposure to all PIs studied except NFV. The best-studied combinations are LPV/r 533/133 mg (gel capsule formulation) + EFV in standard doses (*Antimicrob Agents Chemother* 2003;47:350; *Antiviral Ther* 2002;17:165) and IDV/r/EFV in standard doses (*N Engl J Med* 1999;341:1865). This combination (without NRTIs) performed well in ACTG 5142 with 83% showing a VL <50 c/mL at 96 weeks. Currently, the strongest case for using this regimen is in the somewhat unusual circumstance of EFV + LPV susceptibility with contraindication of NRTIs due to toxicity or resistance. In patients with some PI resistance, it may be necessary to use a higher dose of LPV/r (3 tabs [600/150 mg] bid) when it is combined with EFV, but this regimen has not been studied.
4. The favored PIs for salvage have been DRV/r, LPV/r, ATV/r. LPV/r and ATV/r appear comparable in patients who have failed one prior PI-based regimen (*Clin Infect Dis* 2004;38:1599). DRV/r was introduced in 2006 and appears to have an important role for patients who have failed PI-based HAART. Both RESIST (TPV/r) and POWER (DRV/r) were studies in patients with 3-class resistance, virologic failure, and nearly identical study entry criteria. Results with DRV/r showed 46% achieved a VL <50 c/mL compared to 23% of TPV/r patients (Hill AM, 46th ICAAC, San Francisco 2006, Abstr. H1386). Both RESIST and POWER results were significantly better in patients who also received enfuvirtide. In the POWER studies, virologic suppression to <50 c/mL was achieved at very similar rates regardless of which PI regimen had been used previously: 44% after failing TPV/r, 40% after failing LPV/r, and 42% after failing FPV/r (LeFebvre E, 46th ICAAC, San Francisco 2006, Abstr. H1387).
5. A number of investigational drugs are improving the response to salvage therapy in patients with PI resistance, including MK-0518, etravirine, and maraviroc (see discussion of Rescue Therapy below).

- **NNRTI-based regimen with failure:** Resistance to EFV or NVP usually results in cross-resistance to all currently available members of the class; resistance is high-level, meaning it cannot be overcome with pharmacologic modification or within-class switches. Most importantly, there is no apparent benefit to maintaining resistant strains with respect to either reducing replication capacity or

providing partial virologic suppression (*J Med Virol* 2003;69:1; *J Infect Dis* 2005;192:1537). Furthermore, continuation of NNRTIs in a failing regimen leads to accumulation of additional resistance mutations that may lead to cross-resistance to second-generation NNRTIs currently in development, including etravirine (TMC 125), which shows activity inversely correlated with the number of NNRTI resistance mutations.

- **NRTI resistance with virologic failure:** The dual-NRTI component of HAART is standard and is usually superior to nucleoside-sparing combinations of PIs and NNRTIs tested to date (*N Engl J Med* 1999;341:1865; *N Engl J Med* 2003;349:2293). A possible exception is EFV/LPV/r, which was comparable to EFV or LPV/r combined with 2 NRTIs as summarized above from ACTG 5142 (Riddler SA, XVI Int AIDS Conference, Toronto, Aug. 2006, Abstr. JHLB-0204). In general, 3TC or FTC are included in most regimens even with the 184V mutation due to good tolerability, documented antiviral effect attributed to reduction in replication capacity and/or partial antiviral effect, and increased activity of AZT, TDF, and d4T (*J Infect Dis* 2005;192:1537; *AIDS* 2006;20:795; *Antimicrob Agents Chemother* 2003;47:3478). The optimal nucleoside backbone is selected by resistance tests and avoidance of incompatible combinations (e.g., AZT/d4T, ddI/d4T, ddI/TDF).

- **Rescue therapy: treatment following three class failures:** The definition of "rescue" has changed during the HAART era. This discussion applies to patients with virologic failure and exposure to all three classes of antiretrovirals. This is the group showing the most impressive recent progress in new drug development with the introduction of new antiretrovirals, such as ENF (T20), DRV, and TPV, which show efficacy against resistant strains. It is also the source of substantial new drug development including etravirine (ETV), an NNRTI active against strains resistant to EFV and NVP, and three new classes: CCR5 attachment inhibitors (maraviroc and vicriviroc), integrase inhibitors (e.g., MK-0518 and GS-9137), maturation inhibitors (*Bevirimat*), and TNX-355, an anti-CD4 monoclonal antibody. All these drugs are now available with expanded access, or are expected to be available in 2008 or sooner. They offer great promise to patients whose substantial resistance to other drugs has limited their treatment options among agents now on the market.

  Summary of recommendations for 3-class resistance:

  1. The regimen should include ≥2 active drugs.
  2. 3TC or FTC is usually continued, despite resistance.
  3. NNRTIs should be stopped once resistance is observed.
  4. Make optimal use of newer agents (DRV/r), by using them in combination with at least one other active drug.

5. Seek access when appropriate to experimental drugs through clinical trials or expanded access programs.
6. If the 2-active-drug option is not available, the goal of treatment is to (a) reduce VL as much as possible, (b) maintain CD4 count, (c) reduce drug toxicity, and (d) limit use of drugs likely to lead to resistance mutations that may limit future treatment options. Note that in salvage studies (POWER, TORO, RESIST), control groups had a viral failure rate of 85-90%, but mean CD4 count went up with the optimal background regimen.

The urgency of these decisions is usually driven by the risk of progression, which is largely reflected by a low baseline CD4 count.

Mega-HAART, recycling, and treatment interruption, all historic tactics for salvage, are antiquated and generally should not be used.

- ***Criteria for success:*** In some patients the standard goal of viral suppression to <50 c/mL is simply unrealistic. The goal of therapy in these cases may be redirected to maintaining or increasing the CD4 count and preventing opportunistic infections. Studies indicate that HIV viral loads <10,000 c/mL are usually associated with stable or increasing CD4 count in patients on HAART (*AIDS* 1999;13:1035).
- ***Discontinuation of HAART due to virologic failure:*** This is usually not recommended because prior reports showed that discontinuation resulted in a median increase in VL of 0.8-1.0 $\log_{10}$ c/mL and a decrease in CD4 of 85-100/mm^3 within 3 months (*N Engl J Med* 2003;349:837; *J Infect Dis* 2000;181:946). Nevertheless, the decision to continue a failing regimen must be considered carefully, because agents continued may allow further accumulation of resistance mutations, with loss of future treatment options (*J Infect Dis* 2003;188:1001). Considerations must include current options, future drugs and disease stage. Aggressive treatment becomes critical with a CD4 count of <50/mm^3 and far less compelling with a CD4 count of >200/mm^3. Patients with virologic failure and triple class resistance have been studied with selective continuation of antiretrovirals to determine the components responsible for residual effect. This work shows that NRTIs, especially 3TC (and presumably FTC) are responsible for sustained antiviral activity despite 184V mutations, presumably due to reduced fitness (*J Infect Dis* 2005;192:1537). Thus, one theoretically attractive option is to continue 3TC monotherapy or as *Trizivir* to provide some antiviral activity without the risk of accumulating resistance mutations.

TREATMENT INTERRUPTION STRATEGIES

- **Virologic failure:** The proposed strategy is to suspend antiretroviral therapy in patients with virologic failure and multiple resistance mutations to allow replacement by drug-susceptible wild-type HIV when antiviral pressure is eliminated. The largest controlled trial was CPCRA 064, in which 270 patients with VL >5000 c/mL and three-class exposure with resistance were randomized to treatment interruption (TI) for 16 wks vs continued HAART (*N Engl J Med* 2003;349:837). The TI group had a significant decrease in CD4 count (mean decrease 85/mm^3 at 4 mos) and a significant increase in AIDS-defining events (17 vs. 5). Similarly poor results were reported in a study from Spain (*Clin Infect Dis* 2004;39:569).

- **Intermittent treatment interruption (ITI):** The rationale for ITI is to reduce drug cost, toxicity and inconvenience while maintaining viral suppression. Two small NIH studies used ITI with EFV or IDV-based HAART given every other week after achieving good viral suppression with standard therapy (*Proc Natl Acad Sci* 2001;98:15161; *J Infect Dis* 2004;189:174). Results at 48 wks showed persistent viral suppression with no resistance. However, other ITI trials have been far less successful. The STACCATO trial attempted the alternate-weeks strategy (also called WOWO for "week-on, week-off") with various regimens; the rate of virologic failure was 53% in the experimental treatment group compared to 5% in controls given continuous HAART (*Lancet* 2006;368:459). This study also showed a high rate of new resistance mutations in the WOWO group (*Clin Infect Dis* 2005;40:728). A more recent variation of 8 weeks on, 8 weeks off was used in the DART study, which was stopped early due to an excessive number of HIV-related complications in the ITI group (XVI Int AIDS Conference, Toronto, Aug. 2006, Abstr. THLB-0207). Another ITI study is called FOTO, "five [days] on, two off." With its long half-life, the NNRTI presumably maintains its antiviral activity over the weekend. The initial experience with 20 participants in the FOTO trial has shown continued viral suppression in 19/20 taking NNRTI-based HAART at 1 year (IAS Conf., Rio de Janeiro 2005, Abstr. WePe 12.4.C10). This strategy should be reserved for patients in clinical trials until more experience is achieved.

- **CD4-guided treatment interruption:** The rationale is that antiretroviral therapy is not recommended with a CD4 count >350/mm^3, but many patients have immune reconstitution to much higher levels, suggesting it may be safe to suspend therapy when there is a good response. Many small and retrospective studies were generally supportive, but the most definitive study was the SMART study, the largest clinical trial ever of HIV infection. The SMART trial

had 5,472 patients with CD4 counts >350/mm^3 and VL <50 c/mL who were randomized to interrupted therapy until the CD4 count was <250/mm^3 or to remain on continuous treatment. The study was stopped early due to significantly more HIV-related events (93 vs. 44), drug-related complications (59 vs. 37), and deaths (47 vs. 29). In the STI group all three differences were statistically significant (El-Sadr W, 13th CROI, Denver 2006, Abstr. 106-LB). Subsequent analysis showed no benefit for any subset of the STI patients (El-Sadr W, 13th CROI, Denver 2006, Abstr. WEAB-204). This strategy is now considered experimental.

MONOTHERAPY: Nearly all studies have shown that durable viral suppression requires at least 2 ARV agents active against the patient's HIV strain, and 3 agents (but not 4) are preferred. The Monark trial (Del Fraissy JF, XVI Int AIDS Conference, Toronto, Aug. 2006, Abstr. THLP-0202) compared LPV/r monotherapy with LPV/r + 2 NRTI therapy in treatment-naïve patients with a baseline VL <100,000 c/mL and CD4 counts >100/mm^3. The 48-week data for 83 monotherapy participants showed a VL <50 c/mL in 71% compared to 75% in the standard combination therapy group. Other short studies of monotherapy with new classes of agents suggest this approach may be effective, but experience is limited. This tactic must be considered experimental until the database is larger and candidate characteristics are better defined.

THERAPEUTIC DRUG MONITORING: TDM is an attractive method for determining appropriate dosing regimens for HIV-infected patients with issues including problematic adherence, potential drug interactions, pregnancy, concentration-dependent toxicities, or altered physiology due to hepatic, renal, or GI complications. (This type of analysis cannot be done with NRTIs because their *in vivo* correlates are with intracellular concentrations.)

- Target trough levels for wild-type virus are taken from DHHS guidelines.
- Limitations of TDM are:
  - lack of prospective studies showing improved outcomes;
  - lack of consistent data indicating clinically significant levels that correlate with therapeutic response or toxicity;
  - general unavailability of reliable laboratory resources to do this work;
  - requirement of fastidious technique for collecting and processing specimens (see www.hivpharmacology.com; free registration required);
  - substantial intrapatient variation.

Clinical trial data show that even with highly qualified labs and careful technique, results vary enormously. In one study with an average of 40

samplings per drug per patient, the coefficient of variation in levels was 44% for PIs and 25% for NNRTIs (*Clin Infect Dis* 2006;42:1189).

BLIPS: A blip is defined as an isolated low-level VL of 50-800 c/mL that is not sustained). Blips were studied in VL assays taken 3x/week for 4 months from 10 patients with sustained viral suppression (*JAMA* 2005;293:817). Blips were noted in 24/714 (3.1%) of specimens. Values between 50 c/mL and 200 c/mL could not be confirmed in duplicate specimens sent to another lab or the normal laboratory variation of the VL assay. Erroneous elevations of VL have also been caused by improper VL specimen processing, as with the use of spun and frozen PPT tubes (*J Clin Virol* 2006;35:420). Nevertheless, blips cannot be completely ignored. First, a blip should be classified as such only when a repeat test shows it is not sustained. Second, some studies show that patients with frequent blips may be less adherent to treatment regimens or at greater risk for virologic failure and resistance (*J Infect Dis* 2005;51:195).

STOPPING NNRTI-BASED HAART: There are many reasons to discontinue HAART, including severe drug toxicity, intercurrent severe illness or major procedure, CD4-guided interruption (described above), lack of drug supply or discontinuation when ART is given only to prevent perinatal transmission. The standard recommendation is to stop all drugs together, but there is concern about the long half-life and low genetic barrier to resistance of EFV and NVP (*Clin Infect Dis* 2006;42:401). Discontinuation of NNRTI-based regimens results in monotherapy, which can lead to NNRTI resistance. The concern is based largely on the experience with single-dose NVP to prevent perinatal transmission, which has resulted in class resistance due to K103N mutations in up to 60-80% of women (*J Infect Dis* 2005;192:24). The issue has not been studied adequately to give precise recommendations, but these are suggested options:

- Discontinue EFV or NVP and continue the NRTIs for 5-7 additional days (IAS-USA guidelines, *JAMA* 2006;296:827); the DHHS guidelines for pregnancy (July 7, 2006) suggest continuing NRTIs for 3-7 days (*J Infect Dis* 2006;193:482).
- Discontinue EFV or NVP and substitute a PI for 1 wk, then stop all drugs together (British HIV Association guidelines, 2005). The Moore Clinic recommendation is to substitute PIs for 3-4 wks due to prolonged and variable half-life of EFV (36-100 h) and NVP (25-30 h).

Antiretroviral Agents

Antiretroviral Agents Approved by the MCC, Medicines Control Council of South-Africa

For a list of all approved ARV agents, including those not easily available in South Africa, refer to page 339.

■ TABLE 4-10: **Antiretroviral Drugs Approved by the FDA and MCC for Treatment of HIV Infection**

APPLICANT	PROPRIETARY NAME	ACTIVE	REGISTRATION DATE
GLAXO SMITHKLINE (PTY) LTD	RETROVIR 100 MG CAPSULES	ZIDOVUDINE	30-May-89
GLAXO SMITHKLINE (PTY) LTD	RETROVIR 250 MG CAPSULES	ZIDOVUDINE	25-Jul-89
INGELHEIM PHARMACEUTICALS (PTY) LTD	VIRAMUNE 200 MG TABLETS	NEVIRAPINE	16-Feb-98
INGELHEIM PHARMACEUTICALS (PTY) LTD	VIRAMUNE 50 MG/5ML SUSPENSION	NEVIRAPINE	14-Dec-99
BRISTOL-MYERS SQUIBB (PTY) LTD	VIDEX BUFFERED in all forms	DIDANOSINE	8-Jul-92
GLAXO SMITHKLINE (PTY) LTD	3TC 300 MG TABLETS	LAMIVUDINE	19-Nov-92
GLAXO SMITHKLINE (PTY) LTD	RETROVIR S 50MG/5ML SOLUTION	ZIDOVUDINE	14-Mar-94
GLAXO SMITHKLINE (PTY) LTD	RETROVIR IV 200MG/20ML	ZIDOVUDINE	19-Aug-95
GLAXO SMITHKLINE (PTY) LTD	3 TC 150MG TABLETS	LAMIVUDINE	13-Jun-96
GLAXO SMITHKLINE (PTY) LTD	3 TC 10MG/ML SOLUTION	LAMIVUDINE	13-Jun-96
ROCHE PRODUCTS (PTY) LTD	INVI-RASE 200MG CAPSULES	SAQUINAVIR	22-Jan-97
MSD (PTY) LTD	CRIXIVAN 200 MG CAPSULES	INDINAVIR	31-Oct-96
MSD (PTY) LTD	CRIXIVAN 400 MG	INDINAVIR	31-Oct-96
ABBOTT LABORATORIES SA (PTY) LTD	NORVIR 100 mg CAPSULES and solution	RITONAVIR	9-Jul-97
BRISTOL-MYERS SQUIBB (PTY) LTD	ZERIT in all forms	STAVUDINE	3-Feb-98
ROCHE PRODUCTS (PTY) LTD	FORTO-VASE 200MG CAPSULES	SAQUINAVIR	18-Jun-99
GLAXO SMITHKLINE (PTY) LTD	COMBIVIR (150MG/300MG)	LAMIVUDINE / ZIDOVUDINE	10-Nov-00

continued on next page

■ TABLE 4-10: **Antiretroviral Drugs Approved by the FDA for Treatment of HIV Infection *Continued***

APPLICANT	PROPRIETARY NAME	ACTIVE	REGISTRATION DATE
ROCHE PRODUCTS (PTY) LTD	VIRA-CEPT 250 mg CAPSULES	NELFINAVIR	8-Oct-99
GLAXO SMITHKLINE (PTY) LTD	RETROVIR/3TC PEP(150MG/300MG	LAMIVUDINE / ZIDOVUDINE	30-Jun-98
MSD (PTY) LTD	STOCRIN 50, 100 and200 CAPSULES	EFAVIRENZ	10-Sep-99
GLAXOSMITHKLINE	PRECLIR 15 MG SOLUTION	AMPRENAVIR	20-Sep-01
GLAXOSMITHKLINE	PRECLIR 15 MG SOLUTION	AMPRENAVIR	20-Sep-01
GLAXO SMITHKLINE (PTY) LTD	ZIAGEN 300MG and solution TABLETS	ABACAVIR	20-Jun-01
ABBOTT LABORATORIES SA (PTY) LTD	NORVIR SEC 100 mg CAPSULES	RITONAVIR	31-Jul-00
ABBOTT LABORATORIES SA (PTY) LTD	KALETRA TABLETS and solution	LOPINAVIR / RITONAVIR	5-Aug-02
GLAXO SMITHKLINE (PTY) LTD	RETROVIR 300 TABLETS	ZIDOVUDINE	13-Mar-03
MSD (PTY) LTD	STOCRIN 600 CAPSULES	EFAVIRENZ	7-May-04
CIPLA LIFE SCIENCES (PTY) LTD	STAVIR-40 CAPSULES	STAVUDINE	25-Jul-03
GLAXO SMITHKLINE (PTY) LTD	TRIZIVAR TABLETS	ABACAVIR/ LAMIVUDINE / ZIDOVUDINE	24-Oct-03
GLAXOSMITHKLINE SA (PTY) LTD	COMBIVIR PEP(150MG/300MG)	LAMIVUDINE / ZIDOVUDINE	7-May-04
BRISTOL-MYERS SQUIBB	REYATAZ	ATAZANVIR	7-Mar
PHARMACARE LIMITED	VIREAD	TENOFOVIR	May 07
PHARMACARE LIMITED	TRUVADA	TENOFOVIR / EMTRICITABINE	May 07

■ TABLE 4-11: **Drugs That Should Not Be Used with PIs or NNRTIs**

Category	Drugs	PIs or NNRTIs contraindicated
Antiarrhythmics	■ Flecainide ■ Propafenone ■ Amiodarone ■ Quinidine	■ LPV/r, all PIs ■ All PIs ■ All PIs ■ All PIs
Lipid-lowering agents	■ Simvastatin* ■ Lovastatin*	■ All PIs and DLV ■ All PIs and DLV
Antimycobacterials	■ Rifampin	■ All PIs and NNRTIs except EFV
Ca^{++} channel blockers	■ Bepridil	■ All PIs
Antihistamines	■ Astemizole† ■ Terfenadine†	■ All PIs, all NNRTIs but NVP ■ All PIs and NNRTIs but NVP
Neuroleptics	■ Pimozide	■ All PIs and DLV
Psychotropics	■ Midazolam‡ ■ Triazolam‡ ■ Alprazolam	■ All PIs, EFV, and DLV ■ All PIs, EFV, and DLV ■ DLV
Ergot alkaloids	■ Ergots	■ All PIs and NNRTIs except NVP
Herbs	■ St. John's wort	■ All PIs and NNRTIs
GI agents	■ Proton pump inhib ■ Cisapride	■ ATV, NFV* ■ All PIs and NNRIs except NVP
Antifungals	■ Voriconazole	■ RTV (including low-dose RTV), EFV, NVP
Nasal steroids	■ Fluticasone	■ All boosted PIs†
Anticonvulsants	■ Phenytoin§ ■ Carbamazepine§ ■ Phenobarbital§	

IMPACT OF HEPATIC FAILURE

- **Impact of hepatic dysfunction on ART dosing** (*J Infect Dis* 2005;40:174)
  - **NRTIs:** Minimal effect because these drugs have limited first-pass metabolism and low protein binding and are eliminated primarily by renal excretion. No dose adjustments with liver disease except ABC; consider 200 mg bid for Child-Pugh Class A; avoid for Class B and C. Limited clinical data.
  - **NNRTIs:** Liver dysfunction has minimal effect on trough levels of EFV and NVP.
  - **PIs:** These are extensively metabolized by CYP enzymes; recommendations are:
    - **NFV:** Standard regimen; use with caution.
    - **IDV:** Recommended dose is 600 mg q 8h; for boosting: IDV/r 200/100 mg bid. Limited clinical data.
    - **SQV/r:** Standard regimen; use with caution.
    - **LPV/r:** No data; use with caution.
    - **ATV:** Child-Pugh B – 300 mg qd; C – avoid; 300-400 mg qd: RTV boosting not recommended. Limited clinical data.
    - **DRV/r:** Use with caution.
- **Child-Pugh Score:** Assign points for clinical observations. Total of 5-6 points = C-P score of A; 7-9 points = B, >9 points = C.

Observation	1 point	2 points	3 points
Encephalopathy*	None	Grade 1-2	Grade 3-4
Ascites	None	Mild	Marked
Albumin (g/l)	>35	2.8 - 35	< 28
Bilirubin (µmol/L)	< 34	40	> 50
Prothrombin time *or* INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

* Encephalopathy grade 1 – confusion, restlessness, tremor;
grade 2 – drowsy, disoriented, asterixis;
grade 3 – somnolent, severe confusion, incontinent;
grade 4 – comatose, flaccid, decerebrate posturing.

■ TABLE 4-12: **Drug Interactions Requiring Dose Modifications or Cautious Use**

Drugs Affected	IDV	SQV	NFV	LPV/r
Antifungals				
Ketoconazole	■ Levels: IDV ↑68% ■ IDV 600 mg tid	■ Levels: SQV ↑3x ■ Dose: Standard	■ No dose adjustment necessary	■ Ketoconazole ↑3x ■ LPV ↑13% ■ Do not exceed 200 mg/d of ketoconazole
Itraconazole	■ No data ■ Do not exceed 200 mg/d	■ No data ■ Monitor levels with >400 mg/d	■ No data	■ Do not exceed 200 mg/d
Antimycobacterials				
Rifampin	■ IDV ↓89% ■ Contra-indicated	■ SQV ↓84% ■ Contra-indicated	■ NFV ↓82% ■ Contra-indicated	■ LPV AUC ↓75% ■ Contraindicated
Rifabutin	■ IDV ↓32% ■ Rifabutin ↑2x ■ ↓ Rifabutin to 150 mg qd or 300 mg 3x/wk IDV 1,000 mg tid ■ IDV/RTV: See RTV	■ SQV ↓40% ■ SQV + RTV: See RTV	■ NFV: No change with 1250 mg bid ■ Rifabutin ↑2x ■ ↓ Rifabutin to 150 mg qd or 300 mg 3x/wk ■ NFV: 1250 mg bid	■ LPV ↓17% ■ Rifabutin: ↑3x, ↓ Rifabutin dose to 150 mg qd or 150 mg 3x/wk ■ LPV/r standard
Clarithromycin	■ Clarithro-mycin ↑53% ■ No dose adjustment	■ Clarithro-mycin ↑45% ■ SQV ↑177% ■ Adjust SQV/r dose for renal insufficiency	■ No data	■ Clarithromycin AUC ↑ 77%, adjust dose with renal failure

ATV	TPV	NVP	EFV	DRV/r
Antifungals				
■ Unboosted – no dose change ■ No dose change ■ Keto dose ≤200 mg/d	■ Ketoconazole levels ↑ ■ Do not exceed 200 mg/d	■ Ketoconazole ↓63% ■ NVP ↑15% to 30% ■ Not recommended	■ No data	■ DVR AUC ↑ ■ Azole ↑3-fold ■ Do not exceed keto 200 mg/d
■ No data	■ No data ■ Do not exceed 200 mg/d	■ No data	■ No data	■ No data ■ Do not exceed 200 mg/d
Antimycobacterials				
■ Contra-indicated	■ Contraindicated	■ NVP ↓20-58% ■ Not recommended due to potential hepatotoxicity; if used – monitor LFTs	■ EFV ↓25% ■ EFV dose 600-800 mg/d	■ Contraindicated
■ Rifabutin ↑2.5x ■ Rifabutin 150 mg qod or 150 mg 3x/wk ■ ATV standard ■ ATV/r: See RTV	■ RBT ↑3x ■ RBT dose 150 mg qod or 3x/wk	■ NVP ↓16% Rifabutin: No change ■ NFV: No dose change ■ Rifabutin: standard dose	■ EFV unchanged ■ Rifabutin ↓35% ■ Dose ↑ Rifabutin to 450 mg/day or 600 mg 3x/wk ■ EFV dose: Standard	■ No data
■ Clarithromycin ↑94%, risk ↑ QTc ■ Clarithromycin ↓ dose 50%; consider azithro.	■ TPV ↑ 66% ■ No dose change except with renal failure: ↓ clari dose 50% for CrCl 30-60 mL/min + 75% of CrCl <30	■ NVP ↑26% ■ Clarithromycin ↓30% ■ Dose: Standard; consider azithro	■ Clarithromycin ↓39% but 14-OH metabolite ↑34% ■ High rate of rash ■ Monitor for efficacy or use azithromycin	■ Clarithromycin ↑57% ■ Reduce clarithro dose by 50% for CrCl 30-60 mL/min and 75% for CrCl <30 mL/min.

continued on next page

■ TABLE 4-12: **Drug Interactions Requiring Dose Modifications or Cautious Use *(Continued)***

Drugs Affected	IDV	SQV	NFV	LPV/r
Oral contraceptives	■ No dose adjustment	■ Use alternative method	■ Use alternative method	■ Use alternative method
Lipids				
Atorvastatin	■ Caution – start 10 mg/d ■ No data	■ SQV/RTV – statin ↑450% ■ Start 10 mg/d	■ Statin ↑74% ■ Start 10 mg dose	■ Statin ↑5.9x ■ Start 10 mg dose
Pravastatin	■ No data	■ SQV/RTV-statin ↓50% ■ Standard dose	■ Pravastatin↓ ■ No data	■ Statin ↑33% ■ Standard dose
Anticonvulsants				
Phenobarbital Phenytoin Carbamazepine	■ Carbamazepine ↓IDV levels substantially ■ Use alternative ART or RTV + IDV or IDV TDM ■ Consider valproic acid or levetiracetam	■ Unknown, but may ↓ SQV levels substantially ■ Monitor anticonvulsant levels ■ Consider valproic acid or levetiracetam	■ Phenytoin AUC ↓ 20-40% ■ May ↓ NFV: Consider NFV TDM ■ Monitor anticonvulsant levels ■ Consider valproic acid or levetiracetam	■ Phenytoin:↓ levels LPV, RTV and ↓ phenytoin – Avoid or LPV TDM ■ Carbamazepine ↑ with RTV ■ Monitor anticonvulsant levels ■ Consider valproic acid, levetiracetam or lamotuigine
Miscellaneous	■ Grapefruit juice ↓DV levels by 26% ■ Sildenafil: Do not exceed 25 mg/48 h ■ Vardenafil: ≤2.5/72 hrs with RTV ■ Tadalafil: ≤10 mg/72 hrs ■ Amlodipine: AUC amlodipine ↑90% with IDV/r; monitor	■ Grapefruit juice ↑SQV levels ■ Dexamethasone ¬SQV levels ■ Sildenafil: Do not exceed 25 mg/48 h ■ Vardenafil: ≤2.5/72 h with RTV ■ Tadalafil: ≤10 mg/72 h	■ Sildenafil: Do not exceed 25 mg/48 h ■ Vardenafil: ≤2.5/72 h with RTV ■ Tadalafil: ≤10 mg/72 hr ■ PPI: Contraindicated	■ Sildenafil: Do not exceed 25 mg/48 h ■ Vardenafil: ≤2.5/72 h ≤ith RTV ■ Tadalafil: ≤10 mg/72 h ■ Digoxin AUC ↑81%*

* Digoxin interaction is likely to apply to all boosted PIs.

ATV	TPV	NVP	EFV	DRV/r
■ Use alternative method	■ Use alternative method	■ Use alternative method	■ Use alternative method	■ OC significantly decreased. Use alternative contraception.
Lipids				
■ No data, anticipate ↑↑ statin AUC ■ Caution – start 10 mg/d	■ Statin ↑9x ■ Start 10 mg/d	■ No data	■ Atorvastatin AUC ↓43% ■ Do not exceed maximum dose	■ Atorvastatin may increase ■ Start with 10 mg/d
■ No data	■ No data	■ No data	■ Pravastatin (10 mg) AUC ↓40%	■ Pravastatin AUC 81%, but up to 5x in some cases; start with lowest dose
Anticonvulsants				
■ May ↓ ATV substantially ■ Monitor anticonvulsant ■ Consider valproic acid, levetiracetam or lamotuigine ■ Consider TDM ATV	■ Decrease TPV levels ■ Effect on anticonvulsants variable – monitor or use valproic acid levetiracetam or lamotuigine	■ Unknown ■ Monitor anticonvulsant level	■ Avoid ■ Use with caution ■ Monitor anticonvulsant levels ■ Carbamazepine ¬27% ■ ↑EFV 36%	■ Significant decrease in DLV AUC; contraindicated
■ H_2 receptor antagonist – ATV/r 2 h before or 1 h after H_2 blocker ■ Antacids give – ATV 2 h before or 1 h after ■ PPIs: Avoid ■ Vardenafil: ≤2.5 mg/d; ≤2.5/72 h with RTV ■ Sildenafil: Do not exceed 2.5 mg in 48 h ■ Tadalafil: Do not exceed 10 mg/72 h ■ Ca^{++} channel blockers: Titrate dose, monitor EKG	■ Sildenafil: Do not exceed 25 mg/48 h ■ Vardenafil: Do not exceed 2.5 mg/72 h ■ Antacids: Separate coadministration by ≥2 h ■ AZT: AUC ¬31-42% dose adjustment, clinical significance unknown ■ ddI: Separate dosing by ≥2 h ■ Disulfuram with metronidazole ■ Paroxetin and sertraline AUC ↓	■ Fluconazole: NVP levels ↑ 100% – possible hepatotoxicity	■ Monitor warfarin when used with EFV	■ Sildenafil: Do not exceed 25 mg/48 h ■ Vardenafil: Do not exceed 2.5 mg/24 h ■ Tadalafil: Do not exceed 10 mg/72 h ■ Paroxetine and sertraline AUC decreased. Titrate to effect. ■ Digoxin AUC may be increased. Monitor levels.

■ TABLE 4-13: Drug Interactions: Effect of PIs and NNRTIs on Drug Levels (AUCs)/Dose*

Drugs Affected	RTV	SQV	NFV	LPV/r	ATV
IDV	■ IDV↑2 to 5x ■ Dose: IDV 800 mg bid + RTV 100 mg bid	■ IDV no effect ■ SQV↑4-7x† ■ Dose: Insufficient data	■ IDV ↑50% NFV ↑80% ■ Dose: Limited data for IDV 1200 mg bid + NFV 1250 mg bid	■ IDV ↑ C_{min} 240% ■ Dose: IDV 600 or 666 mg bid + LPV/r standard	■ Not recommended
RTV	—	■ RTV no effect ■ SQV↑20x*† ■ Dose: 1000/100 mg bid or 2000/100 mg qd	■ RTV no effect ■ NFV ↑1.5x ■ Dose: Inadequate data) ■ ↑ GI toxicity	■ Co-formulated	■ ATV ↑2.4x ■ ATV 300 mg + RTV 100 mg qd
SQV	—	—	■ SQV ↑3-5x ■ NFV ↑20%† ■ Dose: NFV 1250 mg bid; SQV 1200 mg bid (*Fortovase*)	■ SQV ↑AUC ■ Dose: *Invirase* 1000 mg bid + LPV/r standard	■ SQV: 1500 mg qd + ATV 300/100 mg qd
NFV	—	—	—	■ LPV ↓27% ■ NFV ↑25% ■ Avoid	■ NFV: No data
LPV/r	—	—	—	—	■ ATV/r 300/100 mg + LPV/r standard
ATV	—	—	—	—	—
FPV	—	—	—	—	—
EFV	—	—	—	—	—
NVP	—	—	—	—	—

* TPV/r should not be co-administered with another PI.

DRV	EFV	NVP
■ IDV and DRV AUCs ↑ ■ Regimen not determined	■ Levels: IDV ↓31% ■ Dose: IDV 1000 mg q8h; EFV 600 mg qhs ■ Consider IDV 800 mg bid + RTV 200 mg bid + EFV 600 mg hs	■ IDV ↓28% ■ NVP no effect ■ Dose: IDV 1000 mg q8h; standard NVP or IDV 1000 bid + RTV 100-200 mg bid + NVP standard
■ ↑ DRV levels 14x with RTV 100 mg bid ■ DRV/r 600/100 mg bid is standard	■ Levels: RTV ↑18% ■ EFV ↑21% ■ Dose: Standard for both drugs	■ RTV ↓11% ■ NVP no effect ■ Dose: Standard for both drugs
■ DRV AUC ↓26% ■ Data inadequate for dose recommendation ■ Avoid	■ Levels: SQV ↓62% ■ EFV ↓12% ■ Consider SQV/r 400/400 mg bid + EFV standard or 1000/100 mg bid + EFV standard	■ SQV ↓25% ■ NVP no effect ■ Dose: NVP standard + *Invirase* 1000 mg bid + RTV 100 mg bid
■ No data	■ Levels: NFV ↑20% ■ Dose: Standard for both drugs	■ NFV ↑10% ■ NVP no effect ■ Dose: Standard for both drugs
■ DRV AUC ↓53%; LPV AUC ↑37% ■ Avoid	■ Levels: LPV ↓40% ■ EFV – no change ■ LPV/r – 600/150 mg bid + EFV SD	■ LPV ↓55% ■ LPV/r 600/150 mg bid + NVR standard
■ DRV + ATV levels unchanged with ATV 300 mg/d ■ Use ATV 300 mg qd + DRV/r 600/100 mg bid	■ ATV AUC ↓74% ■ ATV 300 + RTV 100 mg + EFV standard (may need to ↑ATV dose in PI-experienced patient)	■ ATV ↓ ■ Not recommended
■ No data ■ Avoid	■ APV C_{min} ↓36% ■ Dose: FPV/r 700/100 bid or 1400/300 mg qd + EFV standard	—
■ DRV AUC ↓13%; EFV ↑21% ■ Standard doses (dose not established)	—	■ Not recommended
■ NVP AUC ↑27%, DRV unchanged ■ Standard doses (dose not established)	■ Not recommended	—

■ TABLE 4-14: Dosing of Antiretroviral Agents in Renal and Hepatic Failure

Drug	Standard Dose	Dose for Renal Insufficiency CrCl = mL/min			Dosing in Hemodialysis	Hepatic Dysfunction
AZT	300 mg bid	CrCl <15: 100 mg tid or 300 mg qd			100 mg tid or 300 mg qd†	Consider decreased dose
ddI	>60 kg 400 mg qd <60 kg 250 mg qd	CrCl*	>60 kg	<60 kg	As with CrCl <10 mL/min†	Usual dose
		30-59	200 mg/d	125 mg/d		
		10-29	125 mg/d	100 mg/d		
		<10	125 mg/d	75 mg/d		
d4T	>60 kg; consider 30 mg bid <60 kg 30 mg bid	CrCl*	>60 kg	<60 kg	As with CrCl 10-25 mL/min†. Dose after HD	Not defined; use caution
		26-50	20 mg bid	15 mg bid		
		10-25	20 mg qd	15 mg qd		
TDF	300 mg qd	CrCl 30-49: 300 mg q 48h 10-29: 300 mg 2x/wk <10: no recommendation			300 mg/wk after HD	Usual dose
3TC	300 mg qd or 150 mg bid	CrCl 30-49: 150 mg qd 15-29: 150 mg, then 100 mg qd 5-14: 150 mg, then 50 mg qd <5: 50 mg, then 25 mg qd			25-50 mg qd	Usual dose
FTC	200 mg qd	CrCl 30-49: 200 mg q 48h 15-29: 200 mg q 72h <15: 200 mg q 96h			200 mg q96h	Not defined
ABC	300 mg bid	Usual dose	Usual dose	Usual dose	Usual dose	200 mg bid CPC class A contra-indicated class B & C

Drug	Usual Adult Dose	Dosing for GFR >50 mL/min	Dosing for GFR 10-50 mL/min	Dosing for GFR <10 mL/min	Dosing in Hemodialysis	Hepatic Failure
EFV	600 mg qd	Usual dose likely	Usual dose	Usual dose likely	Usual dose	Use with caution
NVP	200 mg qd x 14 days then 200 mg bid	Usual dose	Usual dose	Usual dose	Usual dose	Avoid use with severe liver disease
NFV	1250 mg bid	Usual dose	Usual dose	Usual dose	Usual dose Must give post dialysis	Use with caution
IDV	800 mg tid§	Usual dose	Usual dose	Usual dose	Usual dose	600 mg q8h
RTV	600 mg bid§	Usual dose	Usual dose	Usual dose	Usual dose	Use with caution
TPV/r	500/200 mg bid	Usual dose	Usual dose	Usual dose	Usual dose	Avoid with CP score of 7-9

*Lactic acidosis syndrome should be ruled out before treating for hepatic failure.

(For other notes, see next page)

■ TABLE 4-14: **Dosing of Antiretroviral Agents in Renal and Hepatic Failure *(Continued)***

Drug	Usual Adult Dose	Dosing for GFR >50 mL/min	Dosing for GFR 10-50 mL/min	Dosing for GFR <10 mL/min	Dosing in Hemodialysis	Hepatic Failure
SQV/r	Boosted	Usual dose	Usual dose	Usual dose	Usual dose	Use with caution
LPV/r	400/100 mg bid	Usual dose	Usual dose	Usual dose	Usual dose	Use with caution
ATV	400 mg qd§ ATV/r 300/100 qd	Usual dose	Usual dose	Usual dose	Usual dose	CP Score¶ 7-9: 300 mg qd >9: Avoid
FPV	1400 mg bid§ FVP/r 700/100 bid	Usual dose	Usual dose	Usual dose	Usual dose	CP Score¶ 5-8: 700 mg bid 9-12: Avoid Avoid RTV boosing with liver disease
DRV/r	600/100 mg bid	Usual dose	Usual dose	Usual dose	Usual dose	Use with caution
ENF	90 mg SC bid	Usual dose	Usual dose	Usual dose	Usual dose	Usual dose

* CrCl = creatinine clearance in mL/min (Cockcroft-Gault equation). For men it is $\frac{(140 - \text{age in yrs}) \times \text{wt (kg)}}{72 \times \text{serum creatinine}}$; for women multiply the result x 0.85.

† Administer post-dialysis on dialysis days. Hemodialysis removes significant amounts of ddI (*Clin Pharm Ther* 1996;60:535); d4T (*Antimicrob Agents Chemother* 2000;44:2149); ddC; 3TC; TDF; and NFV (*AIDS* 2000;14:89). Hemodialysis removes little or none of the following: AZT (*J Acquir Immune Defic Syndr* 1992;5:242); ABC; EFV (*AIDS* 2000;14:618); NVP (*Nephrol Dial Transplant* 2001;16:192); IDV (*Nephrol Dial Transplant* 2000;15:1102); RTV (*Nephron* 2001;87:186); SQV (*Nephron* 2001;87:186); and LPV/r (*AIDS* 2001;15:662). There are sparse data for most antiretroviral agents for dose adjustments based on removal with peritoneal dialysis. Removal is anticipated or established with d4T, and ddC, which should be dosed post dialysis. TDF is not recommended with peritoneal dialysis. Others are not removed or are not expected to be removed.

‡ Avoid APV liquid due to its propylene glycol content.

§ Dose modified when combined with second PI.

¶ CP Score = Child-Pugh Score

Adverse Drug Reactions (ADRs) to Antiretroviral Agents

To be reported to http://www.mccza.com/main.asp

Lipodystrophy

(*N Engl J Med* 2005;352:48)

One or both of lipodystrophy's two components, fat accumulation and fat atrophy, may be seen in a patient. **Fat accumulation** is seen within the abdominal cavity ("protease paunch"), the upper back (dorsocervical fat pad or "buffalo hump"), the breasts (gynecomastia), and in subcutaneous tissue (peripheral lipomatosis). Some patients show the combination of abdominal obesity, hypertension, dyslipidemia and insulin resistance that simulates the metabolic syndrome, or "syndrome X" (*J Intern Med* 1994;764:13). **Lipoatrophy** includes loss of subcutaneous fat in the face, extremities, and buttocks. Lipoatrophy is ascribed to NRTIs, especially d4T, and to a lesser extent to AZT and ddI (*Sex Trans Infect* 2001;77:158). The cause of fat atrophy is less clear.

- **Frequency and risk factors:** Lipodystrophy is reported in 20% to 80% of patients receiving antiretroviral therapy, a wide range reflecting a heterogeneous population and the lack of a standard case definition (*Clin Infect Dis* 2006;43:645). The incidence based on perceived changes in body fat sufficiently severe to be detected by both the patient and physician in patients receiving 2 NRTIs plus a PI was 17%, with a median follow-up of 18 months (*Lancet* 2001;357:592). A meta-analysis of 5 series with 5435 HAART recipients showed fat accumulation was reported in 17% to 67% of studies and fat atrophy in 20% to 75% of studies (*Clin Infect Dis* 2003;36:S84). Rates of lipoatrophy reflected the experience with extensive use of thymidine analogs;. Risk factors for lipoatrophy are treatment with thymidine analogues, older age and nadir CD4 count <200/mm^3. Risk factors for fat accumulation are prior obesity, low CD4 count prior to treatment, and older age (*Clin Infect Dis* 2006;43:645).
- **Antiretroviral Agents**
  - Fat accumulation is often associated with PI-based HAART (*AIDS* 2001;15:231; *AIDS* 1999;13:2493) with an odds-ratio in controlled trials of 2.6 to 3.4 (*Clin Infect Dis* 2003;36[suppl 2]:S84). Nevertheless, it may be seen with HIV infection in the absence of PI exposure. The changes may occur without hyperlipidemia (*J Acquir Immune Defic Syndr* 2000;23:351; *Arch Intern Med* 2000;150:2050).
  - Lipoatrophy is more closely linked with NRTIs, especially d4T and less frequently ddI and AZT (*AIDS* 2000;14;F25; *AIDS* 1999;13:1659; *Clin Infect Dis* 2006;43:645). The presumed

mechanism is inhibition of DNA polymerase gamma resulting in depletion of mitochondrial DNA (*N Engl J Med* 2002;346:81).

- **Evaluation** (*Lancet* 2000;356:1412; *Lancet* 2001;357:592; *AIDS* 1999;13:2493; *Clin Infect Dis* 2003;36[suppl 2]:S63)
  - Lipoatrophy: Self-report is probably the best indicator, and may be augmented by anthropometric measurement of skin folds and limb diameter. Fat can be quantitated by CT scan, MRI, and DEXA (*J Acquir Immune Defic Syndr* 2002;31:2510), but these are expensive and not demonstrably better than self-report (*Clin Infect Dis* 2006;43:645).
  - Fat accumulation: A waist-hip ratio >0.95 in men or >0.85 in women is useful. Some regard a waist circumference 102 cm (40 in) in men or >88 cm (35 in) in women as a better measure (*BMJ* 1995;311:158). Utility of CT scans or MRI is not clinically useful (*Clin Infect Dis* 2006;43:645) and DEXA is not recommended.

- **Treatment**
  - **Low-fat diet and aerobic exercise** can be partly effective in treating fat accumulation (*AIDS* 1999;13:231; *Cochrane Database Syst Rev* 2005;18:CD001796), although they may exacerbate lipoatrophy.
  - **Regimen changes** with a switch from PIs to an NNRTI are sometimes partially successful in reversing fat accumulation, although data are conflicting and changes are slow (*J Infect Dis* 2001;184:914; *Clin Infect Dis* 2000;31:1266). Switches from d4T to ABC or TDF may lead to gradual improvements in lipoatrophy with follow-up 2 years (*JAMA* 2002;288:207; *Clin Infect Dis* 2004;38,263; *AIDS* 2005;19:15). The TARHEEL study showed that the switch from d4T to ABC or AZT was associated with significant increases in arm, leg, and trunk fat at 48 wks, but improvement was noted in <40% and was greater with DEXA than by self-report (*Clin Infect Dis* 2004;38:263).

Lactic Acidosis/Hepatic Steatosis

According to the SAHIVSC the following guidelines for lactic acidosis are recommended.

(http://www.sahivsoc.org/index.php/guideline/index/5/45)

A normal venous lactate level is less than 2.5 mmol/l and arterial lactate less than 2.0 mmol/l.

DEFINITION

Hyperlactataemia is present when lactate is raised but blood pH is > 7.35 and standard bicarbonate > 20 mmol/l, and may be asymptomatic or symptomatic. Asymptomatic hyperlactataemia is common in patients on NRTIs (occurs in up to 25% of patients), but does not pre-

dict for the symptomatic form of the disease. It represents a state of physiological compensation. Symptomatic hyperlactataemia carries a good prognosis if recognized early and if there is no liver dysfunction.

Lactic acidosis is diagnosed when pH < 7.35 and/or standard bicarbonate < 20 together with raised lactate. The lactate level in this setting is typically > 5. Reaching this stage means that significant failure of the physiological compensating mechanisms is present, and this carries a much worse prognosis. In lactic acidosis the pH may be in the normal range (due to respiratory compensation) but the standard bicarbonate is always < 20. There is invariably multiple organ dysfunction, especially hepatic.

Symptomatic hyperlactataemia occurs in 0.4 - 9% of patients on NRTI therapy, whereas lactic acidosis occurs in 0.1 - 0.4%.

RISK FACTORS

The following have been identified as risk factors:

- High body mass index (BMI) - evidence from one of the South African cohorts suggests that rapid weight gain is also a risk factor.
- Gender - women are at greater risk.
- Pregnancy - a high risk of lactic acidosis has been noted in pregnancy when the ddI and d4T combination has been used.
- Underlying liver disease - this may impair lactate clearance.
- Age - symptomatic hyperlactataemia/lactic acidosis appears to be unusual in younger children, as are the other manifestations of mitochondrial toxicity, although cases have been reported in South Africa.

It is unclear whether co-administration with metformin is a risk factor. Metformin can also cause lactic acidosis in patients with organ dysfunction. However, it is a key drug in the treatment of diabetes, and its co-administration with NRTIs that have a high potential for hyperlactataemia (i.e. ddI, d4T) needs to be considered carefully, weighing the risks and benefits in the individual patient.

Apply the rule: if you consider the diagnosis, do the laboratory investigations immediately. Delays in diagnosis may be life-threatening.

Many conditions may result in raised lactic acid and acidosis.

Hyperlactataemia/lactic acidosis secondary to NRTIs is therefore a diagnosis of exclusion.

Symptoms may be very nonspecific and vague, and have generally been present and getting worse for weeks and occasionally months.

KEY SYMPTOMS AND SIGNS INCLUDE:

- Unintentional loss of weight (LOW) (especially > 5%).
- Gastrointestinal (GIT) symptoms, including nausea, vomiting, loss

of appetite, abdominal pain and hepatomegaly.

- Weakness and fatigue.
- Dyspnoea, tachypnoea without respiratory cause.
- Unexplained tachycardia.
- Myalgia.
- Peripheral edema.
- Peripheral neuropathy and lipoatrophy often herald the onset of symptomatic hyperlactataemia.

TABLE I. CAUSES OF HYPERLACTATAEMIA/LACTIC ACIDOSIS OTHER THAN NRTIs

- Sepsis
- Severe cardiac failure
- Severe anemia
- Severe dehydration
- Hepatic failure
- Thiamine deficiency
- Renal failure
- Other drugs (e.g. INH overdose, Pancreatitis metformin)

The diagnosis is often missed initially, with symptomatic therapy being prescribed for GIT complaints. It is essential to maintain a high index of suspicion.

Symptomatic hyperlactataemia/lactic acidosis usually occurs after patients have been on NRTIs for several months (median 9 months). Typically the patient has initially experienced resolution of HIV- and opportunistic infection-related symptoms, has gained weight in the months after starting HAART and is virologically suppressed, then experiences a deterioration with the onset of hyperlactataemia and its associated weight loss and symptoms. However, we have documented rare cases in our cohorts that have occurred after only 2 months. It is unusual for symptomatic hyperlactataemia/lactic acidosis to develop after 2 years on therapy, but we have seen exceptions to this.

Clinical assessment should include evaluation of respiratory rate, abdominal examination and assessment for peripheral neuropathy. Tachypnoea in the absence of a respiratory cause is suggestive of metabolic acidosis.

The diagnosis is made by measuring venous or arterial lactate. The blood sample should be taken without the use of a tourniquet in a sodium fluoride tube and should reach the laboratory within 20 minutes on ice. However, if the sample is centrifuged on site and serum separated the serum sample then has 24 hours to reach a central laboratory.

Point-of-care devices for lactate measurement are particularly useful

for primary care and rural facilities where access to a laboratory that is able to measure lactate is difficult. These devices have been validated in ICU settings and reliably determine lactate levels within 1 mmol/l of the laboratory measurement. However; they have not yet been validated in a busy clinic setting. It is important that the blood used for the measurement is taken by venepuncture without a tourniquet and is not a fingerprick sample - the latter method has been shown to falsely elevate the lactate level at sites using these devices.

When doing blood gas sampling it is important to expel all residual heparin from the syringe before taking the sample. Failure to do this will cause a false lowering of pH.

Liver function tests, creatinine kinase, lipase and lactate dehydrogenase may be elevated in association with the lactate, but these do not have the necessary sensitivity or specificity to be used as reliable diagnostic tests. It is, however, important to check lipase and liver functions in all patients with confirmed symptomatic hyperlactataemia/lactic acidosis to assess for coexistent pancreatitis and steatohepatitis. Blood gas levels should also be checked in all patients with symptomatic hyperlactataemia to confirm or exclude metabolic acidosis.

Once NRTI-associated lactic acidosis is established, it represents a profound metabolic insult. When the NRTIs are removed, it takes weeks to months to resolve.

DIFFERENTIAL DIAGNOSES

Other causes for LOW and abdominal pain may mimic or coexist with hyperlactataemia/lactic acidosis.

Other causes for LOW to consider:

- Opportunistic infections (ask about tuberculosis symptoms).
- Lipoatrophy.
- Chronic diarrhea with malabsorption.
- Virological failure.
- Depression.
- Malignancy.
- Undiagnosed diabetes.
- Poor diet and poor social circumstances.
- Hyperthyroidism.

Other causes for abdominal pain/symptoms to consider:

- Pancreatitis (check lipase).
- Hepatitis/steatohepatitis (check ALT/alkaline phosphatase and assess for hepatomegaly).
- Opportunistic infections or immune reconstitution inflammatory syndrome (IRIS) (e.g. abdominal TB).
- GIT intolerance of medication, especially if on concomitant TB

treatment. Hyperlactataemia is often incorrectly diagnosed as this. GI intolerance to drugs rarely develops after months of therapy.

- Unrelated causes (e.g. pregnancy, diabetic ketoacidosis, appendicitis, peptic ulcer disease, pelvic inflammatory disease, urinary tract infections, pneumonia).

Other causes of tachypnoea and tachycardia, with or without the above:

- Respiratory conditions.
- Cardiac conditions.
- Anemia.
- Sepsis.
- Diabetic ketoacidosis.
- Hyperthyroidism.
- Hypoperfusion due to diarrhea, vomiting or inadequate fluid intake.

Recognizing the syndrome before the person becomes acidotic is the most effective prevention, and symptoms tend to occur long before severe laboratory abnormalities are present. The mortality and morbidity of the condition dramatically increases in the presence of acidosis. The mortality rate with lactic acidosis is 30 - 60%. A practical approach is to educate patients to report any loss of weight, abdominal pain or vomiting lasting more than a few days, excessive fatigue, lipoatrophy or peripheral neuropathy symptoms (see addendum - patient education poster). Weights should be monitored at every clinic visit, and when they drop by > 5% the lactate level should be measured, even if no other symptoms are present. Any patient with a severe or rapidly progressive NRTI-induced neuropathy (typically due to d4T or ddI) should also have the lactate level measured.

There is evidence that reducing the dose of d4T is associated with less toxicity (including hyperlactataemia) and equal efficacy. Patients developing other d4T-induced side-effects (e.g. peripheral neuropathy) should have their dose reduced (e.g. from 40 mg bd to 30 mg bd for those weighing > 60 kg, and from 30 mg bd to 20 mg bd in those < 60 kg) or switched to AZT. Another preventive strategy is to start women with a BMI > 28 on NRTIs with a lower risk of hyperlactataemia (3TC, ABC or TDF - but in the South African public sector AZT rather than d4T in the first-line regimen) or to switch them to these NRTIs if they gain weight to a BMI > 28 on HAART. This is a particularly high-risk group. It is prudent to avoid using ddI and d4T in the same HAART regimen as this combination carries the highest risk for mitochondrial toxicity. This combination should only be used if there are no other options available.

Routine lactate measurement in asymptomatic patients is not recommended, as the correlation with the development of symptoms is poor. Up to 25% of patients on NRTIs have asymptomatic hyperlactataemia with mild elevations in lactate levels, but only a minority will develop

symptoms. Elevated lactate levels in the absence of symptoms are not a good predictor of symptomatic hyperlactataemia.

Once the diagnosis is confirmed (raised lactate and exclusion of other causes), the following guidelines are suggested. Different facilities will have different treatment and monitoring options.

Stop the regimen even before the diagnosis is biochemically confirmed if you have a high index of suspicion. Do not stop the NRTIs alone - stop the entire regimen. It is better to interrupt a regimen for a short period than to continue a toxic regimen in the presence of suspected lactic acidosis.

The treatment guidelines presented below are largely based on anecdotal experience with the condition, by local and international clinicians and other published guidelines.

There are no prospective studies on the treatment of hyperlactataemia/lactic acidosis, and caution and common sense is urged by the guideline authors in all cases. These guidelines are based on the experience in South Africa being that most cases of symptomatic hyperlactataemia/lactic acidosis are caused by d4T in first-line therapy. We strongly urge that you consult an experienced treater in all cases, especially if d4T is not the offending drug.

MILD HYPERLACTATAEMIA AND MINIMAL SYMPTOMS (LACTATE 2.5 -5 AND NO METABOLIC ACIDOSIS - STANDARD BICARBONATE > 20)

The NRTI regimen should be switched to agents that are less likely to cause lactic acidosis (3TC, ABC or TDF if available - in the South African public sector switch from d4T to AZT in the first-line regimen) and the lactate rechecked within 3 days and then weekly until normalised. If symptoms are severe or the lactate continues to rise, or symptoms get worse despite the switch, HAART should be stopped and an expert treater consulted regarding the decision as to which HAART to restart when the lactate level has normalised.

If the lactate cannot be monitored in the way described, treatment should be stopped and treatment restarted when the lactate level has normalised and symptoms have resolved, following the guidelines below.

MODERATELY SEVERE HYPERLACTATAEMIA/MODERATE METABOLIC ACIDOSIS (LACTATE 5 -10 AND/OR STANDARD BICARBONATE 15 -20)

These patients should stop HAART, be observed as an inpatient for 1 - 2 days, and given oral vitamins (vitamin B complex 2 tablets bd and thiamine 100 mg bd), be well hydrated (orally or IVI) and have sepsis/opportunistic infections excluded. The lactate level should be rechecked, and when it is falling the patient can be discharged for outpatient follow-up provided he or she is clinically stable. HAART should only be recommenced when lactate and bicarbonate have normalised (this may take months), and the decision regarding what regimen to

restart should be discussed with an experienced treater.

The choice as to what to recommence is one of:

1. AZT, 3TC and non-nucleoside reverse transcriptase inhibitor (NNRTI) with lactate monitoring at 2 weeks, 4 weeks and then monthly for a further 2 months and at any time symptoms recur. This is not an option if the patient had metabolic acidosis (standard bicarbonate < 20). It is important to note that there is limited evidence for the safety of recommencing AZT in this setting.
2. TDF/3TC/NNRTI or ABC/3TC/NNRTI with lactate monitoring as above.
3. NNRTI with Kaletra (Kaletra dose here is 4 capsules bd due to NNRTI induction of Kaletra metabolism). Lactate monitoring not required.
4. Dual-boosted PI regimen (e.g. Kaletra + saquinavir).

Lactate monitoring not required. This option is preferable to (3) if NNRTI resistance is documented or strongly suspected, but the option is not available in many southern African public sector programmes.

This decision is based on the prior HAART history, clinical picture, lactate level, arterial blood gas, degree of steatohepatitis at presentation and ability to monitor lactate on recommencement.

Patients with more severe disease should be recommenced on (3) (or (2) or (4) if available in the private sector), whereas those with a milder syndrome could be recommenced on (1).

If a metabolic acidosis was present (1) should not be recommenced. There is no risk of recurrence of hyperlactataemia with (3) or (4), whereas with (1) there is a risk that AZT may cause relapse of hyperlactataemia (although the risk is lower than with d4T). There is less of a risk of recurrence with (2) than with (1), as ABC, TDF and 3TC have been infrequently associated with hyperlactataemia and usually when used in combination with a drug that is more likely to cause mitochondrial toxicity.

Also, the decision as to when to restart HAART is a balance between the patient's nadir CD4, their current CD4 and the severity of the hyperlactataemia/lactic acidosis. Patients with low nadirs should not have HAART withheld for too long, as they run the risk of acquiring new opportunistic infections. If lactate levels are persistently elevated in a patient with a low nadir CD4 count, a regimen without a risk of occurrence (NNRTI/Kaletra or dual-boosted protease inhibitor (PI)) should be considered and can be commenced before lactate has normalised.

Patient education is critical. Patients with hyperlactataemia/lactic acidosis being rechallenged with a safer NRTI should understand the need for regular follow-up.

Patients who live far from the health care facility, have transport difficulties, are unreliable or have follow-up compromised in any way, should not have NRTIs reintroduced.

SEVERE HYPERLACTATAEMIA (LACTATE > 10 WITHOUT METABOLIC ACIDOSIS) OR SIGNIFICANT LACTIC ACIDOSIS (RAISED LACTATE REGARDLESS OF LEVEL AND SIGNIFICANT METABOLIC ACIDOSIS - STANDARD BICARBONATE < 15)

These patients should preferably be managed in a high-care facility as follows:

- Stop HAART
- IVI thiamine 100 mg 12-hourly and B-complex vitamins 1 amp 12-hourly.
- IVI fluids.
- Blood culture/urine culture/septic search and broad-spectrum antibiotic (e.g. third-generation cephalosporin or co-amoxyclav). This is important because sepsis may mimic or precipitate NRTI-associated lactic acidosis.
- Consider IVI NaHCO3 if profound acidosis (e.g. 150 ml of 8.5% sodium bicarbonate added to a vacolitre of 5% dextrose water and infused at 80 -100 ml per hour).
- Consider ventilation if respiratory fatigue occurs.
- Dialysis, inotropes and other supportive measures as necessary.
- Coenzyme Q, L-carnitine and other mitochondrial cofactors are used by some when available, but have very limited evidence for efficacy.
- If pancreatitis is present patients should be kept nil per mouth.
- Monitor lactate, blood gas, lipase, ALT and alkaline phosphatase.

Some of these patients demonstrate a biphasic course with initial improvement and then deterioration, often when they develop a superimposed pancreatitis.

These patients should be recommenced on Kaletra (lopinavir/ritonavir) 4 capsules bd and NNRTI or a dual boosted PI regimen (options (3) and (4) above) when lactate has normalised (this may take months). Other regimens that could potentially be used in these patients with less severe presentations are TDF/3TC/NNRTI or ABC/3TC/NNRTI with lactate monitoring on rechallenge as described above (option (2) above).

COVERING THE 'NNRTI TAIL' WITH LOPINAVIR/RITONAVIR (KALETRA)

When a HAART regimen containing an NNRTI (nevirapine or efavirenz) is stopped the NNRTI persists in the plasma for 1-2 weeks because of the long half-life of these drugs, unlike the NRTI component. This 'NNRTI tail' means that there is effective monotherapy with the NNRTI after the HAART is stopped, which predisposes to the development of NNRTI resistance. Provided patients are not vomiting and do not have

either significant steatohepatitis or pancreatitis, it is suggested that when an NNRTI-containing regimen is stopped because of hyperlactataemia or lactic acidosis, 7 days of Kaletra (lopinavir/ritonavir) 4 tablets bd are prescribed to cover the NNRTI tail, thereby preventing effective monotherapy and the risk of NNRTI resistance developing.

PROGNOSIS

Poor prognostic markers are high lactate level, severe acidosis and coexistent pancreatitis. Patients who require ventilation and/or dialysis appear to have an extremely poor prognosis.

SWITCHING TO AZT

When d4T is switched to AZT it is frequently forgotten that monitoring for AZT haematological toxicity is required. The full blood count and differential count should be checked at baseline, then at 1, 2, 3 and 6 months, then 6-monthly. Do not start AZT in patients with a hemoglobin concentration < 8 g/dl.

INSULIN RESISTANCE

Insulin resistance (impaired uptake of glucose by muscle and inhibition of hepatic glucogenesis) is common with PI-based HAART, but diabetes (fasting blood sugar >126 mg/dL) is infrequent and rarely requires insulin, except in patients who are prone to diabetes (first-degree relative).

- **Definitions**
  - Insulin resistance: Tissues targeted by insulin fail to respond, leading to increased production of pancreatic insulin
  - Impaired glucose tolerance: Blood glucose of 140-199 mg/dL 2 h after a 75-gm glucose loading dose, or fasting blood glucose of 100-125 mg/dL after an 8-h fast.
  - Diabetes: Blood glucose >200 mg/dL 2 h after a 75-gm glucose loading dose or fasting blood glucose ≥126 mg/dL after 8-h fast
- **Frequency:** Insulin resistance is noted in 30% to 90% of patients treated with protease inhibitors, and overt diabetes occurs in 1% to 11%, with a mean of approximately 7% at 5 years (*AIDS* 1999;13:F63; *Lancet* 1999;353:2093; *Arch Intern Med* 2000;160:2050). In an analysis of the MACS database, the incidence of diabetes mellitus was 4.7/100 person-years for HAART recipients, a 4.1-fold risk compared to untreated controls (*Arch Intern Med* 2005;165:1179). Insulin resistance has been demonstrated with administration of LPV/r, IDV, and RTV to uninfected individuals. No changes are seen with ATV (*AIDS* 2006;20:1813; *J Infect Dis* 2004;182:209). No data are available for SQV, FPV, or NFV. The changes in blood glucose are usually apparent within 2 to 3 months

and can be detected with a fasting blood glucose test (*Lancet* 1999;353:2093). With IDV, insulin resistance can be detected after a single dose (*AIDS* 2002;16:F1).

SCREENING: Blood glucose on PI every 6 months.

RISK: Insulin resistance is important because it is a risk factor for atherosclerosis (*N Engl J Med* 1996;334:952; *Am J Med* 1997;103:152), especially when accompanied by dyslipidemia, hypertension, and visceral fat accumulation, e.g., the components of metabolic syndrome or "syndrome X" (*J Intern Med* 1994;736:13). Risk assessment should include assessment of risk factors for diabetes and atherosclerosis, including family history, smoking, hypertension, obesity, and dyslipidemia. Other risks for disordered glucose metabolism are obesity, most PIs other than ATV, d4T, advanced age, family history of diabetes, nonwhite race, and possibly HCV coinfection (*J Acquir Immune Defic Syndr* 2003;32:298; *AIDS* 2005;19:1375). Drugs other than HIV agents associated with greater risk include steroids, niacin, growth hormone, and some antipsychotics.

TREATMENT: Standard guidelines are recommended for management of diabetes (*Diabetes Care* 2000;23[suppl 1]:S32). Most cases are type 2 and can be managed with diet and exercise. The daily diet should consist of 50% to 60% carbohydrate, 10% to 20% protein, and <30% fat, with <100 mg cholesterol per day and <10% of total calories from saturated fat. When drug therapy is necessary, insulin is most commonly prescribed. Included in this class of drugs are metformin and the thiazolidinediones, which have the potential advantage of reducing insulin resistance and decreasing visceral fat accumulation (*AIDS* 1999;13:100; *JAMA* 2000;284:472; *Ann Intern Med* 2005;143:337), with a possible reduction in cardiovascular risk. LFTs need to be monitored (ALT q 2 months x 12 months) with thiazolinediones; a baseline ALT >2.5x ULN contraindicates use. A baseline elevation of creatinine or lactic acid to 2x ULN contraindicates metformin. Sulfonylureas, drugs in a different class, reduce blood glucose but do not reverse insulin resistance. An alternative strategy is to change the HAART regimen to a non-PI-based regimen or a PI-based regimen less likely to cause insulin resistance, such as ATV, FPV, SQV, or NFV (*AIDS* 1999;13:805; *J Acquir Immune Defic Syndr* 2001;27:229; *Clin Infect Dis* 2000;31:1266).

Hyperlipidemia

Changes in blood lipids have emerged as an important concern with HAART, due to the potential for premature atherosclerosis and coronary artery disease. The risk of this complication with relatively short-term follow-up appears to be modest but real (*N Engl J Med* 2003;349:1993). Studies in the pre-HAART era showed that HIV

progression was associated with elevated triglyceride levels and decreased cholesterol levels (*Am J Med* 1991;90:154; *JAMA* 2003; 289:2978). With PI-based HAART there is usually an increase in triglycerides, total cholesterol, and LDL cholestrol, with a decrease in HDL cholesterol (N Engl J Med 2005;352:48). Most cholesterol is carried in low-density lipoprotein (LDL-C); high concentrations of LDL-C are associated with increased risk of atherosclerosis, especially coronary artery disease. High triglyceride levels also increase this risk and levels above 1000 mg/dL are associated with an increased risk of pancreatitis. LDL cholesterol levels increase an average of about 30 mg/dL, but there is substantial individual patient variation, which is poorly understood (*J Acquir Immune Def Syndr* 2000;23:35; *Arch Intern Med* 2000;160:2050; *J Aquir Immune Defic Syndr* 2000;23:261; *Lancet* 1998;352:1031; *AIDS* 1998;12:F51; *Circulation* 1999;100:700; *J Infect Dis* 2004;189:1056). With regard to agents, the analysis of 23,000 HIV-infected patients in D:A:D showed the highest risk was with RTV and RTV-boosted PIs (*J Infect Dis* 2004;189:1056). Lipid changes with ATV are nil (*J Acquir Immune Defic Syndr* 2004;36:1011), but there are modest increases in total cholesterol and triglycerides with boosted ATV (13th CROI, Denver, 2006, Abstr. 107LB). d4T is also associated with elevated triglyceride levels (*JAMA* 2004;292:191). Effects are less with NNRTIs in general and less with NVP compared to EFV (*AIDS* 2003;17:1195). HAART-associated changes are usually apparent within 2 to 3 months of initiating therapy.

- **Risk:** An increased risk of cardiovascular disease associated with HAART was initially assumed based on serum lipid changes. The most comprehensive study of serum lipid changes is D:A:D (Data Collection on Adverse Events of anti-HIV Drugs), an observational study of 11 HIV cohorts with data on >20,000 HIV-infected patients in 188 clinics. The initial results showed 126 myocardial infarctions among 23,468 patients. The relative rate for HAART recipients was 1.25; for smoking it was 2.2 (*N Engl J Med* 2003;349:1993). Long-term (>4 yrs) follow-up shows the rate of myocardial infarcts in patients receiving HAART is about 26% above predicted rates (*HIV Med* 2006;7:218). Other studies also show a modest increased risk of coronary events with use of HAART (*JAMA* 2003;289:2978; *AIDS* 2003;17:1179). Assessment needs to include a review of other cardiovascular risk factors as defined by NCEP, summarized in Table 4-15 (*JAMA* 2001;285:2486). The risk of cerebrovascular events is also increased by about 25% (*AIDS* 2004;18:1811).
- **Management:** Based on recommendations of ACTG and IDSA (*Clin Infect Dis* 2003;37:613), the academic consortium (*Clin Infect Dis* 2006;43:645), IAS-USA Guidelines, and the National Cholesterol Education Program guidelines III (*JAMA* 2001;285:2486). Note that LDL-C guidelines were modified based on more recent data to target

LDL-C at 70 and 100 mg/dL in the two highest risk groups (*J Am Coll Cardiol* 2004;44:720).

- **Baseline assessment:** Lipid panel, including cholesterol, LDL + HDL cholesterol, and triglycerides after fasting at least 8 (preferably 12) hours. Nevertheless, non-fasting lipid panels provide useful information about cholesterol subsets. Fasting is necessary for accurate measurement of triglycerides and the calculation of LDL cholesterol but has minimal effect on total cholesterol. LDL cholesterol measurements are unreliable with triglyceride levels >400 mg/dL. In this situation, clinicians can subtract HDL cholesterol levels from total cholesterol to obtain a non-HDL cholesterol level (*JAMA* 2001;285:2486). Interpretation must take into account secondary causes of dyslipidemia including nephrosis, alcoholism, thiazides, testosterone treatment, estrogen treatment, hypogonadism, uncontrolled diabetes, and cocaine abuse. Goals of therapy for LDL cholesterol levels are summarized in Table 4-15.
- **Monitoring:** The lipid profile should be repeated at 3 to 4 months, and then with a frequency depending on the 3- to 4-month values and risk assessment. It should be repeated at least once per year.

■ TABLE 4-15: **National Cholesterol Education Program Guidelines (*Circulation* 2004;110:227)**

Risk category	LDL goal (mg/dL)	Lifestyle change	Drug therapy
Atherosclerosis, diabetes, or multiple risk factors	<70	>100	>130 optional – 100-130
2 risk factors: smoking, HBP, HDL >40 mg/dL, hereditary factors*			
10-yr risk 10-20%	<100	<130	>130
10-yr risk <10%	<130	<130	>160
0-1 risk factors*	<160	<190	optional 160-190 >190

* Age: male >45 yrs, female >55 yrs; HDL-C <40 mg/dL; BP >140/90 or antihypertension drugs; smoking; coronary artery disease in a first-degree male relative <55 yrs or female relative <65 yrs

TREATMENT OF HYPERLIPIDEMIA

- **Lifestyle changes**
  - Diet – Reduce saturated fat to <7%; reduce cholesterol to <200 mg/dL; increase fiber intake to 20-30 gm/d; LDL-lowering plant stanols/sterols 2 gm/d; protein, 15% of calories; carbohydrates, predominantly complex and 50-60% of calories
  - Exercise – aerobic exercise 30-60 minutes ≥5x/wk
  - Weight reduction
  - Smoking cessation
  - Control of hypertension, diabetes
- **Antiviral substitution:** Substituting an NNRTI or ATV, with or without boosting, has improved lipid profiles (*J Acquir Immune Defic Syndr* 2005;39:174); *AIDS* 2005;19:917). Switching ABC or TDF for d4T may also be effective (*AIDS* 2004;18:1475).
- **Drug therapy**
  - **LDL-C or non-HDL cholesterol reduction statins**:
    - ***Basics:*** Statins are the most effective drugs to reduce LDL-C; they also decrease triglycerides. Statins may produce a modest increase in HDL-C and decrease CRP (*N Engl J Med* 2005;352:73). The clinical benefit correlates with the LDL-C decrease. Meta-analysis of 58 placebo-controlled trials showed coronary artery events decreased by 20%, 31%, and 51% with decreases of 20 mg/dL, 40 mg/dL, and 62 mg/dL, respectively. Once started, statins are usually continued for a lifetime. If stopped, lipid levels return to baseline within 2-3 wks.
  - ***PI interactions:*** Many statins are metabolized using cytochrome P3A4; all PIs inhibit CYP3A4. The greatest effect is with lovastatin and simvastatin; atorvastatin is only partially metabolized by CYP3A4; fluvastatin is metabolized mainly by CYP2C9; pravastatin and rosuvastatin are not metabolized by this mechanism (see Table 4-13).
  - ***Adverse effects:*** Myalgias and muscle weakness, with or without elevated CPK, are common (*JAMA* 2003;289:1681). Rhabdomyolysis and myoglobinemia with renal failure are rare but serious. Symptoms are muscle pain, weakness and/or tenderness with red or cola-colored urine. Urine is positive for hemoglobin without RBCs on urinalysis. These risks are dose-related and increased with PIs. Obtain baseline CPK levels and repeat the test if myalgias develop; some recommend discontinuing statins or lowering the dose if the level is 3-5x ULN (*Treatment Guidelines, Med Letter* 2003;3:15). Other ADRs include increased transaminase levels in 1-2%, which is often corrected by use of an alternative statin. A rare polyneuropathy has been reported (*Neurology* 2002;58:1333).

■ TABLE 4-16: **Statins**

Agent	Form	Dose (FDA)		Decrease LDL
		Initial mg/day	Max mg/day	
Atorvastatin (*Lipitor*)	Tabs – 10, 20, 40, 80 mg	10	80	35-60%
Fluvastatin (*Lescol*)	Caps – 20, 40 mg; 80 mg XL	20-40	80	20-40%
Pravastatin (*Pravachol*)	Tabs – 10, 20, 40, 80 mg	20-40	80	30-40%
Rosuvastatin (*Crestor*)	Tabs – 5, 10, 20, 40 mg	10	40	45-60%

Lovastatin (*Mevacor*) and simvastatin (*Zocor*) are not included due to major drug interactions with all PIs and EFV.

■ TABLE 4-17: **Drug Interactions: Effect of ART Agents on AUC of Statins**

Statin*	ATV	FPV	IDV	LPV/r	NFV	RTV	SQV/r	EFV	NVP	FPV/r
Atorvastatin	ND	1.5x	↑	↑5.9x	↑74%	↑4.5x	↑4.5x	¬0.4x	↓	↑9x
Pravastatin	ND	ND	ND	↑33x	↓	↓	↓50%	↓	↓	ND

ND = no data; ↑ = anticipated increase in AUC of statin; ↑0.7x = statin AUC increased 70%; ↑4.5x = statin AUC increased 450%

* Data are not provided for simvastatin or lovastatin because they are contraindicated for concurrent use with all PIs; EFV decreases AUC of simvastatin 58%. No data for NVP.

- ***Triglyceride levels >400 mg/dL:*** Preferred treatment is with fibrates, either micronized fenofibrate 48-145 mg qd or gemfibrozil 100 mg bid. If triglyceride levels remain >500 mg/dL, consider fish oil 3-6 gm/d (*Clin Infect Dis* 2005;41:1498).

■ TABLE 4-18: **Triglycerides: Preferred Fibrates**

Agent	Form	Regimen
Gemfibrozil (*Lopid*)	Tabs – 600 mg	600 mg bid before meals
Fenofibrate (*TriCor*) Generic	Tabs – 48, 145 mg Caps – 67, 100, 200 mg	48-145 mg qd 200 mg qd

Hepatotoxicity (see *Clin Liver Dis* 2003;7:475)

Most antiretroviral agents have been implicated as potential causes of hepatotoxicity, but frequency, severity, and mechanism are highly variable (Table 4-19). Many cases are confounded by the presence of pre-existing liver disease ascribed to HBV, HCV, or alcoholism. The most common manifestation is an asymptomatic increase in transaminase levels, which often resolves without discontinuation of the implicated agent.

■ TABLE 4-19: **Grading of Hepatotoxicty (ACTG)**

Grade	ALT/AST (x ULN)	AlkPhos x ULN	Bili x ULN
1	1-2.5x	1-2.5x	1.0-1.5x
2	2.5-5x	2.5-5x	1.5-2.5x
3	5-10x	5-10x	2.5-5x
4	>10x	>10x	>5x

■ TABLE 4-20: **Hepatotoxicity of Antiretrovirals***

Class & Agents	Frequency Grade 3-4	Mechanism
NRTI		
d4T, AZT, ddI	6-13%	Mitochondrial toxicity with hepatic steatosis; d4T most common
FTC, TDF, 3TC; withdrawal or development of HBV resistance with chronic HBV	6% (?)	HBV hepatitis flare; resistance most likely with 3TC and FTC
ABC	5%	Hypersensitivity; genetic predisposition
PI		
All agents	3-10%	Mechanism unknown; consequences unknown; transaminase levels may return to normal while continuing PI. Greatest risk with HCV or HBV coninfection.
IDV and ATV	>50%	Elevated indirect bilirubin; jaundice; 3-5%; not associated with hepatotoxicity.
TPV	<1%	Symptomatic hepatitis that may progress to hepatic failure and death.
NNRTI		
NVP	1-11%	Symptomatic hepatitis (usually with nausea, vomiting, rash and/or fever in the first 12-16 wks of treatment; *J Infect Dis* 2005;191:825). Risks: baseline CD4 count >250/mm^3 in women, >400/mm^3 in men; rate is 11% in women initally treated with CD4 >250/mm^3 and <2% with CD4 <250/mm^3. Delayed hepatotoxicity can also occur. Mechanism is unknown. Also cause transaminitis, as with EFV and with PIs. Greatest risk with HBC or HCV co-infection.
EFV, DLV	8-15%	Mechanism unknown Analogous to hepatitis with PIs. Greatest risk with HBV or HCV co-infection.

* Adapted from Olgledigbe, A and Sulkowski, M, *Clin Liver Dis* 2003;7:475 and Sanne I, *J Infect Dis* 2005;191:825)

- **HBV or HCV co-infection:** Both are associated with increased mortality with HIV co-infection, although the mechanisms are unclear. HCV often represents a marker of injection drug use, which may account for the difference (*J Acquir Immune Defic Syndr* 2003;33:365; *Clin Infect Dis* 2003;36:363). HBV is immune-mediated, so immune restoration with HAART may account for an increase in HBV progression.

- **NRTIs:** Three mechanisms of liver injury are described: 1) hepatic steatosis that accompanies lactic acidosis, 2) abacavir hypersensitivity, and 3) flares of chronic hepatitis due to HBV that accompany either withdrawal of drugs active against HBV or the development of HBV resistance to those drugs (*J Infect Dis* 2002;186:23). Antiretroviral agents that are active against HBV include 3TC, FTC, and TDF. The frequency of resistance to 3TC and presumably FTC is 30% to 50% after 1 year of exposure; it is <2% with TDF (*AIDS* 2003;17:1649). The abacavir hypersensitivity reaction is a serious multisystem reaction that is seen in 4% to 5% of abacavir recipients with >90% occurring in the first 6 weeks of treatment. This requires immediate withdrawal of the drug without rechallenge, which could be fatal (*Clin Infect Dis* 2002;34:1137). Lactic acidosis usually occurs after months of treatment with NTRIs, primarily with regimens that include d4T, ddI, and/or AZT (*Clin Infect Dis* 2003;36[suppl 2]:S96) (see pp. 104-106).
- **NNRTIs:** All three NNRTIs may cause hepatotoxicity with elevated transaminases. Reported rates of grade 3-4 hepatotoxicity are 8% to 15%, and are highest with NVP (*HIV Clin Trials* 2003;4:115; *AIDS* 2003;17:2191; *J Hepatol* 2002;36:283). NVP appears to cause liver disease by two possibly distinct mechanisms. The serious form is symptomatic hepatitis, sometimes associated with hepatic necrosis, usually occurs in the first 6 weeks of treatment, is accompanied by a systemic response (fever, rash, GI symptoms), and resembles a hypersensitivity reaction (*AIDS* 2003;17:2209). This reaction is reported in 11% of women who start NVP as initial treatment with a CD4 count >250/mm^3; the risk is also increased in previously untreated men who initiate NVP with a CD4 count >400/mm^3. This reaction may not be reversible even when detected early. Frequent monitoring of transaminase levels is commonly advocated, but there is no evidence that this predicts the event. See management guidelines. The second type of hepatotoxicity usually occurs later in the course, presents with elevated transaminase levels, and is similar to the transaminitis seen with PIs, NVP, DLV, and EFV, especially in patients with HBV or HCV co-infection. Most are asymptomatic. Current recommendations are to discontinue the NNRTI only when there are symptoms or the transaminase levels reach an arbitrary threshold of 5x or 10x ULN, plateau. Many will spontaneously resolve even when treatment is continued with ALT levels >10x ULN (*Clin Liver Dis* 2003;7:475; *AIDS* 2003;17:2209).
- **PIs:** Hepatotoxicity with PIs is usually characterized by asymptomatic elevations in transaminase levels caused by unknown mechanisms. Liver biopsies in such cases are usually nonspecific and do not show drug-induced injury. Most have resolution of the abnormal tests despite continuation of the implicated drug. Grade 3-4 toxicity (ALT to 5-10x ULN) is most common in patients with HBV or HCV

co-infection; it appears to be most frequent with RTV (*JAMA* 2000;283:74) and is dose-related. The recommended intervention is to alter therapy if hepatitis is symptomatic or if the ALT increases above an arbitrary threshold of 5x-10x ULN in the absence of symptoms, especially if the high levels of ALT persist.

Recommendations for Antiretroviral Therapy in Pregnancy

Department on Health guidelines in pregnancy

Eligibility criteria for starting ARVs in pregnancy do not differ from other adults. However the default first-line regimen to all women will include nevirapine as the NNTRI rather than efavirenz.

Provider Initiated Testing and Counselling (PITC)

The provider-initiated approach should be applied to all clients seeking health care where HIV is prevalent and antiretroviral treatment is available.

The conditions of confidentiality, counseling and consent must be upheld at all times.

Guide to administration of HAART and ARV prophylaxis for PMTCT

	Eligible for ART • CD4<200 regardless of clinical stage • Clinical stage 4 regardless of CD4 • Clinical stage 3 with CD4<350	Not eligible for ART: • Clinical stages 1&2 with D4>200 • Clinical stage 3 with CD4>350
Mother Antepartum Intrapartum Postpartum	 AZT + 3TC +NVP AZT + 3TC +NVP AZT + 3TC +NVP	 AZT from 28 weeks Sd NVP + AZT/3TC AZT/3TC for 7 days
Infant	AZT for 7 days	Sd NVP + AZT for 7 days

All eligible HIV positive pregnant women should offered HAART whether on site or through referral to a CCMT site.

All pregnant women NOT eligible for HAART will be offered the dual prophylaxis regimen of AZT antenatal starting from 28 weeks of gestation or any time thereafter and continuing for one week after delivery in combination with 3TC. At the beginning of labour, these women should receive one single dose of nevirapine

In order to reduce the risk of nevirapine resistance, women on dual prophylaxis should receive a combination of AZT and 3TC starting from labour and continuing for one week after delivery.

■ TABLE 4-21: **Recommended Antiviral therapy in pregnancy**

Recommendation	Agent	Comment
NRTIs		
Recommended	AZT	Should be in regimen unless toxicity or d4T use.
	3TC	AZT/3TC is standard NRTI backbone.
Alternatives	ddI	Avoid use with d4T.
	FTC	No studies in pregnant humans.
	d4T	Do not use with AZT or ddI.
	ABC	Concern for hypersensitivity reaction.
Inadequate data	TDF	Concern based on lack of data in pregnant humans and studies in primates showing decreased fetal growth and reduced bone porosity.
NNRTIs		
Recommended	NVP	Avoid in women with baseline CD4 >250/mm^3.
Not recommended	EFV	FDA Pregnancy Class D. Neural tube defects in 3/20 primates and 5 anecdotal cases of women given EFV in first trimester. Consider use in second trimester only if there are no other alternatives and if contraceptive use is assured after pregnancy.
PIs		
Recommended	LPV/r	Limited studies in pregnant women with tablet formulation. Based on studies with prior formulation, the recommended dose is 2-3 tablets bid during the third trimester (3 tabs bid based on PK studies).
	NFV	Good pharmacokinetics with 1250 mg bid (take with meals).
Alternatives	IDV	Theoretical concern for hyperbilirubinemia.
	RTV	Recommended for boosting PIs, especially in third trimester.
	SQV/r	Most studies in human pregnancy were done with *Fortovase*, which is no longer available.
Insufficient data	ATV	Inadequate data in pregnant humans.
	FPV	Inadequate data in pregnant humans.
	TPV	Inadequate data in pregnant humans.
	DRV	Inadequate data in pregnant humans.

Principles (*N Engl J Med* 2002;346:1879)

- **HIV progression:** Pregnancy has no clear effect on HIV progression.
- **Pregnancy complications:** Data from developing countries show HIV infection is associated with increased rates of preterm delivery, low birth weight, and stillbirth. This has not been observed in industrialized countries.

- **Viral load:** Probability of perinatal transmission is directly related to viral load at the time of delivery. Other risks include substance abuse, premature rupture of membranes, HCV coinfection, and preterm gestation.
- **When to treat:** All pregnant women should be offered antiretroviral agents to reduce perinatal transmission and improve maternal health. HAART is recommended for treatment of HIV in the pregnant woman based on guidelines that apply to the general population, with few exceptions for agent selection (see next bullet). HAART is also recommended to prevent perinatal transmission in any woman with a VL >1000 c/mL. With VL <1000 c/mL (without treatment), some authorities accept AZT monotherapy.
- **Drugs to use:** Avoid hydroxyurea, EFV, TDF, and d4T + ddI. When possible, include AZT (but not AZT + d4T). Preferred regimens in DHHS guidelines: AZT/3TC + either NFV 1250 mg bid or LPV/r using standard dose in first and second trimesters, then 3 tabs bid in third trimester.
- **NVP:** New data suggest NVP should be avoided in women who initiate treatment with a CD4 count >250/mm^3 (*J Infect Dis* 2005;19:825). This does not pertain to the single dose of NVP given intrapartum to prevent perinatal transmission.
- **C-section:** Elective cesarean section reduces risk of perinatal transmission and should be offered at 38 weeks to pregnant women have VL likely to >1,000 c/mL at delivery. There is no evidence of benefit after onset of labor, after rupture of membranes, or with VL <1000 c/mL.

HIV Testing and Counseling

HIV TESTING: Standard serologic test with counseling is required in some states and opt-out testing is used in others. All pregnant women should be tested and the test should be repeated in high-risk patients in the third trimester at 28 weeks. The rapid test is recommended for previously untested women presenting in labor. Women with symptoms suggesting acute HIV infection in the third trimester should have HIV RNA assays. Lengthy counseling and written consents are seen as possible barriers to case detection because testing is more common in states that use the opt-out testing model. "Opt-out testing" is strongly recommended (*MMWR* 2006;55:RR14).

Factors that Reduce Perinatal Transmission

For women who do not breastfeed, intrauterine transmission previously accounted for 25% to 40% and delivery for 60% to 75% (*MMWR* 2001;50[RR-19]:63). It should be emphasized that all three components of the AZT regimen (pre-natal, perinatal, and post-natal) have merit.

VIRAL LOAD: There is a direct correlation between maternal viral load and probability of perinatal transmission varying from 41% with a VL >100,000 c/mL to 0% with a VL <1000 c/mL (*N Engl J Med* 1999;13: 407; *J Infect Dis* 2001;183:206; *J Acquir Immune Defic Syndr* 2002;29: 484). Despite these findings, there is no viral load that can be regarded as safe because other factors also play a role (*AIDS* 1999;13: 1377; *AIDS* 1999;13:407; *J Infect Dis* 1999;179:590). In an analysis of seven prospective studies, there were 44 cases of HIV in babies born to 1,202 women with viral loads <1,000 c/mL (*J Infect Dis* 2001;183:539).

AZT: This drug should be included when possible because it has the largest experience for safety and efficacy. This includes significant reduction in perinatal transmission that is independent of viral load (*N Engl J Med* 1996;335:1621; *Lancet* 1999;354:156) and possibly independent of AZT resistance (*J Infect Dis* 1998;177:557). Analysis of ACTG 076 showed that AZT significantly reduces perinatal transmission even in women with baseline VL <1,000 c/mL (*J Infect Dis* 2001;183:539). This provides the rationale for AZT monotherapy in untreated pregnant women with a baseline VL <1,000 c/mL, although many authorities would recommend this treatment only if a standard HAART regimen was refused.

NVP: NVP is the best studied drug other than AZT. Single-dose NVP is the regimen now used most frequently to prevent maternal-to-child transmission in resource-limited countries (*BJOG Int J Obstet Gynecol* 2005;112:1196). However, concerns with this approach include evidence of HIV resistance, even with a single dose at delivery (*N Engl J Med* 2004;351:229), that spawned a vigorous public debate in 2004 (*Science* 2004;306:2168). This was largely quelled by an independent review reported by the Institute of Medicine in 2005. Efficacy in preventing perinatal transmission has been shown in multiple studies, most performed in resource limited areas with a single maternal dose of 200 mg PO at delivery and one infant dose of 2 mg/kg. This regimen proved easy to implement, cheap, and effective, and transmission rates fell to 7%-12% (*J Acquire Immune Defic Synd* 2005;39:121; *J Infect Dis* 2003;187:725). Addition of AZT, with or without 3TC, at 28-32 weeks as a single intrapartum dose of NVP further reduced transmission rates to 3%–7% (*N Eng J Med* 2004;351:217; *AIDS* 2005;19:309). Single-dose NVP is slightly superior to a 6-week course of AZT (*AIDS* 2005;19:1289). However, an analysis of 229 participants given NVP at 6 to 8 weeks postpartum showed NVP resistance mutations in 66 (32%), including the K103N mutation in 48 (21%) (*N Engl J Med* 2004;351:229). More recent reports using allele-specific PCR to detect genotypic resistance in minority species show that K103N resistance mutations are present in 60%-80% of patients after single-dose NVP (*J Infect Dis* 2005;192:24; *AIDS* 2006;20:995). The single-dose NVP regimen has also resulted in NVP resistance in

20%–50% of HIV-infected neonates (*AIDS* 2001;15:1951). The resistance mutations disappear with time. Using allele-specific PCR that detects >0.002 of the total viral population, the K103 mutation was present in 87%, 64%, 39%, and 11% at baseline, 3, 7, and 12 months respectively (*AIDS* 2006;20:995). The clinical significance of this resistance is the issue. Treatment of 269 Thai women with NVP-based HAART showed virologic suppression to <50 c/mL at 6 months was greater in women who did not receive intrapartum NVP (49% vs 68%; *P* <0.03) (*N Eng J Med* 2004;351:229). A subsequent study has shown that this difference is limited to women who received treatment within 6 months of intrapartum NVP (viral failure in 0 vs 42%; *P*=0.001). With treatment started >6 months postpartum, there was no difference in response (92% vs 88%) (*N Engl J Med* 2007;356:135).

CESAREAN SECTION:

■ TABLE 4-22: **Rates and Results of Cesarean Section to Prevent HIV Infection in Europe and the U.S.**

	Europe* *n* = 1579	U.S.† *n* = 1398
Mode of Delivery		
Vaginal	369 (23%)	1098 (79%)
Elective C-section	971 (61%)	108 (8%)
HIV transmission		
Vaginal	24/369 (6.5%)	38/1398 (3.5%)
C-section (elective)	16/971 (1.7%)	1/108 (1%)

* *Clin Infect Dis* 2005;40:458

† *J Acquir Immune Defic Syndr* 2005;38:87

Elective cesarean section performed to prevent perinatal transmission should be done at 38 weeks instead of the usual 39 weeks.

BREASTFEEDING: The risk of HIV transmission with breastfeeding is 10%-16% (*J Infect Dis* 1996;174:722; *JAMA* 2000;283:1167; *Lancet* 1992;340:385; *JAMA* 2000;283:1175). The risk appears to be greatest in the first 4 to 6 months (*JAMA* 1999;282:744). The risk is increased 2-fold with mastitis and 50-fold with a breast abscess. Other risk factors include cracked nipples, infant with thrush, primary HIV infection during pregnancy, and prolonged breastfeeding. Breastfeeding is consequently discouraged for HIV-infected women in the developed world; the issue is more complex in developing countries, where breastfeeding is critical for infant nutrition and survival (*JAMA* 2000;238:1167). It is estimated, for example, that 1.7 million babies develop HIV each year due to breastfeeding but that 1.5 million babies would die each year if not breastfed (*Br Med J* 2001;322:511).

SAFETY OF ANTIRETROVIRAL THERAPY : Existing data support the safety of all commonly used antiretroviral agents in pregnancy except ddI + d4T, EFV, and hydroxyurea (*J Acquir Immune Defic Syndr* 2000;25:306; *MMWR* 2002;51[RR-7]:1; *N Engl J Med* 2002;346:1879). The combination of **ddI + d4T** should be avoided or used cautiously due to reports of 3 maternal deaths ascribed to lactic acidosis and/or hepatotoxicity. **EFV** should be avoided in the first trimester due to neural tube defects in 3/20 monkeys and neural tube defects in 5 infants born to women exposed in the first trimester of pregnancy (EFV package insert). Safety in the second and third trimesters is not established. EFV exposures should be reported to the Pregnancy Registry (contact information on next page). **NVP** appears safe when given at delivery (*J Acquir Immune Defic Syndr* 1999;354:795) but shows high rates of hepatotoxicity, including fatal hepatic necrosis and death when given to pregnant women with a CD4 count >250/mm^3 (see Nevirapine). **TDF** given in high doses to gravid monkeys caused a reduction in body length and reduction in insulin-like growth factor (*J Acquir Immune Defic Syndr* 2002;29:207). A report from France suggested mitochondrial toxicity with neurologic sequelae in 8 of 1754 infants exposed to **AZT** alone or AZT/3TC *in utero* (*Lancet* 1999;354:1084). Evaluation of over 16,000 infants exposed to AZT *in utero* has not confirmed the report and showed no evidence of immunologic, cardiac, oncogenic, or neurologic consequences (*N Engl J Med* 2000;3:805). The conclusion is that AZT exposure *in utero* causes mitochondrial toxicity in ≤0.3% (*N Engl J Med* 2002;346:1879). Rodent studies show an increase in vaginal tumors but only at 30x the size-adjusted dose in humans (*J Nat Cancer Inst* 1997;89:1602). There are no supporting data in humans (*J Acquir Immune Defic Syndr* 1999;20:43). A recent study from the Pregnancy Registry suggested a relationship between AZT exposure in the first trimester and hypospadius (*J Acquir Immune Defic Syndr* 2006;PMID 17159659). Liquid **APV** contains large quantities of propylene glycol and should be avoided in pregnancy.

THE ANTIRETROVIRAL PREGNANCY REGISTRY

Antiretroviral Pregnancy Registry
Research Park, 1011 Ashes Drive
Wilmington, NC 28405
Toll-free from US and Canada (800) 258-4263
Fax (800) 800-1052
From other countries (910) 256-0238
www.apregistry.com

The purpose of the registry is to detect major teratogenic effects of antiretroviral agents. The summary from January 1, 1989 to July 31, 2004 showed 110 outcomes with birth defects among 4391 live births

(2.5/100), which is similar to 3.1/100 rate in the CDC population-base surveillance system. First trimester exposures compared to second- and third-trimester exposures also showed no significant difference (3.1/100 vs. 2.2/100 live births). The largest experience is with AZT (2.8%) and 3TC (3.0%). The sample size was large enough to have detected a 2-fold increase in birth defects, but none was noted (www.apregistry.com, accessed Jan. 18, 2007).

PHARMACOLOGY: All NRTIs and NVP cross the placenta; PIs cross poorly (*AIDS* 2002;16:889). Passage of antiretrovirals into breast milk is assumed; it is established for AZT, 3TC, and NVP. NFV shows favorable pharmacokinetics with 1250 mg bid. SQV/RTV also shows favorable pharmacokinetic results in pregnancy (*HIV Clin Trials* 2001;2:460). These studies were done with *Fortovase* in the regimen of 800/100 mg bid. It assumed that *Invirase* will be similar, but this is not established. Other PIs either show low serum levels during the third trimester of pregnancy (IDV, LPV, RTV) or have not been adequately studied (ATV, APV, FPV) (*AIDS* 2003;17:1195; *N Engl J Med* 2002;346:1879).

REGIMEN DISCONTINUATION: Discontinuation of EFV- or NVP-based HAART is complicated by the long half-lives of these drugs, giving a prolonged period of monotherapy with the risk of resistance.

ISSUES FOR DEVELOPING COUNTRIES (*Lancet* 2002;359:992): The rate of perinatal transmission without intervention is 19% to 36% (*AIDS* 2001;15:379). The prevalence of HIV in pregnant women in some locations is as high as 25%. Antiretroviral drugs, including AZT, AZT + 3TC and NVP ± AZT/3TC, have established merit in preventing perinatal transmission and are cost-effective (*Br Med J* 1999;318:1650). Nevertheless, there is concern about resistance consequences of these regimens. For AZT, resistance requires 4 to 6 months, and AZT-resistant strains are infrequently transmitted (*Clin Infect Dis* 1995;20:1321; *J Infect Dis* 2001;183:1688; *AIDS* 1998;12:2281). By contrast, 3TC and NVP may develop high-level resistance rapidly and with a single mutation. In trials of single-dose NVP, up to 80% of women had NVP-resistant virus at 6 weeks postpartum that was detected at a much lower frequency of 6 months post partum (see NVP, pp. 118-119) 12 months. The obvious concern is the archiving of resistant strains that could limit subsequent HAART response, both in individual patients and on a population basis (*J Acquir Immune Defic Syndr* 2003;34:308). The high rate of virologic failure in women exposed to NVP during delivery compared to those not exposed supports this concern (*N Engl J Med* 2004;351:229). However, the most recent reports suggest that NVP-based HAART started after 6 months postpartum shows virologic response rates are comparable for women who did and did not receive intrapartum NVP (*N Engl J Med* 2007;356:135).

Adverse Effects of Antiretroviral Agents

GI INTOLERANCE: Nausea and vomiting associated with early pregnancy may complicate drug administration or exacerbate the GI side effects of HAART regimens. Possible solutions are delay in initiation of antiretroviral therapy or temporary suspension of treatment.

HYPERGLYCEMIA: Some PIs are associated with insulin resistance, and gestational diabetes is a concern with pregnancy. Some authorities advocate a glucose tolerance test with a 50-gm glucose load in early pregnancy with retesting at 24 to 28 weeks' gestation.

MITOCHONDRIAL TOXICITY: Pregnancy is associated with increased susceptibility to mitochondrial toxicity with lactic acidosis (*N Engl J Med* 1999;340:1723; *Semin Perinatol* 1999;23:100), so caution is advised when using d4T, ddI, and, to a lesser extent, AZT with respect to this complication.

NEVIRAPINE: This drug has been widely advocated for pregnant women based on extensive experience, but most support is for single-dose treatment to prevent perinatal transmission at delivery. NVP is associated with severe rashes and symptomatic hepatitis including death in at least 6 pregnant women (*J Acquir Immune Defic Syndr* 2004;36:772). Most severe rash reactions and liver toxicity occur in the first 6-18 weeks. The risk of symptomatic hepatitis is up to 11% in women who initiate NVP with a CD4 count >250/mm^3, so the drug should be avoided in this group. With lower CD4 counts the drug may be given with careful monitoring in the first 18 weeks to detect hepatotoxicity (transaminase levels), rash, fever and GI symptoms. Women already receiving NVP should simply continue it.

ACTG 076 Protocol (*MMWR* 2002;51[RR-7]:1)

ANTEPARTUM: AZT 300 mg bid or 200 mg tid from week 14 to delivery*

INTRAPARTUM: AZT IV 2 mg/kg 1st hour, then 1 mg/kg/hour until delivery

POSTPARTUM: AZT syrup, 2 mg/kg q6h (or 1.5 mg/kg q6h IV) x 6 weeks for the infant

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* Even when AZT resistance or AZT intolerance requires use of alternative drugs, the mother should receive IV AZT intrapartum, and oral AZT should be given to the infant (DHHS Guidelines, April 7, 2005).

SCENARIOS

- **No prior HIV therapy**
  - Standard clinical, immunologic, and virologic testing
  - VL >1000 c/mL: HAART including the 3-part AZT regimen of PACTG 076 (usually AZT/3TC + NFV or SQV/r)
  - VL <1000 c/mL: May give HAART or AZT only using the PACTG protocol
  - May delay initiation of therapy to 10-12 weeks gestation
- **HIV-infected women receiving antiretroviral therapy**
  - First trimester: counsel on benefits and risks of antiretroviral therapy. If therapy is stopped in the first trimester, discontinue all drugs simultaneously; note precautions with NNRTIs.
  - Include AZT in the regimen according to the PACTG 076 protocol after the first trimester when feasible.
- **Presents postpartum**
  - Infant should receive 6-week course of AZT per ACTG 076 protocol, starting ASAP.
  - Mother should have standard evaluation for HIV.
  - Infant should have HIV testing.

MONITORING DURING PREGNANCY: CD4 counts, viral load, and resistance tests should be performed according to standards for non-pregnant patients.

■ TABLE 4-23: **Treatment Options for Women who Present in Labor and Untreated**

Regimen	Maternal	Infant
NVP/AZT	AZT: 2 mg/kg IV bolus, then 1 mg/kg/h NVP: 200 mg at onset of labor	AZT – 2 mg/kg PO q 6 h x 6 wks + NVP – 2 mg/kg PO at 48-72 h (single dose)†

* AZT for infants <35 wks gestation: give 1.5 mg/kg IV or 2 mg/kg PO q 12 h, then q 8 h and 2-4 wks

† If NVP <1 h prior to delivery, first infant dose should be given ASAP after birth and second infant dose at 48-72 h.

■ TABLE 4-24: **Safety of Antiretroviral Agents in Pregnancy (Adapted from *Guidelines for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the U.S., Oct. 10, 2006; www.aidsinfo.nih.gov/)***

Anti-retroviral Drug	FDA Cate-gory*	Placental Passage Newborn:Maternal Drug Ratio	Long-term Animal Carcinogenicity Studies	Rodent Teratogen
AZT	C	Yes (human) [0.85]	Positive (rodent, vaginal tumors)	Positive (near-lethal dose)
ddC	C	Yes (rhesus) [0.3-0.50]	Positive (rodent, thymic lymphomas)	Positive (hydrocephalus at high dose)
ddI	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
d4T	C	Yes (rhesus) [0.76]	Positive (high doses only)	Negative (but sternal bone calcium decreases)
3TC	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
FTC	B	Unknown	Negative for carcin	Negative
ABC	C	Yes (rats)	Positive (multiple timors in rodents)	Positive (anasarca and skeletal malformations at 1,000 mg/kg, 35 x human exposure, during organogenesis)
TDF	B	Yes (rats and monkeys)	Positive (liver adenomas in mice at high doses)	Negative

Continued.

■ TABLE 4-24: **Safety of Antiretroviral Agents in Pregnancy (Adapted from *Guidelines for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the U.S., Oct. 10, 2006; www.aidsinfo.nih.gov/*) *(Continued)***

Anti-retroviral Drug	FDA Cate-gory*	Placental Passage Newborn:Maternal Drug Ratio	Long-term Animal Carcinogenicity Studies	Rodent Teratogen
SQV	B	Minimal (human)	Negative	Negative
IDV	C	Minimal (human)	Positive (thyroid adenomas)	Negative (but extra ribs in rats)
RTV	B	Minimal (human)	Positive (rodent liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rats at maternally toxic doses)
NFV	B	Minimal (human)	Not completed	Negative
NVP	C	Yes (human) [~1.0]	Positive (hepatic adenomas and cancer)	Negative
EFV	D	Yes (cynomolgus monkeys, rats, rabbits) [~1.0]	Positive (liver adenomas and cancer in female mice)	Anencephaly; anophthalmia; microphthalmia (cynomolgus monkeys)
LPV/r	C	Unknown	Positive (liver adenomas and cancer in mice)	Negative (but delayed ossification and increase in skeletal variations in rats at maternally toxic doses)
ATV	B	Unknown	Positive (adenomas in female mice)	Negative
DRV	B	No studies	Negative in rodents	Negative in rodents
TPV	C	Unknown	Not completed	Negative, but decreased bone formation in mice

* See pregnancy categories.

Postexposure Prophylaxis (PEP)

Occupational Exposure

RISK OF TRANSMISSION (*MMWR* 2005;54:RR-9)

- A total of 23 studies of needle sticks among health care workers (HCWs) demonstrate HIV transmission in 20 of 6,135 (0.33%) exposed to an HIV-infected source (*Ann Intern Med* 1990;113:740). With mucosal surface exposure, there was one transmission among 1,143 exposures (0.09%), and there were no transmissions among 2,712 skin exposures. As of June 2005, there were a total of 57 HCWs in the United States who had occupationally acquired HIV infection as indicated by seroconversion in the context of an exposure to an HIV-infected source. This group includes six HCWs who received PEP using recommended regimens initiated within 2 h after exposure. An additional 136 HCWs who had possible occupationally acquired HIV did not have documented seroconversion in the context of an exposure (*N Engl J Med* 2003;348:826). Occupations among 56 confirmed cases: nurses (23), laboratory technicians (20), and physicians (6). All transmissions involved blood or bloody body fluid except for three involving laboratory workers exposed to HIV viral cultures. Exposures were percutaneous in 48, mucocutaneous in 5, and both in 2 cases. To date, there are no confirmed seroconversions in surgeons and no seroconversions with exposures to a suture needle.
- A retrospective case-control study of needlestick injuries from an HIV-infected source by the CDC included 33 cases who seroconverted and 739 controls (MMWR 1996;45:468; N Engl J Med 1997;337:1485). The risks for seroconversion included: 1) deep injury; 2) visible blood on the device; 3) needle placement in a vein or artery; and 4) a source with late-stage HIV infection (presumably reflecting high viral load). There was also evidence that AZT prophylaxis was associated with a 79% reduction in transmission rates. Nevertheless, there are at least 21 cases of failures with PEP prophylaxis (N Engl J Med 2003;348:826).

■ TABLE 4-25: **Risk of Viral Transmission with Sharps Injury from Infected Source**

Source		Prevalence (U.S. general population)	Risk/exposure with sharps injury
HIV		10-20%	0.3%
HBV	HBsAg	5-8%	1-6%*
	HBeAg		22-31%*
HCV		<1%	1.9%

* Unvaccinated HCW

- **AZT efficacy**: The efficacy of AZT prophylaxis was examined by the CDC in a retrospective case control study which showed a 79% reduction in HIV transmission (OR 0.19). This study was done prior to the HAART era, it is "highly unlikely that a placebo-controlled trial will ever be conducted", and the success of combination therapy for treatment suggests combination treatment should be used for PEP (Cochrane Database Syst Rev 2007; CD002835). Nevertheless at least 21 cases of PEP failure have been reported (N Engl. J Med 2003; 348:826).

PEP RECOMMENDATIONS AND CHOICE OF REGIMEN: Recommendations are based on the type of exposure, HIV status of the source, or, if the status is unknown, the risk status of the source.

MANAGEMENT RESOURCES

- National Clinicians' Postexposure Prophylaxis Hotline (AETC, CDC) (available at all times): 888-448-4911 or http://www.ucsf.edu/hivcntr/
- Hepatitis information line: 888-443-7232 or http://www.cdc.gov/hepatitis
- CDC Reporting (occupationally acquired HIV and PEP failure): 800-893-0485 or www.cdc.gov/ncidod/dhqp/gl_occupational.html
- FDA: To report unusual or severe toxicity of antiretrovirals: 800-332-1088 or http://www.fda.gov/medwatch
- HIV/AIDS treatment information: http://www.aidsinfo.nih.gov

■ TABLE 4-26: **HIV Postexposure Prophylaxis for Percutaneous Injuries**

Exposure	Status of Source		
	HIV + and Low Risk*	HIV + and High Risk*	Unknown
Not severe: Solid needle, superficial	2-drug PEP†	3-drug PEP†	Usually none; consider 2-drug PEP‡
Severe: Large bore, deep injury, visible blood in device, needle in patient artery/vein	3-drug PEP†	3-drug PEP†	Usually none; consider 2-drug PEP‡

* Low risk: Asymptomatic HIV or VL <1,500 c/mL. High risk: Symptomatic HIV, AIDS, acute seroconversion, and/or high VL.

† Concern for drug resistance: Initiate prophylaxis without delay and consult an expert.

‡ Consider 2-drug PEP if source is high risk for HIV or exposure is from an unknown source with HIV infection likely.

■ TABLE 4-27: **HIV Postexposure Prophylaxis for Mucous Membranes and Non-intact Skin Exposures***

Exposure	Status of Source		
	HIV + and Low Risk†	HIV + and High Risk†	Unknown
Small volume (drops)	Consider 2-drug PEP	2-drug PEP	Usually no PEP; consider 2-drug PEP‡
Large volume (major blood splash)	2-drug PEP	3-drug PEP	Usually no PEP; consider 2-drug PEP‡

* Non-intact skin: Dermatitis, abrasion, wound

† Low risk: Asymptomatic or VL <1500 c/mL. High risk: Acute seroconversion or high VL.

‡ Consider if source has HIV risk factors or exposure from unknown source where HIV-infected source is likely.

- **Two-drug regimens:** AZT/3TC (coformulated), AZT/FTC, d4T/3TC, d4T/FTC, TDF/3TC, TDF/FTC (coformulated)
- **Three-drug regimens:** Two NRTIs (above) plus LPV/r; **Alternatives:** SQV/r, ATV/r, ATV, IDV/r, or EFV
- **Drugs not recommended:** NVP, ABC, DLV, ddC

■ TABLE 4-28: **Drugs for PEP**

Agent	Comment
Nucleoside Analogs	
AZT	Only drug with established efficacy; note high rates of GI intolerance, fatigue and headache; monitor CBC
3TC	In most regimens due to good tolerability, potency, and qd dosing; may need to check for 184V/I resistance in source
d4T	Potent; good short-term tolerability; avoid combining with AZT
ABC	Concern for hypersensitivity reaction (reported in 5-9%)
ddI	Concerns are fasting requirement and GI intolerance
TDF	Well tolerated, effective for PEP in primate model, benefit of qd dosing
FTC	Similar to 3TC
Non-nucleoside RTIs	
EFV	Potent, but concern for short-term CNS toxicity in HCW
NVP	Avoid: FDA has reports of 22 PEP recipients with serious reactions to NVP, including 12 hepatotoxicity cases (one requiring a liver transplant) and 14 skin reactions, including 3 with Stevens Johnson syndrome
Protease Inhibitors	
LPV/r	Potent and favored among PIs; note food requirement and probable diarrhea
ATV ± RTV	Potent, well tolerated, qd dosing, boosted well with RTV; note food requirement, risk of jaundice, boosting requirement for TDF, multiple drug interactions
NFV	Well tolerated except for diarrhea that usually responds to fiber supplements or antidiarrheal agents; requires fatty food for absorption
FPV ± RTV	Potent, reliatively low pill burden, option of once-daily therapy; no food effect
IDV/r	Note need for q 8 h dosing unless boosted with RTV; note need for food, ≥1.5 L fluid/day, risk of nephrolithiasis
SQV/r	Potent, option for once daily therapy
Entry Inhibitors	
ENF	Some theoretical advantages with blocking entry, but no experience in PEP and requirement for time-consuming reconstitution and SC injection

TESTING IN THE SOURCE PATIENT: If there is no recent positive or negative serology, a rapid test is preferred. Results should be available in <1 h. Rapid tests are as reliable as standard serology for excluding HIV infection (false negatives in "window" period), and testing is highly cost effective in preventing unnecessary empiric short-term courses of antiretroviral agents (*Infect Control Hosp Epidemiol* 2001;22:289). Standard serologic tests may take 3 to 7 days, but a negative EIA

screening assay is usually available in 24 to 48 hours and is adequate for the decision to discontinue PEP if the rapid test is not available. The CDC recommends opt-out HIV testing, which should facilitate testing the source, although many states have laws that require counseling and signed informed consent (*MMWR* 2006;44:RR14). If the source has had an illness compatible with acute HIV syndrome, testing should include plasma HIV RNA levels.

MONITORING AND COUNSELING THE HCW (HEALTH CARE WORKERS)

- **Testing the HCW:** HIV serology should be performed at the time of injury, and repeated at 6 weeks, 3 months, and 6 months. It should be repeated at 12 months in HCW who acquired HCV with the injury, since this may delay HIV seroconversion (*N Engl J Med* 2003;348: 826; *Am J Infect Control* 2003;31:168).
- **Viral load:** VL testing is sometimes done because HIV viremia precedes positive serology, but is not recommended due to high rates of false positives (*J Infect Dis* 2004;190:598). Confine VL testing to patients with a febrile illness consistent with the acute retroviral syndrome.
- **Precautions to prevent sexual transmission:** The HCW should be advised to practice safe sex or abstain until serology is negative at 6 months postexposure. The greatest risk is the first 6 to 12 weeks, and many authorities recommend these precautions only to the 3-month test.
- **Time:** PEP should be initiated as quickly as possible, preferably within 1 to 2 hours of exposure and up to 36 hours postexposure. The median time from exposure to treatment in 432 HCWs with HIV exposure from October 1996 to December 1998 was 1.8 hours (*Infect Control Hosp Epidemiol* 2000;21:780).
- **Side effects:** For HCWs who receive PEP, about 74% experience side effects, primarily nausea (58%), fatigue (37%), headache (16%), vomiting (16%), or diarrhea (14%). About 50% discontinue treatment before completion of the 4-week course due to multiple factors including side effects of drugs (*Infect Control Hosp Epidemiol* 2000;21:780). A similar experience with PEP was reported from France, where ADRs occurred in 85%, most commonly GI intolerance (*Clin Infect Dis* 2001; 32:1494)
- **Pregnancy:** EFV, TDF, and the combination of ddI + d4T should be avoided in pregnancy. The favored agents for HCWs who are pregnant are summarized on Table 4-21. Note that some authorities delay initiating ART in pregnant women with established HIV infection due to concerns about toxicity of these drugs. In each case there needs to be a risk-benefit assessment, preferably by an HIV expert. CDC guidelines state that pregnancy should not preclude

ART. Counseling non-pregnant HCWs with childbearing capacity should include a discussion of these risks and the limited data regarding safety of many antiretroviral agents, especially during the first trimester. Drugs from the Pregnancy Registry with the most extensive data to establish safety in pregnancy are AZT, 3TC, and d4T.

- **Breastfeeding:** Consider temporary discontinuation of breastfeeding during antiretroviral therapy.
- **Resistance testing:** Guidance for drug selection based on anticipated resistance mutations may be available from prior resistance tests in the source. This testing may also be done in the source at the time of injury if there is an adequate VL, although the time required for test results mandates rapid institution on the basis of empiricism or anticipated resistance according to prior test results or drug history and virologic response. Most authorities recommend that decisions be based on the drug history and viral load of the source. In a review of 52 patients who were the source of occupational exposures, 39% involved stains with major mutations conferring resistance (*N Engl J Med* 2003;348:826). This is another issue for which assistance from an HIV expert is appropriate.

HEALTH CARE WORKER-TO-PATIENT TRANSMISSION

- **History:** This became a topical issue in 1990 a Florida dentist was identified as the source of HIV infection for 6 dental patients (*Ann Intern Med* 1992;116:798; *Ann Intern Med* 1994;121:886). The source of the virus was established by genetic sequencing (*J Virol* 1998;72:4537), but the mechanism of transmission was never established. This disclosure led to a series of "look-backs" in which serologic tests were performed on >22,000 patients who received care from 59 health providers with known HIV infection. No transmissions were identified (*Ann Intern Med* 1995;122:653). Since this time, there have been 2 additional cases in France, one traced to a total hip procedure and the other to a C-section (*Ann Intern Med* 1999;130:1). As of 2002, totals for known transmissions from infected surgeon to patient are 375 for HBV and 7 for HCV (*Hosp Infect Control* 2003;7:88).
- **Management of HIV-infected HCW**
  - Concern about the incident with the Florida dentist led to a federal law in 1991 requiring states to establish guidelines for HIV-positive HCWs. Most states adopted CDC recommendations that required persons who perform "exposure-prone invasive procedures" (surgery in a blind body cavity) to 1) advise the patient of the HCW's serostatus and 2) obtain written informed consent from the patient. This applies to surgeons, nurses, and other members of the operating team.

- A review by Julie Gerberding, an expert in this topic and Director of the CDC, did not mention these recommendations in her review of management of HIV-infected HCW (*Ann Intern Med* 1999;130:64), but emphasized that patients who have exposures analogous to what would be defined as a potentially high-risk occupational exposure from a HCW should be managed by standard guidelines with respect to counseling, serologic testing, and antiretroviral therapy. Concerns are that such disclosure is illegal and unethical for the HCW regarding patient confidentiality issues, but the reverse is not true; the result may be a truncated career despite a risk that is virtually nonexistent. Few hospitals actively endorse these guidelines and many are unaware they exist (*Hosp Infect Control* 2003;7:88).

OCCUPATIONAL EXPOSURE TO HEPATITIS B VIRUS (HBV)

- **Efficiency of transmission:** Highly dependent on vaccine status of HCW and the HBeAg status of the source.
- **HBV postexposure prophylaxis:** Recommendations are based on the vaccine status of the healthcare worker, evidence of serologic response (anti-HBs levels >10 mIU/mL), and the HBsAg status of the source. Responder status of the HCW is best assessed with serology at 1-6 months after completion of the 3-dose series. Response is age-related: 95% for persons 20 to 30 years of age, 86% at 40 to 50 years of age, and 45% at ≥65 years of age. Titers decrease an average of 10%/year, but prior responders with antibody titers >10 mIU/mL are probably protective. Non-responders have a 55% probability of response to re-vaccination.
- **Vaccine efficacy:** 80% to 95% when considering all vaccine recipients; 99% for responders.

■ TABLE 4-29: **HBV Postexposure Prophylaxis**

Vaccination Status of HCW	HBsAg Status of Source	
	HBsAg Positive	**Source Unknown**
Unvaccinated	HBIG* + vaccine series (3 doses)	HBV vaccine (3 doses)
Vaccinated		
Responder†	No Rx	No Rx
Non responder	HBIG x 1 + vaccine series or HBIG x 2‡	Rx as source positive if high risk
Antibody status unknown	Test for anti-HBs ■ Anti-HBs >10 mIU/mL – no Rx ■ Anti-HBs <10 mIU/mL – HBIG x 1 + vaccine booster	Test for anti-HBs ■ Anti-HBs >10 mIU/mL – no Rx ■ Anti-HBs <10 mIU/mL – HBV vaccine series with titer at 1-2 mo

* HBIG = Hepatitis B immune globulin; dose is 0.06 mL/kg IM. Should be given as soon as possible and within 7 days.

† Responder defined by antibody to HBsAg of >10 mIU/mL.

‡ HBIG + the vaccine series is preferred for non-responders who did not complete the 3-dose series; HBIG x 2 doses is preferred if there were 2 vaccine series and no response.

OCCUPATIONAL EXPOSURE TO HEPATITIS C VIRUS (HCV)

- Efficiency of transmission: A review of 25 studies published from 1991 to 2002 found that the rate of HCV transmission following a sharps injury from an HCV-infected source was 44/2357 (1.9%) (*Clin Microbiol Rev* 2003;16:546). Cutaneous exposure to contaminated blood with intact skin does not appear to confer risk.
- **Seroprevalence of HCV (U.S.):** General population, – 1.8%; HCW – 0.5% to 2%; gay men – 2% to 6%; hemophilia patients – 60% to 90%; injection drug users – 60% to 90%.
- **HCV postexposure management**
  - Source testing: Anti-HCV; confirm positives with qualitative PCR
  - HCW: Anti-HCV and ALT at baseline and at 3 to 6 months. Confirm positive serology with qualitative PCR.
  - HCV RNA may be tested at 4 to 6 weeks to detect acute HCV prior to seroconversion. Persons with documented acute HCV infection should have positive quantitative HCV PCR at 2-4 weeks, usually accompanied by asymptomatic elevation of ALT. This precedes anti-HCV seroconversion.
  - No prophylaxis with immune globulin (*Clin Infect Dis* 1993;16:335) or with antiviral agents (interferon + ribavirin) is recommended (*Clin Infect Dis* 1993;16:335; *J Infect Dis* 1996;173:822; *Clin Microbiol Rev* 2003;16:546).

- **Management of patients with occupationally acquired HCV:** Postexposure monitoring with HCV PCR will detect early seroconversion. A controversial issue at this juncture is the utility of treatment with peginterferon + ribavirin. One report from Germany showed a high rate of HCV cure with treatment of acute HCV (*N Engl J Med* 2001;345:1452) and others have had a similar experience in 5/6 HCWs with occupationally acquired HIV (*Infection* 2005;33:30). Nevertheless, this tactic has received varying degrees of endorsement (*Infect Control Hosp Epidemiol* 2001;22:53). The major concerns are the drug-associated toxicity for treatment of an infection that has a 20% to 40% probability of spontaneous clearance (*Hepatology* 2001;34:341; *Hepatology* 2002;S195; *Hepatology* 2001;34:341; *Hepatology* 2002;36:1020), the relatively benign long-term prognosis in persons without additional risk factors (*Hepatology* 1999;29:908), and the lack of data to show treatment at this stage is superior to standard guidelines for management of chronic infection (*Clin Microbiol Rev* 2003;16:546). Treatment in the acute phase should therefore be considered experimental. This strategy is also endorsed by the European guidelines (*Euro Surveill* 2005;10:260).

Non-occupational HIV Exposure (Sexual Contact or Needle Sharing)

RISK OF TRANSMISSION

■ TABLE 4-30: **Risk of HIV Transmission with Single Exposure from an HIV-Infected Source**

Exposure	Source	Risk/10,000 exposures
Blood transfusion	Donegan E, *Ann Int Med* 1990;113:733	9,000
Needle-sharing IDU	*J Acquir Immun Defic Syndr* 1995;10:175	67
Receptive anal intercourse	*Br Med J* 1992;304:809	50
Needlestick injury	*Am J Med* 1997;102:9	30
Receptive vaginal intercourse	*Br Med J* 1992;304:809 *Sex Transm Dis* 2002;29:38 *Am J Epid* 1998;148:88	10
Insertive anal intercourse	*Br Med J* 1992;304:809 *Sex Transm Dis* 2002;29:38	6-7
Insertive vaginal intercourse	*Br Med J* 1992;304:809 *Sex Transm Dis* 2002;29:38	5

■ TABLE 4-31: **Risk of HIV Transmission in 415 Untreated Discordant Couples (*N Engl J Med* 2000;342:921)**

Viral Load	Transmissions/100 Person-years
<400 c/mL	0
400-3,500 c/mL	4.8
3,500-50,000 c/mL	14.0
>50,000 c/mL	23.0

- **Follow-up:** A more recent report indicated the risk was greatest with acute HIV infection when the VL was highest (0.008/coital act in 5 months after conversion compared to 0.0007/coital act in 8 year with chronic infection; *J Infect Dis* 2005;191:1403).

CDC RECOMMENDATIONS (*MMWR* 2004;54[RR-2:1])

Recommendations are based to a large extent on probability of HIV infection in the source, the ability to deliver PEP within 72 hours of exposure and the type of exposure. The recommendations are summarized in the following table.

■ TABLE 4-32: CDC Recommendations for HIV Prophylaxis After Non-occupational Exposure (nPEP)

nPEP is recommended if there is substantial risk of exposure within 72 hours and:

1. Eposure of vagina, rectum, eye, mouth, other mucosal surface, nonintact skin or subcutaneous ***and***
2. Exposure with: Blood, semen, vaginal secretions, rectal secretions, breast milk, bloody fluid ***and***
3. From: Source likely to be infected ***and***
4. Time from exposure: <72 hours

nPEP is not recommended if there is:

1. Delay >72 hours from time of exposure ***or***
2. Negligible risk based on exposure with: urine, nasal secretions, saliva, sweat or tears if not visibly contaminated with blood (regardless of HIV status of source)

nPEP recommended on case-by-case basis if:

1. Substantial risk exposure (defined above)
2. Within 72 hours of exposure ***and***
3. Source patient HIV status unknown

Recommended regimens:

The recommendations follow the 10/29/04 recommendations of DHHS guidelines for initial treatment of HIV infection, with the exception that NVP has been removed from the list.

Preferred regimens

- EFV* + (3TC or FTC) + (AZT or TDF)
- LPV/r + (3TC or FTC) + AZT

Alternative regimens

- EFV* + (3TC or FTC) + (ABC, ddI, or d4T)
- ATV + (3TC or FTC) + (AZT d4T, ABC, or ddI) or (RTV 100 mg/d + TDF)
- FPV + (3TC or FTC) + (AZT or d4T) or (ABC, TDF, or ddI)
- FPV/r + (3TC or FTC) + (AZT d4T, ABC,TDF, or ddI)
- IDV/r + (3TC or FTC) + (AZT d4T, ABC,TDF, or ddI)
- LPV/r + (3TC or FTC) + (d4T, ABC, TDF, or ddI)
- NFV + (3TC or FTC) + (AZT or d4T, ABC, TDF, or ddI)
- SQV/r + (3TC or FTC) + (AZT, d4T, ABC, TDF, or ddI)
- ABC + AZT + 3TC (*Trizivir*)

*Avoid in pregnancy

■ TABLE 4-33: **Recommended Tests on Exposed Person and Source**

Exposed Person	Baseline	During PEP	4-6 wks	3 mo	6 mo
HIV serology	+		+	+	+
FBC/LFT/BUN or creatinine	+	+			
STD (GC, chlamydia, syphilis)	+	+*	+*	–	–
HBV	+	–	+*	+*	–
HCV	+	–	–	+	+
Pregnancy	+	+*	+*		
If HIV seroconversion					
HIV viral load			+	+	+
Resistance test			+	+	+
CD4 count			+	+	+

* As clinically indicated

For source, tests at baseline: HIV serology, STD screen (GC, *C. trachomatis*, and syphilis), HBVsAg, HCV Ab

5 | Drug Information

DRUG PROFILES are listed alphabetically by generic drug names.

TRADE NAME and pharmaceutical company source are provided unless there are multiple providers.

COST The prices that are quoted are the single exit price and were correct at time of going to press. If generics are available the prices are also quoted.

Access priced drugs available in South Africa will also be included if applicable. These are drugs supplied by manufacturer who originally registered the drug.

PHARMACOLOGY, SIDE EFFECTS, AND DRUG INTERACTIONS: Data are from Drug Information 2006, American Hospital Formulary Service, Bethesda, MD; *PDR* 2006.

CREATININE CLEARANCE

- **Males:** $\frac{\text{Weight (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/dL)}}$
- **Females:** Determination for males x 0.85
- **Obese patients:** Use lean body weight.
- **Formula assumes stable renal function.** Assume creatinine clearance (CrCl) of 5-8 mL/min for patients with anuria or oliguria.
- **Pregnancy and volume expansion:** GFR may be increased in third trimester of pregnancy and with massive parenteral fluids.

Access to Antiretroviral therapy is provided to all South Africans though the Operational Comprehensive HIV/AIDS care, management and treatment plan for South Africa. Gauteng province began the program in April 2004.To date there are over 300 accredited sites providing antiretroviral therapy to 280 000 HIV infected South African. In addition, there are 100 000 individuals who access their treatment through private medical finding

CLASSIFICATION FOR DRUG USE IN PREGNANCY BASED ON FDA CATEGORIES: Ratings range from "A" for drugs that have been tested for teratogenicity under controlled conditions without showing evidence of damage to the fetus to "D" and "X" for drugs that are definitely teratogenic. The "D" rating is generally reserved for drugs with no safer alternatives. The "X" rating means there is absolutely no reason to risk using the drug in pregnancy.

Category	Interpretation
A	**Controlled studies show no risk.** Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	**No evidence of risk in humans.** Either animal findings show risk, but human findings do not, or, if no adequate human studies have been performed, animal findings are negative.
C	**Risk cannot be ruled out.** Human studies are lacking, and animal studies are either positive for fetal risk, or lacking as well. However, potential benefits may justify the potential risk.
D	**Positive evidence of risk.** Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
X	**Contraindicated in pregnancy.** Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

PREGNANCY REGISTRY FOR ANTIRETROVIRAL DRUGS: This is a joint project sponsored by staff from pharmaceutical companies with an advisory panel with representatives from the CDC, NIH obstetrical practitioners, and pediatricians. The registry allows anonymity of patients and birth outcome follow-up is obtained by registry staff. Healthcare professionals should report prenatal exposures to antiretroviral agents to: Antiretroviral Pregnancy Registry, Research Park, 1011 Ashes Drive, Wilmington, NC 28405; 800-258-4263; fax 800-800-1052; toll-free multilingual (Europe) 00800-5913-1359; (www.apregistry.com).

ABACAVIR (ABC)

TRADE NAME: *Ziagen* (GlaxoSmithKline)

CLASS: Nucleoside analog

FORMULATIONS, REGIMEN AND PRICE

- ***Ziagen***
  - Formulations: 300 mg tab
  - Regimen: 300 mg bid or 600 mg qd
  - Ziagen 300mg R 895,41 , 240 ml R339,13
  - Trizivir (ABC, AZT and 3TC) (300,300 and 150 mg) R1517.72
  - Kivexa (ABC And 3TC) also known as Epzicom. R922.26
- ***Trizivir*:** AZT/ABC/3TC (300/300/150 mg tab)
  - Regimen: 1 bid

FOOD: Take without regard for meals

RENAL FAILURE: ABC – no dose adjustment; *Trizivir*– not recommended with CrCl <50 mL/min; use separate components with dose adjustment

HEPATIC FAILURE: Standard dose for ABC, *Trizivir*. Based on limited clinical data, may use 200 mg bid for Child-Pugh class A. Contraindicated for classes B and C.

ADVANTAGES: Well tolerated, potent antiviral activity, once-daily therapy, no food effect

DISADVANTAGES: Hypersensitivity reaction in 5%-8% of patients; **Warning:** Avoid ABC/TDF/3TC combination alone due to high virologic failure rates.

POTENCY: With monotherapy, ABC reduced viral load 1.5-2.0 logs – significantly more than AZT, ddI, 3TC, and d4T.

■ TABLE 5-1: **Clinical Trials of ABC in Initial Therapy**

Study	Regimen	*N*	Dur (wks)	VL <50	VL <400
CNA 3014 *Curr Med Res Opin* 2004;20:1103	AZT/3TC/ABC	164	48	60%	66%*
	AZT/3TC/IDV	165		50%	50%
CNA 3005 *JAMA* 2001;285:1155	AZT/3TC/ABC	262	48	31%	51%
	AZT/3TC/IDV	265		45%*	51%
ABCDE 12th CROI, #587	AZT/3TC/EFV	237	96	61%*	
	d4T/3TC/EFV			48%	
ACTG 5095 *N Engl J Med* 2004;350:1850	AZT/3TC/ABC	382	48	61%	74%†
	AZT/3TC/EFV±ABC	765		83%*	89%†
CNA 30024 *Clin Infect Dis* 2004;39:1038	ABC/3TC/EFV	324	48	70%	
	AZT/3TC/EFV	325		69%	
CNA 30021 (ZODIAC) *J Acquir Immun Defic Syndr* 2005;38:417	ABC (qd)/3TC/EFV	384	48	66%	—
	ABC (bid)/3TC/EFV	386		68%	—
ESS 30009 (*J Infect Dis* 2005;192:1921)	ABC/TDF/3TC	102	12**		51%**
	ABC/3TC/EFV	169	48	71%	75%*
ESS 30008 (*J Acquir Immun Defic Syndr* 2005;40:422)	ABC/3TC (qd) + 3rd agent	130	48	82%	
	ABC/3TC (bid) + 3rd agent	130		81%	

* Superior to comparitor ($P<0.05$)

** Study terminated due to high failure rate; VL <50 c/mL at 12 wks was 17% (TDF) vs 50% (EFV).

† VL <200 c./mL

SWITCH STUDIES FOR LIPODYSTROPHY

- **The RAVE Study:** Patients with lipoatrophy attributed to AZT or d4T were switched to TDF or ABC; results with 105 patients at 48 weeks showed significant and comparable increases in limb fat with continued viral suppression (*AIDS* 2006;20:2043).
- **EES 40003:** 104 patients on PI-based HAART complicated by hyperlipidemia were switched to ABC ($n = 52$) or continued PI-based HAART ($n = 52$). Analysis at 28 weeks showed improved cholesterol levels in the ABC group and no changes in viral suppression, insulin resistance or waist-hip ratio (*BMC Infect Dis* 2005;5:2).

Comparison of AZT/3TC vs. ABC/3TC: CNA 30024 compared these two regimens, each with EFV, in 699 treatment-naïve patients. At 48 weeks VL was <50 c/mL in 69% and 70%, respectively, by ITT

analysis (*Clin Infect Dis* 2004;39:1038). ABC/3TC was associated with less anemia, nausea, and vomiting, but more hypersensitivity, than AZT/3TC. This paved the way to coformulation with *Kivexa*

Comparison of ABC/3TC qd vs. bid: ESS 3008 compared twice-daily vs. once-daily regimens in patients with viral suppression with ABC/3TC combined with a PI or NNRTI. Viral suppression was sustained at 48 weeks in 81% in the once-daily group vs. 82% in the twice-daily group. Adherence was better in the once-daily group. (*J Acquir Immune Defic Syndr* 2005;40:422).

***Trizivir* summary:** AZT/3TC/ABC (*Trizivir*) regimen was previously a preferred regimen for initial treatment in much of the world. However, ACTG 5095 demonstrated the superiority of EFV-based HAART compared to *Trizivir* (*N Engl J Med* 2004;350:1850). *Trizivir* is superior to other triple nucleoside regimens (see ESS 3009 study results in Table 5-1) and may be particularly useful in selected patients, including some with active tuberculosis or pregnancy. Disadvantages include the potential for the ABC hypersensitivity reaction, reduced potency compared to recommended HAART regimens, twice-daily dosing, the potential for broad NRTI cross-resistance when continued with persistent virologic failure, AZT-associated side effects, and the lack of advantage when AZT/3TC/ABC is used in place of AZT/3TC as the nucleoside backbone with EFV-based HAART (*JAMA* 2006;296:769). The combination of ABC and 3TC as a dual NRTI component of HAART is attractive due to convenience (1 pill daily), good tolerability, low potential for mitochondrial toxicity, and avoidance of thymidine analog mutations after failure; the disadvantages are the ABC hypersensitivity reaction, as well as the potential for development of the K65R or L74V mutations, with resulting cross-resistance to ddI in the case of L74V and to ddI and TDF in the case of K65R.

RESISTANCE: ABC selects primarily for 74V and, to a lesser extent, K65R. The 184V mutation by itself does not reduce *in vitro* or clinical activity, but when combined with 2 or 3 TAMs there is reduced activity, and with ≥4 TAMs there is no activity (*Topics HIV Med* 2006;14:125; *Antiviral Ther* 2004;9:37). Mutations at RT codons 65R and 74V lead to cross-resistance to ddI, and K65R leads to loss of susceptibility to TDF, especially when not accompanied by M184V. Each of these mutations results in a 2- to 4-fold decrease in susceptibility to ABC. Significant resistance requires multiple mutations, usually in addition to the 184V mutation. In combination with TDF there is selection for 65R (*Antimicrob Agents Chemother* 2004;48:1413). TAMs that accumulate via the 41/210/215 pathway cause higher-level ABC resistance than those in the 67/70/219 pathway.

PHARMACOLOGY

- **Bioavailability:** 83%; alcohol increases ABC levels by 41% (clinical significance unknown).

- **T½:** 1.5 h (serum); intracellular T½: 12-21 h. The active metabolite, carbovir triphosphate, has an intracellular half-life of >20 hours (*AIDS* 2002;16:1196). CSF levels: 27% to 33% of serum levels.
- **Elimination:** 81% metabolized by alcohol dehydrogenase and glucuronyl transferase with renal excretion of metabolites; 16% recovered in stool, and 1% unchanged in urine. Metabolism does not involve the cytochrome P450 pathway. Plasma clearance correlates with body weight, suggesting the possibility of suboptimal levels in patients with greater body weight (*Br J Clin Pharmacol* 2005;59:183).
- **Dose modification in renal failure:** None (*Nephron* 2000;87:186). *Trizivir* and *Epzicom* should not be used when CrCl <50 mL/min because of the need to reduce dosages of the AZT and 3TC components.

SIDE EFFECTS

- **Hypersensitivity reaction (Black box FDA warning):** In an analysis of 30,595 participants in clinical trials and expanded access programs, 1302 (4.2%) had definite or probable hypersensitivity reactions (HSRs), and 19 were lethal, for a mortality rate of 0.03% (3/10,000) (*Clin Ther* 2001;23:1603). Of the 19 deaths, 6 occurred with re-challenge. The median time of onset is 9 days; 90% occur in the first 6 weeks. Clinical features include fever (usually 39°C to 40°C), skin rash (maculopapular or urticarial), fatigue, malaise, GI symptoms (nausea, vomiting, diarrhea, abdominal pain), arthralgias, cough, and/or dyspnea. The rash occurs in 70% (*Clin Infect Dis* 2002;34:1137). Laboratory changes may include increased CPK, elevated liver function tests, and lymphopenia. Nearly all true hypersensitivity reactions have symptoms involving ≥2 organs (12th CROI, Boston, Feb. 2005, Abstr. 836). A more recent FDA review of 2670 ABC recipients in clinical trials indicated an incidence of 8% for investigator-defined HSR (12th CROI, Boston, Feb. 2005, Abstr. 835); none was fatal.

  Susceptibility to this reaction appears to be genetic and has been associated with HLA-B*5701 haplotype. **Africa:** <1%.

  Re-challenge with ABC in a patient with hypersensitivity always results in a reaction within hours and may resemble anaphylaxis in 20% with hypotension, bronchoconstriction, and/or renal failure (*AIDS* 1999:13:999). Treatment of reactions is supportive with IV fluids, ventilator support, dialysis, etc. Steroids and antihistamines are not effective. Re-challenge has been associated with death, but this is rare. Hypersensitivity reactions should be reported to the Abacavir Hypersensitivity Registry at 800-270-0425. For more information call 800-334-0089.

  Patients should be warned to consult their provider immediately if they note two or more of the hallmark symptoms, including fever, skin rash, typical GI symptoms, cough, dyspnea, and/or

constitutional symptoms, especially during the first month of therapy. A warning sheet is usually provided to the patient by the pharmacist. An obvious concern is that common intercurrent illnesses, especially during flu season, or other drug reactions may be erroneously attributed to this reaction, preventing the subsequent use of the drug. In ACTG 5095 the rate of suspected ABC HSR was 37/382 (10%) of those who received ABC and 28/376 (7%) of those who received ABC placebo (*JAMA* 2006;296:769). A possible solution in unclear cases is administration under observation, because patients experiencing true ABC hypersensitivity will predictably experience worsening symptoms.

- **Other side effects** include nausea, vomiting, malaise, headache, diarrhea, or anorexia.
- **Lactic acidosis**. Patients taking ABC can presumably develop lactic acidosis, although this is rare.

BLACK BOX WARNINGS: 1) ABC HSR; 2) lactic acidosis

DRUG INTERACTIONS: Alcohol increases ABC levels by 41%; ABC has no effect on alcohol levels (*Antimicrob Agents Chemother* 2000;283:1811). ABC AUC ¬40% with TPV/r co-administration; clinical significance unknown.

PREGNANCY: Category C. The Pregnancy Registry shows 11/345 (3.2%) birth defects (www.apregistry.com; accessed 1/12/07). Rodent teratogen test showed skeletal malformations and anasarca at 35x the comparable human dose. Placental passage positive in rats. Studies in pregnant women show the ABC AUC is not altered, so standard dose is appropriate (*AIDS* 2006;28:553). It is considered an alternative to AZT/3TC in the DHHS Guidelines (Oct. 10, 2006, p. 95) for antiretroviral drugs for pregnant women. The only concern is for HSRs.

ACYCLOVIR (also includes famciclovir and valacyclovir)

TRADE NAMES: *Zovirax* (GlaxoSmithKline, acyclovir), *Famvir* (Novartis, famciclovir), *Zelitrex* (GlaxoSmithKline, valacyclovir). Acyclovir is also available as a generic. EBV- Best treatment is the use of highly active antiretroviral therapy (HAART).

FORMS AND PRICES

- Generic, acyclovir 200mg, Tablets 25, R 41.71; Zovirax, acyclovir 400mg, Tablets 56, R 1,037.42; Generic, acyclovir 800mg, Tablets 25 R 219.97; Zovirax, acyclovir 200mg/5ml, suspension 125ml, R 452.90; Zovirax, acyclovir 250mg, IV vials, 5, R 1,379.55; Famvir, famcyclovir 250mg, Tablets 10, R 139.27, Famvir, famcyclovir 250mg, Tablets 21, R 595.39; Zelitrex, valacyclovir 250mg, Tablets

60, R 499.17; Zelitrex, valacyclovir 500mg, Tablets 10, R 167.19; Zelitrex, valacyclovir 500mg, Tablets 30, R 501.58; Zelitrex, valacyclovir 500mg, Tablets 42, R702.21;

CLASS: Synthetic nucleoside analogs derived from guanine

INDICATIONS AND DOSES: For oral therapy, acyclovir, famciclovir, or valacyclovir are advocated by the CDC for HSV, although other authorities prefer valacyclovir and famciclovir for the immunosuppressed host (*Lancet* 2001;353:1513). Acyclovir is the only available IV formulation in this class. The following recommendations are based on 2006 CDC guidelines for treating HSV in patients with HIV coinfection (*MMWR* 2006;55[RR-11]:16-20) and the CDC-IDSA recommendations for treating VZV with HIV coinfection (*MMWR* 2004;53[RR-15]:42-44).

- **HSV and HIV**
- **HSV genital and perirectal** (see Table 5-2):
  - Encephalitis: 10-15 mg/kg IV q8h x 14 to 21 days.
- **VZV treatment** (see Table 5-2)**:** Should be started within 4 days or while new lesions are still forming (*N Engl J Med* 2002;347:340).

■ TABLE 5-2: **Comparison of Drugs for Infections Caused by Herpes Simplex and Varicella Zoster** (see Sexually Transmitted Disease Guidelines, *MMWR* 2006;55[RR-11]:16-20)

HERPES SIMPLEX WITH HIV COINFECTION
Episodic genital infection
■ Acyclovir 400 mg PO tid x 5-10 d or famciclovir 500 mg PO bid x 5-10 d or valacyclovir 1 gm PO bid x 5-10 d
Suppressive therapy
■ **Indications:** Multiple recurrences (6/yr); discordant couples. Consider with multiple sex partners. "Some experts" recommend suppressive therapy for all HIV-infected persons with positive HSV-2 serology. ■ **Regimens:** Acyclovir 400-800 mg PO bid or tid or famciclovir 500 mg PO bid or valacyclovir 500 mg PO bid
Acyclovir-resistant HSV strains
■ Consider cidofovir IV.
Severe disease
■ Acyclovir 5-10 mg/kg IV q 8 h
Pregnancy
Risk of perinatal transmission ■ High (30-50%) with initial HSV infection acquired near time of delivery; low (<1%) with recurrent episode at term ■ Acyclovir PO or IV for initial genital HSV or severe recurrent genital HSV ■ For HSV acquired late in pregnancy, options include acyclovir, C-section, or both
VARICELLA ZOSTER WITH HIV COINFECTION
Dermatomal zoster
■ **Extensive or severe:** Acyclovir 10 mg/kg IV q 8 h x 7-10 d; switch to oral therapy after defervescence (see below). ■ **Local dermatomal:** Famciclovir 500 mg PO tid x 7-10 d or valacyclovir 1 gm PO tid x 7-10 d

■ **EBV, oral hairy leukoplakia:** Indications to treat are unclear, but treatment is requested by some patients, usually for cosmetic reasons. One study of 18 patients given valacyclovir 1 gm q 8h x 28 days showed clinical response in 16 (89%) and virologic response in 16 (89%). Recurrence after 1 month off treatment occurred in 2 of 12 patients (17%) (*J Infect Dis* 2003;188:883).

■ TABLE 5-3: **Activity of Antivirals Against Herpesviruses**

	HSV	VZV	EBV	CMV	HHV 6-8
Acyclovir	++	+	+	—	—
Famciclovir	++	+	+	—	—
Valacyclovir	++	+	+	—	—
Ganciclovir	++	+	++	++	+
Foscarnet	+	+	++	+	+
Cidofovir	+	+	++	+	++

PHARMACOLOGY

- **Bioavailability:** Acyclovir, 15% to 20% with oral administration
- **T½:** Acyclovir, 2.5 to 3.3 h, CSF levels: 50% serum levels
- **Elimination:** Renal

■ TABLE 5-4: **Acyclovir Dose Modification in Renal Failure**

Usual Dose	Creatinine Clearance	Adjusted Dose
200 mg 5x/day	>10 mL/min	200 mg 5x/day
	≤10 mL/min	200 mg q12h
800 mg 5x/day	10-50 mL/min	800 mg q8h
	<10 mL/min	800 mg q12h
5-10 mg/kg IV q8h	25-50 mL/min	5-10 mg/kg q 12 h
	10-25 mL/min	5-10 mg/kg q 24 h
	<10 mL/min	5 mg/kg q24h

- **Famciclovir:** CrCl 40-59 = 500 q12h; 20-39 = 500 q24h; <20 = 250 mg q24h (soon after HD on HD days)
- **Valacyclovir:** CrCl 30-49 = 1 gm q12h; 10-29 = 1 gm q24h; <10 = 500 mg q24h (post-HD on HD days)

SIDE EFFECTS

- **IV Acyclovir:** Irritation and phlebitis at infusion site, rash, nausea and vomiting, diarrhea, renal toxicity and crystalluria (especially with rapid IV infusion, prior renal disease, and concurrent nephrotoxic drugs), dizziness, abnormal liver function tests, itching, and headache
- **High doses especially with renal failure:** CNS toxicity-agitation, confusion, hallucination, seizure, coma
- **Others:** Nausea, vomiting, anemia, neutropenia, thrombocytopenia, and hypotension
- Acyclovir and valacyclovir are generally well tolerated.

DRUG INTERACTIONS

- Increased theophylline levels
- Probenecid prolongs half-life of acyclovir. No dose adjustment.

PREGNANCY: Acyclovir, famciclovir, and valacyclovir are category B. Acyclovir is not teratogenic, but has potential to cause chromosomal damage at high doses. The CDC Registry shows no increased incidence of fetal abnormalities among 601 women for whom pregnancy outcome data were available (*MMWR* 1993;42:806). As noted in Table 5-2 above, the CDC recommends use of acyclovir during

pregnancy for severe HSV outbreaks and varicella. Use for prophylaxis in pregnancy is being investigated.

AMPHOTERICIN B

TRADE NAME: Parenteral form, generic; lozenges are available

CLASS: Amphoteric polyene macrolide with activity against nearly all pathogenic and opportunistic fungi.

INDICATION: Conventional amphotericin B is still the first line therapy for cryptococcal meningitis.

FUNGIZONE

ADMINISTRATION – ORAL: Amphotericin lozenge can be used for oral candidiasis.(orally qid) Patients should be encouraged to suck each one for as long as possible. This should not be used if the patient has difficulty in swallowing suggestive of oropharangeal or oesophageal spread. Fungizone lozenges are available.

FORMS AND PRICES: Reyetaz 150mg daily (plus 100mg ritonavir); Reyetaz 150mg daily- unboosted in ARV naïve patients

ADMINISTRATION – IV: Usual dose is 0.3-1.5 mg/kg/day given by slow IV infusion over ≥2-4 hours (*Br Med J* 2000;332:579). Some authorities advocate a test dose (1 mg in 50 mL DSW given over 30 minutes with cardiovascular monitoring for 4 hours) as a test for hypersensitivity.

■ TABLE 5-5: **Systemic (Intravenous) Amphotericin B (*Clin Infect Dis* 2000;30:652)**

Condition	Daily Dose	Total Dose	Comment
Candida Stomatitis Esophagitis Line sepsis Disseminated	 0.3 mg/kg 0.3-0.7 mg/kg 0.3-0.5 mg/kg 0.5-0.8 mg/kg	 200-500 mg 2 to 3 weeks 200-500 mg 20-40 mg/kg	■ Reserved for refractory cases ■ Fluconazole is preferred for systemic treatment of most *Candida* infections. (Check sensitivity of *C. glabrata*.) ■ Voriconazole and caspofungin are preferred for most fluconazole-resistant *Candida* infections (*N Engl J Med* 2002;347:2020; *Clin Infect Dis* 2003;37:415), but cross-resistance is reported with high level azole resistance.
Cryptococcal meningitis (±5FC)	0.7 mg/kg	2 weeks	■ Maintenance with fluconazole (preferred), itraconazole, or amphotericin B 1 mg/wk (inferior) ■ *AmBisone* 4 mg/kg/day + 5 FC is at least as effective as ampho B with less nephrotoxicity (*AIDS* 1997;11:1463)
Histoplasmosis	0.7 mg/kg	3 to 10 days	■ IV amphotericin until clinical response ■ Alternative is *Ambisome* 3 mg/kg/day. ■ Maintenance with itraconazole or amphotericin B 1 mg/kg weekly. ■ Meningitis: Ampho B or *AmBisone* x 12-16 weeks

PHARMACOLOGY

- **Bioavailability:** Peak serum levels with standard IV doses are 0.5-2 µg/mL. There is no significant absorption with oral administration; CSF levels – 3% of serum concentrations.
- **T½:** 24 h with IV administration, detected in blood and urine up to 4 weeks after discontinuation.
- **Elimination:** Serum levels in urine; metabolic pathways are unknown.
- **Dose adjustment in renal failure:** None

SIDE EFFECTS: Oral form: Rash, GI intolerance, and allergic reactions. Toxicity with IV form is dose-related and less severe with slow administration.

- Chills, usually 1 to 3 hours post infusion and lasting for up to 4 hours post infusion. Reduce with hydrocortisone (10-50 mg added to infusion, but only if necessary due to immunosuppression); alternatives that are now often preferred are meperidine, ibuprofen, or napofam prior to infusion.
- Hypotension, nausea, vomiting, usually 1 to 3 hours post infusion; may be reduced with compazine.
- Nephrotoxicity in up to 80% ± nephrocalcinosis, potassium wasting,

renal tubular acidosis. Reduce with gradual increase in dose, adequate hydration, avoidance of concurrent nephrotoxic drugs, and possibly sodium loading. Discontinue or reduce dose with BUN >40 mg/dL and creatinine >3 mg/dL. Lipid amphotericin preparations are less nephrotoxic and could be substituted.

- Hypokalemia, hypomagnesemia, and hypocalcemia corrected with supplemental potassium, magnesium, and calcium.
- Normocytic normochromic anemia with average decrease of 9% in hematocrit.
- Phlebitis and pain at infusion sites: add 1200-1600 units of heparin to infusate.

DRUG INTERACTIONS: Increased nephrotoxicity with concurrent use of nephrotoxic drugs – aminoglycosides, cisplatin, cyclosporine, tenofovir, foscarnet, cidofovir, methoxyflurane, vancomycin; increased hypokalemia with corticosteroids and diuretics. Potential for digoxin toxicity secondary to hypokalemia.

PREGNANCY: Category B. Harmless in experimental animal studies, but no data for humans.

Alternative Preparations

Lipid preparations of amphotericin B include:

- ***AmBisome* (LAmB) (Fugisawa/Gilead Sciences):** Liposomal amphotericin B is a true liposomal delivery system

ADVANTAGES: Compared with amphotericin B, the newer formulations are advocated primarily to reduce nephrotoxicity and infusion-related reactions (*N Engl J Med* 1999;340:764). Other potential advantages are increased daily dose and high concentrations in reticulo-endothelial tissue (lungs, liver, spleen). Comparative trials vs amphotericin B consistently show that the lipid preparations are therapeutically equivalent and sometimes superior, especially *AmBisome*. The only reason these drugs are not generally preferred over amphotericin B is cost. With many infections the lipid formulations may be more cost-effective due to reduced rates of renal failure and dialysis (*Clin Infect Dis* 2001;32:686; *Clin Infect Dis* 2003;37:415). Relative merits are summarized in Table 5-6.

■ TABLE 5-6: **Relative Merits of Amphotericin B Formulations** (*Clin Infect Dis* 2003;37:415; *N Engl J Med* 1999;340:764; *Clin Infect Dis* 2002;35:359)

Preparation	*Amphotericin B*	*AmBisome* (LAmB)
Dose	0.5-1.2 mg/kg/d	3-5 mg/kg/d
Cmax (ug/mL)	0.5-2	83
Adverse reactions*		
Chills	30%	18%
Fever >38^{oo}C	16%	7%
Creatinine >2x base	30-50%	19%

*Comparison of ADR is based on *AmBisome* vs. Ampho, *Amphotec* vs. Ampho.

ATAZANAVIR (ATV)

TRADE NAME: *Reyataz* (Bristol-Myers Squibb)

CLASS: Azapeptide protease inhibitor (*Clin Infect Dis* 2004;38:1599)

FORMULATIONS, REGIMEN AND PRICE

- **Forms:** ATV – caps, 100, 150 and 200, and 300 mg
- **Regimen:** ATV – 400 mg qd (PI-naïve only); ATV/r – 300/100 mg qd (preferred). Must use ATV/r (boosted) with TDF, EFV, and NVP.
- **Food:** Take with food
- **Interactions:** Requires gastric acidity; avoid proton-pump inhibitors (omeprazole, etc.). Dosing separation required with antacids, H2 blockers, etc.; see warnings.
- **Renal failure:** Standard doses
- **Hepatic failure:** With Child-Pugh score 7-9, dose is 300 mg qd (limited clinical data); with Child-Pugh score >9, avoid ATV.
- **Storage:** Room temperature, 15-30°C

WARNINGS

- Avoid unboosted ATV with TDF, EFV, and NVP (*J Antimicrob Chemother* 2005;56:380); avoid buffered ddI (use ddI-EC)
- Caution with drugs that prolong QTc; with clarithromycin, use half-dose clarithromycin or alternative such as azithromycin.
- Proton pump inhibitors: avoid use
- H2 receptor antagonists: take H2 blocker 2 h after ATV
- Antacids: give ATV 2 h before or ≥1 hour after
- Food requirement ↑ ATV AUC 70%. Normal diet.

- Hepatic disease: see dose modification below (Pharmacology)

ADVANTAGES: (1) Potency, esp. with RTV boosting; (2) lowest pill burden among PIs and once-daily regimen; (3) negligible effect on insulin resistance and blood lipids, even with RTV boosting; (4) unique major resistance mutation (I50L) that does not cause PI cross-resistance; (5) generally well tolerated (few GI side effects).

DISADVANTAGES: (1) Indirect hyperbilirubinemia – medically inconsequential but may cause jaundice or scleral icterus (<5%-7%); (2) drug interactions – see warnings; (3) requirement for food and gastric acid; (4) need for RTV boosting when combined with TDF, EFV, and NVP.

MAJOR TRIALS

- **Switch studies:** Two reports with a total of 288 patients switched from PI-based regimens associated with hyperlipidemia showed significant reduction in cholesterol and triglycerides levels at 3-6 months (12th CROI, Boston, Feb. 2005, Abstr. 850 and 858).

RESISTANCE: The signature mutation is I50L in treatment-naïve patients treated with unboosted ATV, which does not cause cross-resistance with other PIs, including FPV, which has the signature mutation I50L. The I50L mutation reduces ATV activity by a median of 10-fold, reduces replication capacity to 0.3-42%, and increases susceptibility to other PIs (although the clinical significance of this is unknown). Among 78 virologic failures in clinical trials, 23 had both phenotypic resistance and the I50L mutation (*J Infect Dis* 2004;189:1802). The I50L mutation is often associated with 71V, which increases susceptibility to other PIs *in vitro* (*Antimicrob Agents Chemother* 2005;49:3825).

PHARMACOLOGY

- **Absorption:** Requires food and gastric acid for optimal absorption, which is highly variable. Food increases AUC 70%. ATV trough levels >150 ng/mL correlate with virologic response (12th CROI, Boston, Feb. 2005, Abstr. 645). RTV boosting (300/100 mg) increases ATV AUC 3- to 4-fold and C_{min} by 10-fold (*Clin Pharmacokin* 2005; 44:1035).
- **Distribution:** Protein-binding 86%, CSF/plasma levels ratio is 0.002-0.02. Penetration into seminal fluid is poor, with a seminal/blood plasma ratio of 0.1 (*Antimicrob Agents Chemother* 2007;51:335).
- **Serum half-life:** 7 h
- **Elimination:** Inhibitor and substrate for P450 3A4. Metabolized by the liver, and metabolites are excreted by the biliary tract; only 13% of unmetabolized drug is excreted in urine.

SIDE EFFECTS: Generally well tolerated with only 2% discontinuation rate for adverse events in one large trial (BMS 008).

- **Common:** Reversible increase in indirect bilirubinemia due to UGT

1A1 inhibition in 22%-47%; this is medically inconsequential but may cause jaundice (reported in 7%). The levels of unconjugated bilirubin correlate with ATV trough levels (12th CROI, Boston, Feb. 2005, Abstr. 645). An increase in bilirubin of ≥0.3 serves as a surrogate marker for ATV adherence (12th CROI, Boston, Feb. 2005, Abstr. 745).

- **Occasional:** GI intolerance with nausea, vomiting, abdominal pain; rash; increase in transaminase.
- **Prolongation of QTc and PR interval**, including asymptomatic first-degree AV block. Studies with ATV/r 300/100 mg qd showed slight but not significant increases in PR interval averaging 3 msec and no change at 1 month (*HIV Med* 2006;7:317). PR interval monitoring should be done in patients with conduction defects or with concurrent use with other drugs that alter cardiac conduction, e.g., diltiazem, verapamil, clarithromycin (use half dose of clarithromycin and diltiazem with slow titration). Consider alternatives: azithromycin, quinidine, amiodarone, lidocaine.
- **Lipodystrophy:** ATV and ATV/r in standard doses appears to have little or no effect on lipid levels (*AIDS* 2006;20:711; *J Acquir Immune Defic Syndr* 2005;39:174). It also has minimal or no effect on insulin resistance (*AIDS* 2006;20:1813). It is unclear whether ATV causes fat accumulation (*Clin Infect Dis* 2006;42:273; *J HIV Ther* 2004;9:41).

BLACK BOX WARNINGS: None

DRUG INTERACTIONS

- **Avoid concurrent use:** Astemizole, bepridil, cisapride, ergotamine, indinavir, irinotecan, lovastatin, midazolam, pimozide, proton pump inhibitors, quinidine, propafenone, flecainide, amiodarone, rifampin, simvastatin, triazolam, St. John's wort,and terfenadine (with boosted ATV).
- **Dose modification:** (ATV standard unless specified): **Rifabutin:** 150 mg qod or 3x/week. **Clarithromycin:** ↑ AUC 94%; use half dose, consider azithromycin. **Oral contraceptive:** Estradiol ↑ AUC 48% and norethindrone ↑ AUC 110%; use lowest dose or alternative contraception. **Statins:** Pravastatin preferred; atorvastatin - use lowest doses. **Anticonvulsants:** Carbamapezine, phenobarbital and phenytoin may ↓ ATV levels substantially; avoid or use with caution. **Sildenafil:** Maximum of 25 mg q48h. **Vardenafil:** No data; use ≤2.5 mg/24 hours, and ≤2.5 mg/72 hours with ATV/r. **Voriconazole** has not been studied, but it is anticipated that co administration will increase ATV levels and decrease voriconazole levels; avoid if possible. **Diltiazem:** ↑ AUC 125%; use half dose and monitor EKG. **Calcium channel blocker:** Monitor EKG. **H2 receptor antagonists** (e.g., ranitidine, famotidine, cimetidine)**:** Separate doses by as much time as possible, preferably; give ATV 2 h before or 10 h after H2 blockers. **Antacids and buffered medications (e.g., ddI):** Give 2 h before or >1 h after ATV. **Proton pump inhibitors** such as

omeprazole should be avoided. Co-administration of 40 mg omeprazole with ATV/r 300/100 mg resulted in a 75% reduction in ATV AUC. Attempts to reduce gastric pH with cola were unsuccessful.

- **PIs:** IDV: Avoid (hyperbilirubinemia)
  RTV: ATV AUC ↑ 230%; ATV/r: 300/100 mg qd
  SQV: ATV/SQV: 400/1200 mg qd performed poorly in a clinical trial (*AIDS* 2004;18:1291) or ATV/SQV/RTV: 300/1600/100 mg qd preferred (*AIDS* 2003;17:1339);
  NFV: No data
  FPV: ↓ ATV AUC 33%; data inadequate
  LPV/r: AUCs unchanged; ATV 300 mg/d + LPV/r
  DRV/r: ATV 300 mg/d + DRV/r 600/100 mg bid
  TPV/r: Avoid.
- **NNRTIs:** EFV and NVP increase ATV clearance – must boost ATV (300/100 mg qd plus standard doses of EFV or NVP (*Eur J Clin Pharmacol* 2006;52:523)
- **Tenofovir:** ↓ AUC 25% and ↑ TDF AUC 24% (*Antimicrob Agents Chemother* 2004;48:2091); use TDF 300 mg qd + ATV/r 300/100 mg qd.
- **NRTIs:** Buffered ddI causes marked decrease in ATV levels; taking ATV with food causes ↓ ddI exposure. Give ddI and ATV at different times.

PREGNANCY: Category B; there have been no studies of safety or pharmacokinetics in pregnant women. It is not known whether the increased indirect bilirubin will increase rates of hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low. The DHHS panel concluded that safety and pharmacokinetic data are inadequate to recommend ATV use in pregnancy (DHHS Guidelines, Oct. 10, 2006, p. 97).

ATORVASTATIN

TRADE NAME: *Lipitor* (Pfizer)

FORMS AND PRICES: Lipitor, atorvastatin 40mg, Daily Tablets; Lipitor, atorvastatin 80mg, Daily Tablets;

CLASS: Statin (HMG-CoA reductase inhibitor)

INDICATIONS AND DOSES: Elevated total and LDL cholesterol and/or triglycerides. Recommended statin for hyperlipidemia with PI-based HAART by IAS-USA (*J Acquir Immune Defic Syndr* 2002;31:257) and HIVMA/ACTG (*Clin Infect Dis* 2003;37:613) Other options are pravastatin, With atorvastatin, the initial dose is 10 mg/day with increases at 2 to 4 week intervals to maintenance doses of 10-80

mg/day in one daily dose. Take with or without food, preferably in the evening.

MONITORING: Blood lipids at ≤4-week intervals until desired results are achieved, then periodically. Obtain transaminase levels at baseline, at 12 weeks, and then at 6-month intervals. Patients should be warned to report muscle pain, tenderness, or weakness promptly, especially if accompanied by fever or malaise. Obtain CPK for suspected myopathy.

PRECAUTIONS: Atorvastatin (and other statins) are contraindicated with pregnancy, breastfeeding, concurrent conditions that predispose to renal failure (e.g., sepsis, hypotension), and active hepatic disease. Alcoholism is a relative contraindication.

PHARMACOLOGY

- **Bioavailability:** 14%
- **T½:** 14 h
- **Elimination:** Fecal (biliary and unabsorbed) – 98%; renal – <2%
- **Renal failure:** No dose adjustment
- **Hepatic failure:** Levels of atorvastatin are markedly elevated.

SIDE EFFECTS

- **Musculoskeletal:** Myopathy with elevated CPK plus muscle pain, weakness or tenderness ± fever and malaise. Rhabdomyolysis with renal failure reported.
- **Hepatic:** Use with caution.Elevated transaminases in 1% to 2%; discontinue if ALT and/or AST shows unexplained increase >3x upper limit of normal (ULN) x 2.
- **Miscellaneous:** Diarrhea, constipation, nausea, heartburn, stomach pain, dizziness, headache, skin rash, impotence (rare), insomnia

DRUG INTERACTIONS

- **PIs:** Potential for large increase in statin AUC with all PIs: Increase with NFV, 74%; LPV/r, 5.8x; SQV/RTV, 4.5x; TPV/r, 9x; FPV, 1.3x; DRV/r, 4x. Start with 10 mg/day and monitor clinically for myopathy or consider pravastatin; avoid doses >40 mg/d with PIs. EFV ↓ atorvastatin AUC 43%.
- **Others: Grapefruit juice** increases atorvastatin levels up to 24%; avoid large amounts before or after administration. **Erythromycin:** Atorvastatin levels increased by 40%. **Antacids:** Atorvastatin levels decreased by 35%. **Other interactions with increased risk of myopathy:** Azoles (ketoconazole, itraconazole), cyclosporine, fibric acid derivatives, niacin, macrolide antibiotics, nefazodone. **Niacin and gemfibrozil:** Increased risk of myopathy; rhabdomyolysis reported only with lovastatin + niacin, but could occur with other statins.

PREGNANCY: Category X – contraindicated

ATOVAQUONE

TRADE NAME: *MWellvone* (*Aspen Pharmcare*)

FORM AND PRICE: Malanil, atovaquone, Tablets 12, R 365.54

INDICATIONS AND DOSE: PCP: Oral treatment of mild to moderate PCP (A-a O_2 gradient <45 mm Hg and P_AO_2 >60 mm Hg; less effective than TMP/SMX) and PCP prophylaxis in patients who are intolerant of TMP-SMX and dapsone; toxoplasmosis treatment (third line) and prophylaxis (third line).

- **PCP treatment:** 750 mg (5 mL) twice daily with meals x 21 days
- **PCP prophylaxis:** 1500 mg qd or 750 mg bid with meals
- **Toxoplasmosis treatment (alternative):** 1500 mg PO bid with meals alone or combined with either pyrimethamine 200 mg x 1, then 50-75 mg/day or sulfadiazine 1.5 g qid (*Clin Infect Dis* 2002; 34:1243).

PHARMACOLOGY

- **Bioavailability:** Absorption of suspension averages 47% in fed state (with meals). Concurrent administration of fatty food increases absorption by 2-fold. There is significant individual variation in absorption. Administration with fatty food needs emphasis.
- **T½:** 2.2 to 2.9 days
- **Elimination:** Enterohepatic circulation with fecal elimination; <1% in urine
- **CSF/plasma ratio:** <1%
- **Effect of hepatic or renal disease:** No data

SIDE EFFECTS: Rash (20%), GI intolerance (20%), diarrhea (20%). Possibly related headache, fever, insomnia. Life-threatening side effects: none. Percent requiring discontinuation due to side effects: 7% to 9% (rash, 4%).

DRUG INTERACTIONS

- Rifampin: ↓ atovaquone by 54%, ↑ rifampin by 30%; avoid co-administration
- Rifabutin: ↓ atovaquone by 34%, rifabutin by 19%. Consider alternative.
- Tetracycline: ↓ atovaquone by 40%; avoid co-administration
- AZT AUC increased 31% due to atovaquone inhibition of AZT gluconuridation (clinical significance unknown).

PREGNANCY: Category C. Not teratogenic in animals; limited experience in humans.

AZITHROMYCIN

TRADE NAME: *Azithromycin*

FORMS AND PRICES: Generic, Azithromycin Daily tablets 3, R 89.82

CLASS: Macrolide

INDICATIONS AND DOSES: see Table 5-7 below.

■ TABLE 5-7: **Azithromycin Regimens by Condition**

Indication	Dose †
M. avium prophylaxis*	1200 mg 8 wk (*MMWR* 2002;51[RR-8]:1)
M. avium treatment*	500-600 mg qd + EMB ± rifabutin (*Clin Infect Dis* 2000;31:1245)
Pneumonia*	500 mg IV qd x ≥2 days (hospitalized patients), then 500 mg PO qd x 7 to 10 days
Sinusitis*	500 mg x 1, then 250 mg PO/day x 4 (Z-pak) or 500 mg/d x 3 days (Tri-pak)
*C. trachomatis** (nongonococcal urethritis or cervicitis)	1 g or 1.2 g (two 600 mg tablets) PO x 1
Gonococcal urethritis or cervicitis	2 g PO x 1 (poor GI tolerance)

† Caps must be taken ≥1 hr before or >2 hrs after a meal; food improves absorption and tolerance of tabs and powder.

ACTIVITY: this drug can be used for community acquired pneumonia in selected patients. The treatment of gonorrhoea with azithromycin is 1g stat. It may also be used in the treatment of Mycobacterium Avium Intracellulare (MAI)with ethambutol. This is inferior to clarithromycin. However, the use of clarithromycin is relatively contraindicated with efavirenz due to the high incidence of rash.

PHARMACOLOGY

- **Bioavailability:** Absorption is ~30% to 40%. The 600 mg tabs and the 1 g powder packet may be taken without regard to food, but food improves tolerability.
- **T½:** 68 hours; detectable levels in urine at 7 to 14 days; with the 1200 mg weekly dose, the azithromycin levels in peripheral leukocytes remain above 32 µg/mL for 60 hours.
- **Distribution:** High tissue levels; low CSF levels (<0.01 µg/mL)
- **Excretion:** Primarily biliary; 6% in urine
- **Dose modification in renal or hepatic failure:** Use with caution.

SIDE EFFECTS: GI intolerance (nausea, vomiting, pain); diarrhea – 14%. With 1200 mg dose weekly, major side effects are diarrhea, abdominal pain, and/or nausea in 10% to 15%; reversible dose-dependent hearing loss is reported in 5% at mean day of onset at 96 days and mean exposure of 59,000 mg (package insert). Frequency of discontinuation in AIDS patients receiving high doses – 6%, primarily GI intolerance and reversible ototoxicity – 2%; rare – erythema multiforme, increased transaminases.

CONTRAINDICATIONS: Hypersensitivity to erythromycin

DRUG INTERACTIONS: Preferred macrolide for PI and NNRTI co-administration. Azithromycin increases levels of theophylline and coumadin. Concurrent use with antiretroviral agents, rifampin, and rifabutin is safe. Concurrent use with pimozide may cause fatal arrythmias and must be avoided.

PREGNANCY: Category B (safe in animal studies; no data in humans). Preferred macrolide for MAC prophylaxis and treatment in pregnancy.

AZT – see Zidovudine

BACTRIM – see Trimethoprim-Sulfamethoxazole

CIPROFLOXACIN – see Fluoroquinolones

TRADE NAME: *Cipro* (Bayer); available as generic

FORMS AND PRICES: Generic, ciprofloxacin 250mg, Tablets 10 R 9.56; Generic, ciprofloxacin 500mg, Tablets 10, R 21.15; Generic, ciprofloxacin 750mg, Tablets 10, R 75.08; Ciprobay, ciprofloxacin 500mg, extended release tablets 3, R 35.78; Ciprobay, ciprofloxacin 1000mg, extended release tablets 7, R 97.65;.

CLASS: Fluoroquinolone

INDICATIONS AND DOSES

- **Respiratory infections:** 500-750 mg PO bid x 7-14 days. *P. aeruginosa*: use 750 mg PO bid or 400 mg IV q8h.
- **Gonorrhea:** 500 mg x 1 (fluoroquinolone resistance in some areas).
- ***M. avium*:** 500-750 mg PO bid (alternative or 3rd or 4th drug with serious disease)
- **Tuberculosis:** 500-750 mg PO bid multidrug-resistant *M. tuberculosis* or liver disease)
- **Salmonellosis:** 500-750 mg PO or 400 mg IV bid x 7-14 d for mild disease or 4-6 wks for CD4 <200 and/or bacteremia (preferred)

- **UTI:** 250-500 mg PO bid x 3-7 d (First line)
- **Traveler's diarrhea:** 500 mg PO bid x 3 d (First line)

ACTIVITY: Active against most strains of *Enterobacteriaceae, P. aeruginosa, H. influenzae, Legionella, C. pneumoniae, M. pneumoniae, M. tuberculosis, M. avium*, most bacterial enteric pathogens other than *C. jejuni* and *C. difficile*. Somewhat less active against *S. pneumoniae* than levofloxacin, and moxifloxacin. There is increasing and substantial resistance by *S. aureus* (primarily MRSA) (*Clin Infect Dis* 2000;32: S114), *P. aeruginosa* (*Clin Infect Dis* 2000;32:S146), and *C. jejuni* (*Clin Infect Dis* 2001;32:1201). There is escalating concern about fluoroquinolone-resistant *S. pneumoniae, N. gonorrhoeae, Salmonella* spp, *C. jejuni, S. aureus*, and *P. aeruginosa*.

PHARMACOLOGY

- **Bioavailability:** 60% to 70%
- **T½:** 3.3 hours
- **Excretion:** Metabolized and excreted (parent compound and metabolites) in urine
- **Dose reduction in renal failure:** CrCl>50 mL/min – 250-750 mg q12h; CrCl 10-50 mL/min – 250-500 mg q12h; CrCl<10 mL/min – 500 mg q24h

SIDE EFFECTS: Usually well tolerated; most common include:

- Fluoroquinolones are now a major cause of *C. difficile*-associated colitis (*Ann Intern Med* 2006;145:758; *New Engl J Med* 2005;353:2433). All agents in the class appear to be implicated.
- **GI intolerance** with nausea – 1.2%; diarrhea – 1.2%
- **CNS toxicity:** Malaise, drowsiness, insomnia, headache, dizziness, agitation, psychosis (rare), seizures (rare), hallucinations (rare)
- **Tendon rupture:** About 100 cases reported involving fluoroquinolones, with ciprofloxacin accounting for 25% (*Clin Infect Dis* 2003;36:1404). The incidence in a review of 46,776 courses was 0.1% with increased age and steroids as confounding risks (*Brit Med J* 2002;324:1306).
- **Torsades de pointes:** Rates/10 million are: Moxifloxacin – 0, ciprofloxacin – 0.3, levofloxacin – 5.4 (*Pharmacother* 2001;21:1468).
- ***Candida* vaginitis**

PREGNANCY: Fluoroquinolones are contraindicated in persons <18 years due to concern for arthropathy, which has been seen in beagle dogs, but application to human disease is debated (*Curr Opin Pediatr* 2006;18:64). Some fluoroquinolones may cause false positive urine screening tests for opiates (*JAMA* 2001;286:3115).

DRUG INTERACTIONS: Increased levels of theophylline, methotrexate, and caffeine; reduced absorption with cations (Al, Mg, Ca) in antacids, sucralfate, milk and dairy products, buffered ddI; gastric achlorhydria does not influence absorption. Take fluoroquinolone 2 h before cations.

PREGNANCY: Category C. Arthropathy in immature animals with erosions in joint cartilages; relevance to patients is not known, but fluoroquinolones are not FDA-approved for use in pregnancy or in children <18 years. Review of >200 first trimester exposures showed no anomalies. Use may be justified in severe MAC or multi-drug-resistant tuberculosis.

CLARITHROMYCIN

TRADE NAME: *Klacid.*

FORMS AND PRICES: Tabs: 250 mg at $5.49, 500 mg at $5.49, 500 mg XL at $5.87 (for qd dosing). Suspension: 250 mg/5 mL at $77.13 per 100 mL. Clarithromycin 500mg bd 10 R 61.99

CLASS: Macrolide

■ TABLE 5-8 **Clarithromycin Indications and Doses**

Indication	Dose Regimen*
Pharyngitis, sinusitis, otitis, pneumonitis, skin and soft tissue infection†	250-500 mg PO bid or 1 g 2XL tabs qd
M. avium prophylaxis†	500 mg PO bid (*MMWR* 1995;44[RR-8]:1)
M. avium treatment† (plus EMB ± moxifloxacin or rifabutin)	500 mg PO bid
Bartonella	500 mg po bid x ≥3 mo

* Doses of ≥2 gm/d are associated with excessive mortality (*Clin Infect Dis* 1999;29:125).

† FDA-approved for this indication.

CLINICAL TRIALS: Clarithromycin is highly effective in the treatment and prevention of MAC disease (*N Engl J Med* 1996;335:385; *Clin Infect Dis* 1998;27:1278). Clarithromycin was superior to azithromycin in the treatment of MAC bacteremia in terms of median time to negative blood cultures 4.4 weeks vs >16 weeks (*Clin Infect Dis* 1998;27:1278). However, this point is debated and may be a dose issue (*Clin Infect Dis* 2000;31:1254). There is no evidence that it is superior to azithromycin for MAC prophylaxis. Clarithromycin should be given with caution with rifabutin due to decreased levels of clarithromycin (*N Engl J Med* 1996;335:428). This is the presumed explanation for the lack of superior outcome with rifabutin plus clarithromycin vs clarithromycin alone for prevention of MAC (*J Infect Dis* 2000;181:1289).

ACTIVITY: *S. pneumoniae* (20% to 30% of strains and 40% of penicillin-resistant strains are resistant in most areas of the United States), erythromycin-sensitive *S. pyogenes, M. catarrhalis, H. influenzae, M. pneumoniae, C. pneumoniae, Legionella, M. avium, T. gondii, C. trachomatis,* and *U. urealyticum.* Activity against *H. influenzae* is often debated, although a metabolite shows better *in vitro* activity than the parent compound, and the FDA has approved clarithromycin for pneumonia caused by *H. influenzae.* There is concern about increasing rates of macrolide resistance by *S. pneumoniae* (*J Infect Dis* 2000;182:1417; *Antimicrob Agents Chemother* 2001;45:2147; *Antimicrob Agents Chemother* 2002;46:265), although clinical trials show *in vivo* results that are superior to *in vitro* activity. Nevertheless, excessive rates of breakthrough pneumococcal bacteremia has been reported (*Clin Infect Dis* 2002;35:556).

PHARMACOLOGY

- **Bioavailability:** 50% to 55%
- **T½:** 4-7 h
- **Elimination:** Rapid first-pass hepatic metabolism plus renal clearance to 14 – hydroxyclarithromycin
- **Dose modification in renal failure:** CrCl <30 mL/min half usual dose or double interval

SIDE EFFECTS: GI intolerance – 4% (vs 17% with erythromycin); transaminase elevation – 1%, headache – 2%, PMC – rare.

DRUG INTERACTIONS: Clarithromycin is a substrate and inhibitor of CYP3A4. It increases levels of rifabutin 56%, and levels of clarithromycin are decreased 50%. May need to decrease **rifabutin** dose and increase clarithomycin dose or use azithromycin. Clarithromycin should not be combined with **rifampin, timetrexate, ergot alkaloid, carbamazepine** (*Tegretol*), **cisapride** (*Propulsid*), **pimozide** (*Orap*), increased levels of **pimozide** and **cisapride** may cause fatal arrhythmias. The same concern for QTc prolongation applies to concurrent use with **atazanavir**. (Use 50% clarithromycin dose or use azithromycin, which has no substantial interaction with these drugs.) May increase serum level CYP3A4 substrates. See Table 5-9 for interactions and dose adjustments for clarithromycin use with NNRTIs and PIs.

■ TABLE 5-9: **Clarithromycin Interactions with PIs and NNRTIs**

Agent	Clarithromycin	PI/NNRTI	Regimen
IDV	↑53%	↑29%	Standard
RTV	↑77%	↓14 OH clarithro	Reduce clarithromycin dose by 50% if CrCl 30-60 mL/min, and by 75% if CrCl <30 mL/min
SQV	↑45%	↑177%	Standard; reduce dose by 50% with SQV/r if CrCl = 30-60 mL/min
NFV	No data	No data	No data
LPV/r	↑77%	—	Reduce clarithromycin dose by 50% if CrCl 30-60 mL/min, and by 75% if CrCl <30 mL/min
NVP	↓30%	↑26%	Standard; monitor for efficacy or use azithro
EFV	↓39%	↑14 OH clarithro 34%	Avoid if possible; consider azithromycin
DLV	↑100%	↑44%	Dose reduction for renal failure
ATV	↑94%	ATV ↑28%	Use half dose clarithromycin and monitor for arrhythmia (QTc prolongation) or use azithromycin
DRV	↑57%	No change	Use half dose clarithromycin if CrCl 30-60 mL/min and reduce 75% if CrCl <30 mL/min
TPV	↑19%	↑66%	Use half dose clarithromycin if CrCl 30-60 mL/min and reduce 75% if CrCl <30 mL/min
FPV	No Change	may ↑	APV ↑18%; standard doses

PREGNANCY: Category C; teratogenic in animal studies and no adequate studies in humans.

CLINDAMYCIN

TRADE NAME: *Dalacin C* (Pfizer) *and generic* (formulations) *Cleocin* (Pharmacia) or generic

FORMS AND PRICES

- **Clarithromycin** 500mg bd 10 R 61.99
- **Generic clindamycin** capsules 20 R71.72

INDICATIONS AND DOSES

- **PCP:** Clindamycin 600-900 mg q6h-q8h IV or 300-450 mg q6-8h PO + primaquine 15-30 mg (base). This is a second line drug and only used in patients with previous severe reactions to cotrimoxazole

- **Toxoplasmosis:** Clindamycin 600 mg IV or PO q6h + pyrimethamine 200 loading dose, then 50-75 mg/day PO/leucovorin, 10-20 mg/day. This is a second line drug.
- **Other infections:** 600 mg IV q8h or 300-450 mg PO q6h-q8h

ACTIVITY: Most Gram-positive cocci are susceptible except *Enterococcus* and some community-acquired MRSA. Most anaerobic bacteria are susceptible, but IDSA guidelines for intra-abdominal sepsis do not include clindamycin due to increasing resistance by *B. fragilis* (20-30%).

PHARMACOLOGY

- **Bioavailability:** 90%
- **T½:** 2-3 h
- **CNS penetration:** Poor
- **Elimination:** Metabolized; 10% in urine
- **Dose modification in renal failure:** None

SIDE EFFECTS: GI – diarrhea in 10% to 30%. Up to 6 percent of patients develop *C. difficile*-associated diarrhea; may be severe (*Ann Intern Med* 2006;145:758); most respond well to discontinuation of the implicated antibiotic ± metronidazole (250 mg qid or 500 mg tid x 10 days). Other GI side effects include nausea, vomiting, and anorexia. Rash – generalized morbilliform is most common; less common is urticaria, pruritus, Stevens-Johnson syndrome.

DRUG INTERACTIONS: Loperamide (*Imodium*) or diphenoxylate/atropine (*Lomotil*) increases risk of diarrhea and *C. difficile*-associated colitis.

PREGNANCY: Category B

CLOTRIMAZOLE

TRADE NAMES: *Lotrimin* (Schering-Plough), *Mycelex* (Bayer), *Gyne-Lotrimin* (Schering-Plough), *FemCare* (Schering), or generic, Many generic formulations available

FORMS AND PRICES

- Canesten, clotrimazole 10mg, Troche 70,R 102.60
- Generic, clotrimazole topical cream 20g, R 7.70
- Canesten, clotrimazole vaginal cream 5g, R 82.73
- Canesten, clotrimazole vaginal cream 35g, R 83.55
- Generic, clotrimazole vaginal cream 50g, R 24.53
- Generic, clotrimazole vaginal tablet 1, R 23.60

CLASS: Imidazole (related to miconazole)

INDICATIONS AND DOSES

- **Oral Thrush:** 10 mg troche 5x/day; must be dissolved in the mouth. Clotrimazole troches are only slightly less effective than fluconazole for thrush and are often preferred to avoid azole resistance (*HIV Clin Trials* 2000;1:47). The problem is the need for 5 doses/day, although treatment with lower doses is often successful.
- **Dermatophytic infections and cutaneous candidiasis:** Topical application of 1% cream, to affected area bid x 2 to 8 weeks; if no improvement, reevaluate diagnosis.
- **Candidal vaginitis:** Intravaginal 100 mg tab bid x 3 days (preferred); alternatives: 100 mg tabs qd x 7; 500 mg tab x 1. Vaginal cream: One applicator (about 5 g) intravaginally at hs x 7 to 14 days.

ACTIVITY: Active against *Candida* species and dermatophytes.

PHARMACOLOGY

- **Bioavailability:** Lozenge (troche) dissolves in 15 to 30 minutes; administration at 3-hour intervals maintains constant salivary concentrations above MIC of most *Candida* strains. Topical application of 500 mg tab intravaginally achieves local therapeutic levels for 48 to 72 hours. Small amounts of drug are absorbed with oral, vaginal, or skin applications.

SIDE EFFECTS: Topical to skin (rare) – erythema, blistering, pruritus, pain, peeling, urticaria; topical to vagina (rare) – rash, pruritus, dyspareunia, dysuria, burning, erythema; lozenges – elevated AST (up to 15% – monitor LFTs); nausea and vomiting (5%)

PREGNANCY: Category C. Avoid during first trimester.

COMBIVIR – see Lamivudine and Zidovudine

CRIXIVAN – see Indinavir

CYTOVENE – see Ganciclovir

DAPSONE

TRADE NAME: Generic

FORMS AND PRICES: Lennon-Dapsone dapsone, Tablets 100, R 182.13

CLASS: Synthetic sulfone with mechanism of action similar to sulfonamides – inhibition of folic acid synthesis by inhibition of dihydropteroate synthetase.

■ TABLE 5-10: **Dapsone Indications and Dose Regimens**

Indication	Dose Regimen
PCP prophylaxis	100 mg PO qd
PCP treatment (mild to moderately severe)	100 mg PO qd (plus trimethoprim 15 mg/kg/d PO, in 3 doses) x 3 weeks
PCP + toxoplasmosis prophylaxis	50 mg PO qd (plus pyrimethamine 50 mg/week plus folinic acid 25 mg/week) or dapsone 200 mg (+ pyrimethamine 75 mg + leucovorin 25 mg) once weekly

EFFICACY: A review of 40 published studies found dapsone (100 mg/day) to be slightly less effective than TMP-SMX for PCP, prophylaxis, but comparable with aerosolized pentamidine and highly cost-effective (*Clin Infect Dis* 1998;27:191). For PCP treatment, dapsone/trimethoprim is as effective as TMP-SMX for patients with mild or moderately severe disease (*Ann Intern Med* 1996;124:792).

PHARMACOLOGY

- **Bioavailability:** Nearly completely absorbed except with gastric achlorhydria (dapsone is insoluble at neutral pH).
- **T½:** 10 to 56 h (average 28 h)
- **Elimination:** Hepatic concentration, enterohepatic circulation, maintains tissue levels 3 weeks after treatment is discontinued.
- **Dose modification in renal failure:** None

SIDE EFFECTS

- **Most common in AIDS patients:** Rash, pruritus, hepatitis, hemolytic anemia, and/or neutropenia in 20% to 40% receiving dapsone prophylaxis for PCP at a dose of 100 mg/day.
- **Most serious reaction:** Dose-dependent hemolytic anemia, with or without G6-PD deficiency, and methemoglobinemia; rare cases of agranulocytosis (0.2-0.4%) and aplastic anemia.
- **GI intolerance:** Common; may reduce by taking with meals.
- **Infrequent ADRs:** Headache, dizziness, peripheral neuropathy. Rare side effect is "sulfone syndrome" after 1 to 4 weeks of treatment, consisting of fever, malaise, exfoliative dermatitis, hepatic necrosis, lymphadenopathy, and anemia with methemoglobinemia (*Arch Dermatol* 1981;117:38).

DRUG INTERACTIONS: Decreased dapsone absorption – buffered ddI, H_2 blockers, antacids, omeprazole, and other proton pump inhibitors. Dapsone levels decreased 7- to 10-fold by rifampin; use alternative. Trimethoprim – increases levels of both drugs; monitor for methemo-globinemia. Coumadin – increased hypoprothrombinemia; pyrimethamine – increased marrow toxicity (monitor CBC); probenecid

– increases dapsone levels; primaquine – hemolysis due to G6-PD deficiency.

RELATIVE CONTRAINDICATIONS: G6-PD deficiency.

PREGNANCY: Category C. No data in animals; limited experience in pregnant patients with Hansen's disease shows no toxicity. Hemolytic anemia with passage in breast milk reported (*Clin Infect Dis* 1995; 21[suppl 1]:S24).

DARUNAVIR (DRV)

TRADE NAME: *Prezista* (Tibotec)

CLASS: Protease inhibitor

FORMULATION, REGIMEN, PRICE:

- **FORM:** 300 mg tabs @ $6.25/tab. Only available on named patient basis from the MCC. (section 21)
- **REGIMEN:** 600 mg (2 tabs) + 100 mg RTV bid
- **FOOD:** Take with food
- **RENAL FAILURE:** No dose adjustment
- **HEPATIC FAILURE:** No data; use with caution
- **STORAGE:** 15-30ºC (59-86ºF)

ACTIVITY: Median EC_{50} against clinical and lab strains range 1.2-8.5 nM; activity includes group M (A-G), O, and HIV-2.

ADVANTAGES: Potent anti-HIV activity; excellent activity against HIV strains that are resistant to other PIs.

DISADVANTAGES: Food requirement, RTV requirement, bid dosing

CLINICAL TRIALS

RESISTANCE: No single PI mutation results in complete loss of DRV activity. Resistance is best determined by the cumulative number of resistance mutations ("DRV score") or by phenotypic resistance testing. Reduced *in vitro* and *in vivo* activity seen with the following mutation patterns.

POWER baseline mutations that correlated with reduced virologic response included the following mutations: 11I, 32I, 33F, 47V, 50V, 54L/M, 73S, 76V, 84V, 89V (DeMeyer S, European HIV Drug Resistance Workshop, Monte Carlo, March 2006; http://www.tibotec.com/content/congresses/www.tibotec.com/De_Meyer_TMC114.pdf).

PHARMACOLOGY

- **Bioavailability:** 37% without RTV, 82% with RTV. RTV increases

DRV exposure 14-fold. Food increases C_{max} and AUC 30%. DRV should always be given with RTV and food.

- **T½:** 15 h when given with RTV
- **Excretion:** Metabolized extensively by CYP3A; 80% recovered in stool, 15% in urine
- **Renal failure:** Pharmacology is not changed in persons with CrCl 30-60 mL/min; no study data for patients with worse renal failure.
- **Hepatic disease:** Patients with HBV or HCV showed no changes in pharmacology; no data for severe hepatic failure.

SIDE EFFECTS

- **Rash:** 7%, usually mild maculopapular but also Stevens-Johnson syndrome and erythema multiforme. Discontinuation rate 0.3%. Contains sulfonamide moiety.
- **Class lypodystrophy:** Glucose intolerance, fat redistribution, and lipodystrophy. Hyperglycemia (blood glucose >161 mg/dL) in 2-6%, triglycerides elevated in 25%.
- **Transaminase elevations:** >2.5 ULN in 10%
- **GI intolerance:** Diarrhea, vomiting, and/or abdominal pain in 2-3%
- **Headache:** 1-4%

DRUG INTERACTIONS

- **Drugs contraindicated for concurrent use: Astemizole, cisapride, ergot derivative, fluticasone, midazolam, pimozide, terfenadine, triazolam, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort, simvastatin, lovastatin, triazolam**
- **Other cautions**

  Anti-arrhythmics (bepridil, lidocaine, quinidine amiodarone): increased levels; monitor drug levels. **Antifungals** (kètoconazole and itraconazole): increased levels of both azoles and DRV. Azole doses ≤200 mg/d. Voriconazole AUC decreased 40% by RTV 200 mg/d; use with caution or avoid. **Rifabutin:** Use 150 mg qod rifabutin. **Calcium channel blockers** (felodipine, nifedipine, nicardipine): concentrations increase; monitor. **Steroids** (dexamathasone, fluticasone): Dexamathasone may decrease levels of DRV; inhaled fluticasone increased levels. Consider alternatives, especially for long-term use. **Statins** (atorvastatin and pravastatin): increased statin levels. Pravastatin AUC level increased by a mean of 81%, but 5-fold in some patients. Use lowest doses and monitor. **Immunosuppressants** (cyclosporine, tacrolimus, sirolimus): levels increase; monitor immunosuppressant levels. **Methadone:** DRV/r may decrease methadone levels; monitor for withdrawal. **Oral contraceptives:** Estradiol levels decrease significantly; use alternative or additional birth control method. **PDE5 inhibitors** (sildenafil, vardenafil, tadalafil): Do not exceed 25 mg sildenafil q 48

h, 2.5 mg vardenafil q 72 h, or 10 mg tadalafil q 72 h. **SSRIs** (sertraline, paroxetine): SSRI levels decreased; monitor antidepressant response. **Clarithromycin:** Levels of clarithromycin increased. Reduce dose 50% if CrCl 30-60 mL/min; reduce dose 75% if CrCl <30 mL/min. **Warfarin:** Levels of warfarin decreased. Monitor INR. **Trazodone:** Levels and side effects (nausea, dizziness, hypotension) of trazadone increased. Use lower dose or use with caution.

■ TABLE 5-11: **Dose Adjustments for Concurrent Use of DRV with Other Antiretrovirals**

Drug	Effect on co-admin. drug	Effect on DRV	Dose
ddI	—	—	ddI requires empty stomach so separate dosing
TDF	↑ AUC 20%	↑ DRV 21%	No dose adjustment
EFV	↑ AUC 21%	↓ AUC 13%	Standard doses both drugs; monitor
NVP	↑ AUC 27%	—	Standard doses both drugs
ATV/r	↑Level 87%	—	Standard DRV dose; ATV 300 mg/d
IDV/r	↑	↑	Dose not established
LPV/r	↑ 37%	↓ AUC 50%	Dose not established; avoid
SQV/r	—	↓ AUC 25%	Dose not established; avoid
FPV, NFV, TPV	?	?	Not studied
RTV	?	↑ 14-fold	Standard regimen: DRV/r 600/100 mg bid

PREGNANCY: Category B. No studies in pregnancy, so pharmacodynamics are unknown. Use only if potential benefit justifies the potential risk.

DAUNORUBICIN CITRATE LIPOSOME INJECTION

TRADE NAME: *DaunoXome* (Gilead Sciences)

NOTE: Liposomal doxorubicin (*Doxil*), 20-30 mg/M^2 every 2 weeks, is equally as effective.

FORM AND PRICE: Vials containing equivalent of 50 mg daunorubicin at $442.19/50 mg vial

CLASS: Daunorubicin encapsulated within lipid vesicles or liposomes

INDICATIONS AND DOSES: (FDA labeling): First-line cytotoxic therapy for advanced HIV-associated Kaposi's sarcoma (KS). Pegylated liposomal doxorubicin plus HAART is often considered the preferred treatment for moderate to advanced KS (*AIDS* 2004;20:1737). Usual indications in trials are symptomatic visceral KS, >25 skin lesions, "B" symptoms, or lymphedema. Administer IV over 60 minutes in dose of 40 mg/M^2; repeat every 2 weeks. CBC should be obtained before each infusion and therapy withheld if absolute leukocyte count is <750/mL. Treatment is continued until there is evidence of tumor progression with new visceral lesions, progressive visceral disease, >10 new cutaneous lesions, or 25% increase in the number of lesions compared with baseline. Dose adjustment for hepatic impairment: bilirubin 1.2-3 mg/dL: 3/4 of a normal dose; bilirubin >3 mg/dL: 1/2 of normal dose.

CLINICAL TRIALS: Controlled trials comparing liposomal doxorubicin (*Doxil*) or liposomal daunorubicin vs chemotherapy show better response and less toxicity with *Doxil* and *DaunoXome*, which are considered equivalent (*J Clin Oncol* 1996;14:2353; *J Clin Oncol* 1998;16:2445; *J Clin Oncol* 1998;16:683).

PHARMACOLOGY: Mechanism of selectively targeting tumor cells is unknown. Once at the tumor, daunorubicin is released over time.

SIDE EFFECTS

- **Granulocytopenia** and mucositis are the most common toxicities requiring monitoring of the CBC (*Clin Cancer Res* 2001;7:3040).
- **Cardiotoxicity** is the most serious side effect. It is most common in patients who have previously received anthracyclines or who have preexisting heart disease. Common features of cardiomyopathy are decreased left ventricular ejection fraction (LVEF) and usual clinical features of congestive heart failure. Cardiac function (history and physical examination) should be evaluated before each infusion, and LVEF should be monitored when the total dose is 320 mg/M^2, 480 mg/M^2, and every 160 mg/m^2 thereafter.
- **The triad of back pain, flushing, and chest tightness** is reported in 14%; this usually occurs in the first 5 minutes of treatment, resolves with discontinuation of the infusion, and does not recur with resumption of infusion at a slower rate.

- **Other:** Alopecia, foot-hand syndrome (painful desquamating dermatitis of hands and feet), erythrodyesthesia.
- Care should be exercised to avoid drug extravasation, which can cause tissue necrosis.

DRUG INTERACTIONS: Additive bone marrow suppression with AZT, ganciclovir, and pyrimethamine; monitor closely with co-administration.

PREGNANCY: Category D. Studies in rats showed severe maternal toxicity, embryolethality, fetal malformations, and embryotoxicity.

ddI – see Didanosine

d4T – see Stavudine

DIDANOSINE (ddI)

TRADE NAMES: *Videx* and *Videx EC* (Bristol-Myers Squibb) and generic

CLASS: Nucleoside analog

FORMULATIONS, REGIMENS AND PRICE

- **Forms**
  - Videx, didanosine 250mg, capsules EC 60, R 120.00
  - Videx, danosine 250mg, Buffered 60, R 121.05; didanosine 400mg, Buffered 60,R112.79
  - Videx, didanosine 400mg, capsules EC 60, R202.38
- **Regimens**
  - Caps: Patients <60 kg, 250 mg qd; with TDF, 200 mg qd. Patients >60 kg, 400 mg qd; with TDF, 250 mg qd. See Warnings. Powder: same as caps.

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* *Videx EC*: Generic form available and comparable EC formulation often preferred due to better tolerance, once-daily dosing and avoidance of buffer-related drug interactions (including ATV and IDV) and buffer-related side effects (diarrhea) (*J Infect Dis* 2001;28:150).

Warning: ddI/TDF: TDF increases intracellular levels of ddI, risking ddI toxicity and poor immune recovery with a blunted CD4 response (*AIDS* 2005;19:1987). Avoid this combination.

FOOD EFFECT: Food decreases ddI EC and buffered ddI levels 27% and 47%, respectively; must take >30 min before or >2 h after meal.

RENAL FAILURE

Wt	CrCl (mL/min)			
	> 60	30-59	10-29	< 10
>60 kg	400 mg/d	200 mg/d	125 mg/d	125 mg/d
<60 kg	250 mg/d	125 mg/d	100 mg/d	75 mg/d

HEPATIC FAILURE: Standard dose

ADVANTAGES: Once daily therapy; extensive experience, no selection of TAMs, active against some AZT- and d4T-resistant strains.

DISADVANTAGES: Need for empty stomach; toxicity profile including pancreatitis, neuropathy, and other mitochondrial toxicities; restricted use with TDF and d4T, and contraindicated with ribavirin. Limited data in regimens not including AZT or d4T. Potential for cross-resistance with TDF and ABC.

RESISTANCE: L74V and K65R are the most important resistance mutations. The L74V mutation results in cross-resistance to abacavir, and the K65R mutation causes cross-resistance with abacavir and tenofovir DF. Susceptibility to ddI is decreased with the accumulation of multiple TAMs. Resistance is associated with the presence of ≥3 of the following: 41L, 67N, 210W, 215Y/F, and 219Q/E. M184 does not cause clinically significant resistance unless combined with other mutations.

PHARMACOLOGY

- **Bioavailability:** Tablet – 40%; powder – 30%; food decreases bioavailability by 47% with buffered ddI, 27% with ddI EC. Take all formulations on an empty stomach.
- **T½:** 1.5 h
- **Intracellular T½:** 25 to 40 h
- **CNS penetration:** CSF levels are 20% of serum levels (CSF: plasma ratio=0.16-0.19).
- **Elimination:** Renal excretion: 50% unchanged in urine. Renal failure.

CAUTION:

SIDE EFFECTS

- **Pancreatitis (Black box FDA warning):** Reported in 1% to 9% (7%-9% in the pre-HAART era; it is <1% in the HAART era). ddI-associated pancreatitis is fatal in 6% (*J Infect Dis* 1997;175:255). The frequency of pancreatitis is dose-related. The drug should be discontinued if there is clinical evidence of pancreatitis. Risk factors for ddI-associated pancreatitis include renal failure, alcohol abuse, morbid obesity, history of pancreatitis, hypertriglyceridemia, cholelithiasis, endoscopic

retrograde cholangio-pancreatography (ERCP), and concurrent use of d4T, hydroxyurea, allopurinol, or pentamidine.

- **Peripheral neuropathy** with pain, numbness, and/or paresthesias in extremities. Frequency is 5% to 12%; it is increased significantly when ddI is given with d4T, hydroxyurea, or both (*AIDS* 2000;14:273). Onset usually occurs at 2 to 6 months of ddI therapy and may be persistent and debilitating if ddI is continued despite symptoms.
- **GI intolerance** with buffered tablets and powder are common. The EC formulation is preferred because it causes fewer GI side effects. If the buffered ddI preparation is used, an alternative is to use ddI pediatric powder reconstituted with 200 mL water and mixed with 200 mL *Mylanta DS* or *Maalox* extra strength with anti-gas suspension in patient's choice of flavor. The final concentration is 10 mg/mL, and the usual dose is 25 mL.
- **Hepatitis** with increased transaminase levels
- **Miscellaneous:** Rash, marrow suppression, hyperuricemia, hypokalemia, hypocalcemia, hypomagnesemia, optic neuritis, and retinal changes
- **Class adverse effect:** Lactic acidosis and severe hepatomegaly with hepatic steatosis caused by mitochondrial toxicity. This complication should be considered in patients with fatigue, abdominal pain, nausea, vomiting, and dyspnea. Laboratory studies show elevated serum lactate (>2 mmol/L), CPK, ALT, and/or LDH and low bicarbonate. CT scan or liver biopsy may show steatosis. This is a life-threatening reaction, and NRTIs should be stopped if the serum lactate level is >2 mmol/L with typical symptoms; most cases are associated with lactate levels >5 mmol/L. The most frequent cause is ddI/d4T. This combination should be avoided, especially in pregnancy (Black box FDA warning), based on reports of at least two fatal cases. Didanosine can presumably cause lipoatrophy, which is also believed to be mediated by mitochondrial toxicity.

DRUG INTERACTIONS

- **Tenofovir:** Concurrent use of TDF and ddI results in a 48-64% increase in the ddI AUC (*Curr Med Chem* 2006;13:2789). This occurs whether given with food or in a fasting state, whether administered simultaneously or separately, and whether ddI is given in buffered or EC formulation. The risk is ddI-associated side effects including lactic acidosis and pancreatitis. The recommendation is to prevent overexposure to ddI, but this has been complicated by suspiciously high failure rates, especially when used with NNRTI-based HAART. A second concern is high risk for selection of K65R and high rates of virologic failure with selection of K65R (*AIDS* 2005;19:1695; *AIDS* 2005;19:1183; *Antiviral Ther* 2005;10:171). A third concern has been raised by several reports of blunted CD4 response with this combination when there is failure to adjust the dose (*AIDS*

2005;19:569; *AIDS* 2005;19:1107; *AIDS* 2005;19:695).

- **Buffered formulation:** Drugs that require gastric acidity for absorption, including IDV, TPV, DLV, ATV, NFV, ketoconazole, tetracyclines, and fluoroquinolones, should be given 1 to 2 hours before or after ddI if the buffered formulation is used. (This limitation does not apply to FPV, SQV, EFV, or NVP, and it does not apply when using ddI EC).
- **Drugs that cause peripheral neuropathy** should be used with caution or avoided: EMB, INH, vincristine, gold, disulfiram, or cisplatin. Concurrent use of d4T and/or hydroxyurea potentiates the risk of peripheral neuropathy and pancreatitis. Co-administration of ddI is contraindicated due to anticipated high rates of peripheral neuropathy and pancreatitis.
- **Atazanavir:** buffered ddI reduces ATV AUC 87%. Food with ATV + ddI EC results in reduced ddI exposure. The combination of ATV and any form of ddI requires separate administration. If using buffered formulation, give ATV 2 hours before or 1 hour after buffered ddI.
- **Allopurinol** increases ddI concentrations. Avoid co-administration.
- **Oral ganciclovir** increases ddI AUC by 100% when administered 2 hours after ddI or concurrently. Monitor for ddI toxicity and consider dose reduction.
- **Ribavirin** increases intracellular levels of ddI and may cause serious toxicity; avoid combination (*Antiviral Ther* 2004;9:133).

PREGNANCY: Category B. No lifetime harm in rodent teratogen and carcinogenicity studies; placental passage in humans shows newborn:maternal drug ratio of 0.5; no controlled studies have been performed in humans. Pharmacokinetics are not altered in pregnancy (*J Infect Dis* 1999;180:1536). ddI appears safe and is recommended as an alternative to AZT/3TC in the DHHS guidelines (July 7, 2006, p. 41). The combination of ddI and d4T should be avoided in pregnancy due to excessive rates of lactic acidosis and hepatic steatosis (*Sex Transm Infect* 2002;78:58).

DIFLUCAN – see Fluconazole

DOXYCYCLINE

TRADE NAMES: *Vibramycin* (Pfizer), *Doryx* (Warner Chilcott), or generic

FORMS AND PRICES: Doxycyl, doxycycline 100mg, capsules 100, R 39.71; Doxycyl, doxycycline 100mg, capsules 500, R 179.70; Doxycyl, doxycycline 100mg, capsules 1000, R 267.90; Doxycyl, doxycycline 50mg, capsules 30, R 48.67

CLASS: Tetracycline

INDICATIONS AND DOSE: 100 mg PO bid

- ***C. trachomatis:*** 100 mg PO bid x 7 days.
- **Bacillary angiomatosis:** 100 mg PO bid x ≥3 months; lifelong with relapse. Tick bite fever- 100mg bid for 7-10 days
- **Syphilis (primary, secondary, and early latent) in patients with contraindication to penicillin:** 100 mg bid x 14 days + close monitoring
- **Respiratory tract infections (sinusitis, pneumonia, otitis):** 100 mg bid x **7-14 days** Tick bite fever- 100mg bid for 7-10 days

PHARMACOLOGY

- **Bioavailability:** 93%. Complexes with polyvalent cations (Ca^{++}, Mg^{++}, Fe^{++}, Al^{+++}, etc.), so milk, mineral preparations, cathartics, and antacids with metal salts should not be given concurrently.
- **T½:** 18 hours
- **Elimination:** Excreted in stool as chelated inactive agent independent of renal and hepatic function.
- **Dose modification with renal or hepatic failure:** None

SIDE EFFECTS: GI intolerance (10% and dose-related, reduced with food), diarrhea; deposited in developing teeth – contraindicated from mid-pregnancy to term and in children <8 years of age (Committee on Drugs, American Academy of Pediatrics); photosensitivity (exaggerated sunburn); *Candida* vaginitis; "black tongue;" rash; esophageal irritation.

DRUG INTERACTIONS: Chelation with cations to reduce oral absorption; half-life of doxycycline decreased by carbamazepine (*Tegretol*), cimetidine, phenytoin, barbiturates; may interfere with oral contraceptives; potentiates oral hypoglycemics, digoxin, and lithium.

PREGNANCY: Category D. Use in pregnant women and infants may cause retardation of skeletal development and bone growth; tetracyclines localizes in dentin and enamel of developing teeth to cause enamel hypoplasia and yellow-brown discoloration. Tetracyclines

should be avoided in pregnant women and children <8 years unless benefits outweigh these risks.

EFAVIRENZ (EFV)

TRADE NAME: *Stocrin* (Merck)

CLASS: NNRTI

FORMULATIONS, REGIMENS AND PRICE

- **Forms and prices:** Stocrin, efavirenz 50mg, capsules 30, R 27.70; Stocrin, efavirenz 200mg, capsules 90, R 262.07; Stocrin, efavirenz 600mg, tablets 30, 161.25
- **Regimens:** 600 mg qd., preferably on an empty stomach (especially in the first 2-3 wks).

FOOD EFFECT: Take on empty stomach or with a low-fat meal; a concurrent meal increases AUC 20% and peak level 40-50%, which may increase side effects. The recommendation to take on an empty stomach applies primarily to the initial weeks of treatment, when CNS side effects are greatest.

RENAL FAILURE: Standard dose

HEPATIC FAILURE: No recommendations; use with caution

INDICATIONS AND DOSE: EFV-based HAART is a favored regimen for treatment-naïve patients without pregnancy potential. The standard dose is 600 mg/day, usually in combination with two nucleosides, taken in the evening to reduce the CNS side effects that are common in the first 2 to 3 weeks. Patients should be warned of these side effects and the possibility of rash. Recommendation for discontinuing EFV-based HAART are summarized.

- **Timing of dose:** EFV is usually taken in the evening so that major CNS effects go unnoticed during sleep. However, morning dosing is safe, effective and preferred by some patients due to sleep disturbances (3rd IAS Conf, Rio, 2005, Abstr. WePe 12.3 C03).

ADVANTAGES: EFV-based HAART is superior or comparable to all comparators for initial treatment in multiple clinical trials; sustained activity with 5-year follow-up; once daily therapy; adherence requirements reduced by long half-life; low pill burden; minimal food effect.

DISADVANTAGES: High rate of CNS effects in first 2-3 weeks; single mutation confers high-level resistance to NNRTI class; NNRTI resistance does not impair fitness; potential for teratogenicity if used in pregnancy.

- **Durability:** Retrospective analysis of 3,565 patients given various HAART regimens showed EFV was the most likely to show sustained viral suppression (*J Infect Dis* 2005;192:1387).
- **Comparison with NVP: 2NN.** The trial randomized 1147 treatment-naïve patients to receive EFV, NVP qd, NVP bid, or EFV/NVP, each in combination with 3TC/d4T. By ITT analysis at 48 weeks, the frequency of VL <50 c/mL was: EFV – 70%, NVP bid – 65.4%, NVP once daily – 70% and NVP/EFV – 62.7% EFV and NVP were comparable, but NVP did not meet FDA requirements for non-inferiority to EFV (*Lancet* 2004;363:1253). The only significant difference in virologic outcome was between EFV and EFV/NVP. The median increase in CD4 count was 150-170/mm^3 in all four groups. NVP therapy was implicated in 2 drug-related deaths.
- **HIV-NAT 009:** Open-label trial of EFV (600 mg qd)/IDV (800 mg bid)/RTV (100 mg bid) in 61 patients with virologic failure with a nucleoside regimen (10 CROI, Boston, MA, 2003, Abstr 566). At 48 weeks 53 (87%) had viral load <50 c/mL, the median VL decrease was –2.3 $\log_{10}$ c/mL and the median CD4 increase was 116/mm^3.
- **Switch studies**
  - **DMP 049** was a study of patients who were responding well to PI-containing HAART regimens with viral load <50 c/mL and were randomized to continue the PI-based regimen or switch to EFV (*J Acquir Immune Defic Syndr* 2002;29[suppl 1]: S19). At 48 weeks, VL was <50 c/mL in 97% of the EFV arm and 85% of the PI continuation arm.
- **NRTI-sparing regimen:** The combination most extensively studied is LPV/r 533/133 mg bid + EFV 600 mg/d, in ACTG 5142. Intent-to-treat analysis showed 83% of LPV/r/EFV recipients had VL <50 c/mL at 96 weeks. This regimen is used in patients who have no nucleoside options. These include lactic acidosis those with anaemia and peripheral neuropathy.

RESISTANCE: The K103N mutation is most common and causes high-level resistance to EFV as well as NVP and DLV. This mutation does not reduce HIV fitness. Patients with NNRTI resistance should not continue EFV. Continued use of EFV with virologic failure is likely to spawn more NNRTI mutations and other NNRTIs in development. Other major RT mutations associated with reduced susceptibility are RT codons 181C/I, 188L, 190S/A, and 225H. The 181C/I mutation is not selected by EFV, but this mutation contributes to low-level EFV resistance. There are limited data on clinical efficacy of EFV in patients with this mutation.

PHARMACOLOGY

- **Oral bioavailability:** Not known. High-fat meals increase absorption of both capsule and tablet forms by 39% and 79%, respectively, and should be avoided in patients who are experiencing CNS side

effects. Serum levels are highly variable for reasons that are unclear (*AIDS* 2001;15:71) and this variation explains some of the variations in virologic response (*Antimicrob Agents Chemother* 2004;48:979).

- **T½:** 36-100 h (11th CROI, San Francisco, 2004, Abstr. 131)
- **Distribution:** Highly protein-bound (>99%); CSF levels are 0.25% to 1.2% plasma levels, which is above the IC_{95} for wild-type HIV (*J Infect Dis* 1999;180:862). Virologic failure correlates with levels <1.1 mg/L (12th CROI, Boston, Feb. 2005, Abstr. 80).
- **Elimination:** Metabolized by cytochrome P450 metabolic pathway, primarily CYP2B6 and, to a lesser extent, CYP3A4. Studies of polymorphisms at codon 516 of the CYP2B6 gene have shown significant differences that correlate with half-life, levels, and CNS toxicity (*Clin Infect Dis* 2006;42:401). Depending on these genetic differences, the median plasma half-life of EFV varied from 23 hours to 48 hours. The duration of therapeutic levels (>46 ng/mL) varied from 5.8 days to 14 days, and the frequency of therapeutic levels lasting >21 days ranged from 5% to 29%. Prolonged half-life and high levels are more common in African-Americans (*Antimicrob Agents Chemother* 2003;47:130). The substantial variations in EFV levels shown by these data may complicate drug discontinuation and correlate with psychiatric side effects.
- **Dose modification with renal or hepatic disease:** No dose modification *(AIDS* 2000;14:618; *AIDS* 2000;14:1062). More frequent monitoring is advocated when given with hepatic disease.

SIDE EFFECTS

- **Rash:** Approximately 15% to 27% develop a rash, which is usually morbilliform and does not require discontinuation of the drug. More serious rash reactions that require discontinuation are blistering and desquamating rashes, noted in about 1% to 2% of patients, and Stevens-Johnson syndrome, which has been reported in 1 of 2,200 recipients of EFV. The median time of onset of the rash is 11 days, and the duration with continued treatment is 14 days. The frequency with which the rash requires discontinuation of EFV is 1.7% compared with 7% given NVP.
- **CNS** side effects have been noted in up to 52% of patients but are sufficiently severe to require discontinuation in only 2% to 5%. Symptoms are noted on day 1 and usually resolve after 2 to 4 weeks. They include confusion, abnormal thinking, impaired concentration, depersonalization, abnormal dreams, and dizziness. Other side effects include somnolence, insomnia, amnesia, hallucinations, and euphoria. Patients need to be warned of these side effects before starting therapy and should also be told that symptoms improve with continued dosing and rarely persist longer than 2 to 4 weeks. It is recommended that the drug be given in the evening on an empty stomach during the initial weeks of treatment, because a high-fat

meal increases absorption by up to 80%. This reduces side effects but does not eliminate them because of the long half-life of EFV. There is a potential additive effect with alcohol or other psychoactive drugs. Patients need to be cautioned to avoid driving or other potentially dangerous activities if they experience these symptoms. This drug should be avoided if possible in attend who work night shifts. This includes nurses, truck drivers and security guards. An occupational history must be obtained. Also women with infants may also have difficulty with this drug if their babies need to be fed at night

- **Psychiatric disorders:** Serious disorders have been reported in recipients of EFV, including severe depression in 2.4% (Bristol-Myers Squibb letter to providers, March 2005).
- **Hyperlipidemia:** The D:A:D study showed that EFV is associated with increased triglyceride and total cholesterol levels; these effects were greater for EFV compared to NVP (*J Infect Dis* 2004;189:1056). One study of 636 patients given IDV-based HAART vs EFV-based HAART showed no significant difference in lipid profiles (*HIV Clin Trials* 2003;4:29).
- **False-positive urine cannabinoid (marijuana) test:** This occurs with the screening test only, and only with the Microgenic's *CEDIA DAU* Multilevel THC assay.
- **Increased transaminase levels:** Levels >5 x ULN in 2% to 8% (*Hepatology* 2002;35:182; *HIV Clin Trials* 2003;4:115). Frequency is increased with hepatitis C or with concurrent hepatotoxic drugs. Hepatotoxicity is less frequent and less severe than seen with NVP – grade 3-4 in 12% given NVP vs 4% given EFV in one study of 298 patients (*HIV Clin Trials* 2003;4:115). The mechanism is unknown. Discontinuation of EFV is recommended if hepatotoxicity is symptomatic (infrequent) or ascribed to hypersensitivity, or if the transaminase levels are >10x ULN in the absence of other causes (grade IV) (*Clin Liver Dis* 2003;7:475). Some authorities recommend discontinuation with transaminase levels >5x ULN.

BLACK BOX WARNINGS: None.

DRUG INTERACTIONS: EFV both induces and, to a lesser extent, inhibits the cytochrome P450 CYP3A4 enzymes *in vitro*. Enzyme induction has been observed in the majority of PK studies.

CONTRAINDICATED DRUGS FOR CONCURRENT USE: Astemizole, terfenadine, midazolam, triazolam, cisapride, ergot alkaloids, St. John's wort, and voriconazole

OTHER DRUGS WITH SIGNIFICANT INTERACTIONS: Drugs contraindicated for concurrent use are **astemizole**, **terfenadine**, **cisapride**, **midzolam**, **trizolam**, **ergot derivatives**, **voriconazole** and **St. John's wort**. EFV may reduce concentrations of **phenobarbital**, **phenytoin**, and **carbamazepine**; monitor levels of anticonvulsant. **Rifampin** decreases

EFV levels by 25%; rifampin levels are unchanged: **Rifabutin** has no effect on EFV levels, but EFV reduces levels of rifabutin by 35%; with concurrent use, the recommended dose of rifabutin is 450-600 mg/day or 600 mg 3x/week plus the standard EFV dose (*MMWR* 2002;51[RR-7]:48). Concurrent use with **ethinyl estradiol** increases levels of the contraceptive by 37%; implications are unclear, but a second form of contraception is recommended. Some authorities suggest an increase in the does of EFV to 800mg. EFV ↓ **simvastatin** AUC by 58%, ↓ **atorvastatin** AUC by 43%, and **pravastatin** by 40%. An increase in statin dose may be needed, but do not exceed the maximum dose (*J Acquir Immune Defic Syndr* 2005;39:307). **Atorvastatin**, **pravastatin**, **rosuvastatin**, or **fluvastatin** may be preferred. Monitor carefully when using **warfarin** with EFV. There is a 46% incidence of rash reactions when combining EFV and **clarithromycin**, and levels of clarithromycin are decreased 39%; consider **azithromycin**. Interactions and dose recommendations for EFV in combination with PIs are listed in Table 5-12 below.

■ TABLE 5-12: **PI Interactions and Dose Recommendations**

PI	PI AUC	EFV AUC	Recommendation
IDV	↓31%	No change	IDV 1000 mg q8h + EFV 600 mg qhs or IDV 800 mg bid + RTV 200 mg bid + EFV 600 mg qd
NFV	↑20%	No change	NFV 1250 mg bid + EFV 600 mg qhs
SQV	↓62%	↓12%	Consider SQV/RTV 1000/100 mg bid
SQV/RTV	No change	No change	Standard doses; qd dosing not recommended
LPV/r	↓40%	No change	LPV/r 600/150 mg (3 caps) bid + EFV 600 mg qhs
ATV	↓74%	No change	ATV 300 mg qd + RTV 100 mg qd + EFV 600 mg qd; unboosted ATV not recommended
DRV	↓13%	↑21%	Limited data; standard doses both drugs

PREGNANCY: Category D. This drug caused birth defects (anencephaly, anophthalmia, and microphthalmia) in 3 of 20 gravid cynomolgus monkeys. There have been four cases of neural tube defects in infants born to women with first-trimester exposures to EFV, including three with meningomyeloceles and one with Dandy-Walker syndrome (Bristol-Myers Squibb letter to providers, March 2005). The Antiretroviral Pregnancy Registry (through January 2006) shows birth defects in 6 of 244 exposures in the first trimester, none with neural tube disorders. Birth defects were reported in 1 of 15 neonates with exposure after the first trimester. EFV should be avoided in the first trimester, and women with childbearing potential should be warned of this. Safety in the second or third trimester is not established but should be safe since the neural tube has closed. Pregnant women exposed to EFV should be reported to the Antiretroviral Pregnancy Registry, 800-258-4263 (8:30 am-5:30 pm EST, Mon-Fri.).

EMTRICITABINE (FTC)

FTC alone is not registered in South Africa, only co formulated with Tenofovir as Truvada

TRADE NAME: *Emtriva* (Gilead Sciences)

CLASS: NRTI

FORMULATIONS, REGIMENS AND PRICE

- **Forms:** Truvada 300/200 qd R327.90; TDF/FTC (*Truvada*) – tab 300/200 mg; EFV/TDF/FTC (*Atripla*) – tab 600/300/200 mg; Truvada 300/200 qd R327.90
- **Regimens:** FTC, 200 mg qd; TDF/FTC, 1 tab qd; EFV/TDF/FTC, 1 tab hs on empty stomach

FOOD EFFECTS: None

RENAL FAILURE: Adjust dosing of FTC as follows for CrCl levels: 30-49, 200 mg q 48 h; 15-29 mL/min, 200 mg q 72 h; <15 mL/min or dialysis, 200 mg q 96 h. Adjust *Truvada* as above for CrCl levels ≥30 mL/min, but avoid co-formulation at <30 mL/min. Do not use *Atripla* with CrCl <50 mL/min.

HEPATIC FAILURE: No dose adjustment

ADVANTAGES: Potent antiretroviral activity, well tolerated, no food effect, longer intracellular half-life than 3TC, once-daily dosing coformulated with TDF (*Truvada*). Delays TAMs. Possible decreased risk of K65R with TDF/FTC vs. TDF/3TC and decreased risk of M184V with TDF/FTC vs. AZT/3TC. Active against HBV.

DISADVANTAGES: Rapid selection of 184V RT mutation in non-suppressive regimen with substantial loss of activity. 3TC has an advantage in co-formulations with AZT (*Combivir*), AZT/ABC (*Trizivir*), and ABC (*Epzicom*). Cutaneous hyperpigmentation (usually palms and soles) noted in 3% of patients, especially dark skinned individuals. **Note:** Most authorities consider 3TC and FTC to be very comparable.

3TC COMPARISON: Similar to 3TC in activity against HIV, loss of most activity and rapid selection of M184V mutation, prolonged intracellular half-life and activity against HBV (*Antimicrob Agents Chemother* 2004;48:3702; *Clin Infect Dis* 2006;42:126). 3TC has been more extensively used and studied. FTC has a longer intracellular half-life.

CLINICAL TRIALS

- **Hepatitis B**: FTC is considered equivalent to lamivudine for activity against HBV. One study found that resistance by YMDD mutants was delayed with FTC compared to 3TC (*AIDS* 2005;19:221). Another study found no dedectable HBV DNA levels with FTC monotherapy

in 65% of patients at 24 weeks (*Antimicrob Agents Chemother* 2006;50:1642). Current recommendations for coinfected patients are for TDF/FTC or TDF/3TC when treatment of HIV is indicated. For HIV-infected patients without indication to treat HIV, agents used to treat HBV should not be active against HIV: interferon, entecavir, adefovir, or telbivudine (*Clin Infect Dis* 2006;43:904).

RESISTANCE: Non-suppressive therapy with FTC results in the rapid selection of the M184V mutation, which confers high-level resistance to 3TC and FTC, modest decreases in susceptibility to abacavir and ddI. and increased susceptibility to TDF, AZT, and d4T. K65R, and multiple TAMS reduce activity of FTC 3- to 7-fold. With maximum selection pressure, the TDF/FTC combination produces mutants with the K65R and M184V genotype (*Antimicrob Agents Chemother* 2006; PMID 16982781), although K65R has not been observed in clinical trials (GS 934 and Abbott 418) using this combination. All of these changes apply to 3TC as well (*J Acquir Immune Defic Syndr* 2006; PMID 17075395).

PHARMACOLOGY

- **Bioavailability:** 93%, not altered by meals
- **Levels:** C_{max} 1.8 ± 0.7 µg/mL; C_{min} 0.09 µg/mL
- **Distribution:** Protein-binding <4%, concentrated in semen
- **T½:** plasma, 10 h; intracellular, 39 h (*Antimicrob Agents Chemother* 2004;48:1300).
- **Elimination:** 13% metabolized to sulfadioxide and glucoronide metabolites. Unchanged drug and metabolites are renally eliminated.

SIDE EFFECTS: Generally well tolerated with minimal toxicity. Occasionally, patients note nausea, diarrhea, headache, asthenia, or rash; about 1% discontinue the drug due to adverse effects. Lactic acidosis and steatosis, including fatal cases, have been reported with nucleosides. Rare patients who do not tolerate FTC will tolerate 3TC (*J Antimicrob Chemother* 2006;58:227). Skin hyperpigmentation has been noted primarily on palms and soles in 2% and almost exclusively in Africans and African-Americans. FTC is active against HBV, so discontinuation may result in HBV exacerbation **(FDA black box warning)**.

DRUG INTERACTIONS: None of clinical consequence are known.

PREGNANCY: Category B. There are no studies of FTC in pregnancy. TDF/FTC is not recommended due to insufficient data on the safety of TDF (DHHS Guidelines, Oct. 10, 2006, p. 95).

EPIVIR – see Lamivudine (3TC)

EPZICOM – see Abacavir and Lamivudine

ETHAMBUTOL (EMB)

TRADE NAME: *Ethambutol*

FORM AND PRICE: Sandoz-ethambutol, ethambutol 400mg, Tablets 10, R 91.0

INDICATIONS AND DOSE: Ethambutol is co-formulated with Rifampicin, INH and Pyrazinamide for the intensive phase of TB treatment. There are a number of formulations of this including Rifafour–e- 275 that contains 275mg of ethambutol. Active tuberculosis or infections with *M. avium* complex or *M. kansasii*. Ethambutol dosing for MAI: 15 mg/kg/d + macrolide.

■ TABLE 5-13: **Ethambutol Dosing for Tuberculosis**

Dosing interval	Weight		
	40-55 kg	56-75 kg	76-90 kg
Daily	800 mg	1200 mg	1600 mg
2x/wk	2000 mg	2800 mg	4000 mg
3x/wk	1200 mg	2000 mg	2400 mg

PHARMACOLOGY

- **Bioavailability:** 77%
- **T½:** 3.1 h
- **Elimination:** Renal
- **Dose modification in renal failure:** CrCl >50 mL/min – 15-25 mg/kg q24h; CrCl 10-50 mL/min – 15-25 mg/kg q24h-q36h; CrCl <10 mL/min – 15-25 mg/kg q48h

SIDE EFFECTS: Dose-related ocular toxicity (decreased acuity, restricted fields, scotomata, and loss of color discrimination) with 25 mg/kg dose (0.8%), hypersensitivity (0.1%); peripheral neuropathy (rare); GI intolerance. These changes often improve when the drug is discontinued, but recovery is often partial (*J Commun Dis* 2003;35:230).

WARNINGS: Patients to receive EMB in doses of 25 mg/kg should undergo a baseline screening for visual acuity and red-green color perception; this examination should be repeated at monthly intervals during treatment (*MMWR* 1998;47[RR-20]:31).

DRUG INTERACTIONS: Aluminum-containing antacids may decrease absorption.

PREGNANCY: Category C. Teratogenic in animals; no reported adverse effects in women with >320 case observations.

FAMCICLOVIR – see Acyclovir

FENOFIBRATE

TRADE NAME: *Lipanthyl,* fenofibrate 200mg, capsules 30, R 246.24l

CLASS: Fibrate

INDICATIONS AND DOSES: Hypertriglyceridemia, especially levels of >500-700 mg/dL. Starting dose 48 mg/day then increase if necessary at 4 to 8 week intervals; maximum dose – 145 mg/day; some authorities consider this the usual dose (*Clin Infect Dis* 2006;43:645). Take as a single daily dose with meal.

MONITORING: Triglyceride levels – discontinue use if response is inadequate after 2 months at 145 mg/day. Warn patients to report symptoms of myositis and obtain CPK if there is muscle tenderness, pain, or weakness. Monitor AST + ALT – discontinue if there is an otherwise unexplained increase to ≥3x ULN.

PRECAUTIONS: Avoid or use with caution with gallbladder disease, hepatic disease, renal failure with CrCl <50 mL/min.

PHARMACOLOGY

- **Bioavailability:** Good, improved 35% with food.
- **T½:** 20 h
- **Elimination:** Renal – 60%; fecal – 25%
- **Renal failure:** 54 mg/day; increase with caution due to risk of myopathy, and monitor CPK.

SIDE EFFECTS

- **Hepatic:** Dose-related hepatotoxicity with increased transaminase levels to >3x ULN in 6% receiving doses of 134-201 mg/day; most had return to normal levels with drug discontinuation or with continued treatment.
- **Influenza-like syndrome**
- **Rash, pruritus, and/or urticaria** in 1% to 3%
- **Myositis:** Warn patient regarding symptoms of muscle pain, tenderness, and/or weakness, especially with fever or malaise. Draw CPK and discontinue if significantly typical symptoms occur.
- **Rare:** Pancreatitis, agranulocytosis, cholecystitis, eczema, thrombocytopenia.

DRUG INTERACTIONS

- **Oral anticoagulants:** Potentiates warfarin activity.
- **Cholestyramine and colestipol:** These drugs bind fenofibrate – take fenofibrate >1 hour before or 4 to 6 hours after bile acid binding agent.
- **Statins:** Increased risk of rhabdomyolysis with renal failure.

PREGNANCY: Category C

FLAGYL – see Metronidazole

FLUCONAZOLE

TRADE NAME: *Diflucan* (Pfizer) and generic

FORMS AND PRICE: Generic, fluconazole 150mg, capsule 1; Diflucan, fluconazole 150mg, capsules 4; Diflucan, fluconazole 200mg, capsules 28; Diflucan, fluconazole 200mg/5ml, suspension 35; Generic, fluconazole 50mg, capsules 14; Diflucan, fluconazole 50mg, suspension 35; Diflucan, fluconazole 200/100, injection 1

CLASS: Triazole related to other imidazoles – ketoconazole, clotrimazole, miconazole; triazoles (fluconazole and itraconazole) have three nitrogens in the azole ring.

ACTIVITY: *Candida* – active vs 95% of all strains in fluconazole-naïve patients *Cryptococcus*.

DOSE: See Table 5-14

RESISTANCE: Fluconazole is the preferred azole for systemic treatment of candidiasis, but the major concern with long-term use is azole-resistant candidiasis, which correlates with azole exposure and CD4 count <50/mm^3 (*J Infect Dis* 1996;173:219). All oral systemically active azoles predispose to resistance. Some cases involve evolution of resistance by *C. albicans*, and others reflect substitution with non-*albicans* species such as *C. glabrata* or *C. krusei* (*Antimicrob Agents Chemother* 2002;46:1723). Resistance is uncommon when fluconazole is used to treat vaginitis (*Clin Infect Dis* 2001;33:1069; *Med Mycol* 2005;43:647). Fluconazole-resistant strains of *Candida* can often be treated with caspofungin (*Antimicrob Agents Chemother* 2002;46:1723), (*Clin Infect Dis* 2001;33:1447), micafungin (*Clin Infect Dis* 2004;39:842), (*Clin Infect Dis* 2006;42:1179), or amphotericin and possibly voriconazole, posaconazole, and itraconazole.

PHARMACOLOGY (see Table 5-14)

- **Bioavailability:** >90%
- **CSF levels:** 50% to 94% serum levels
- **T½:** 30 h
- **Elimination:** Renal; 60% to 80% of administered dose excreted unchanged in the urine
- **Dose modification in renal failure:** CrCl >50 mL/min – usual dose; 10-50 mL/min – half dose; CrCl <10 mL/min – quarter dose; hemodialysis – standard dose (200-400 mg) after each dialysis.

SIDE EFFECTS: Headache, nausea, and abdominal pain, the most common side effects, are dose-related and most common with >400 mg/d (*J Antimicrob Chemother* 2006;57:384). GI intolerance (1.5% to 8%, usually does not require discontinuation); rash (5%); transient increases in hepatic enzymes (5%), increases of ALT or AST to >8x upper limit of normal requires discontinuation (1%); dizziness, hypokalemia, and headache (2%). Reversible alopecia in 10% to 20% receiving ≥400 mg/day at median time of 3 months after starting treatment (*Ann Intern Med* 1995;123:354).

DRUG INTERACTIONS: Inhibits cytochrome P450 (2C8/9/19 and 3A4) hepatic enzymes resulting in increased levels of atovaquone, some benzodiazepines, clarithromycin, opiate analgesics, warfarin, SQV, phenytoin (?88%), oral hypoglycemics, rifabutin, cisapride (*Propulsid*), terfenadine and astemizole may cause life-threatening arrhythmias. Fluconazole levels are reduced with rifampin; with rifabutin there is no effect on fluconazole levels, but rifabutin AUC increases 80% – consider rifabutin dose of 150 mg/day. Fluconazole increases AZT AUC 74% due to decreased AZT glucuronidation; monitor for AZT toxicity.

PREGNANCY: Category C. Animal studies show reduced maternal weight gain and embryolethality with dose >20x comparable to doses in humans; no studies in humans. Recommendation is for use only with systemic fungal infections. Avoid use for prophylaxis, thrush and vaginitis.

■ TABLE 5-14: **Dose Recommendations for Fluconazole** (*Clin Infect Dis* 2000;30:652)

Indications	Dose Regimen	Comment
CANDIDA		
Oral Thrush		
Acute	100 mg PO x 7-14 days	Response rate 80% to 100%, usually within 5 days; may need up to 400-800 mg/day. Maintenance therapy often required in late-stage disease without immune reconstitution. Topical therapy (e.g., clotrimazole) preferred. Chronic treatment: Indication is severe or frequent recurrence. Options are topical agent prn or chronic suppressive oral fluconazole. Risk of fluconazole resistance is increased (*Clin Infect Dis* 2000;30:749).
Prevention	100-200 mg PO qd	
Esophagitis		
Acute	200 mg/day PO or IV up to 800 mg/day x 14-21 days	Relapse rate is 85-90%. Relapse rate is >80% within 1 year in absence of maintenance therapy.
Vaginitis	150 mg x 1 Multiple recurrences: Fluconazole 150 mg weekly	Response rate 90% to 100% in absence of HIV infection. Topical azoles generally preferred.
CRYPTOCOCCOSIS		
Non-meningeal, acute	400 mg/day PO or Amphotericin B	Fluconazole is recommended by the IDSA as the preferred treatment + flucytosine (100 mg/kg/day) for cryptococcal pneumonia (*Clin Infect Dis* 2000;3:710).
Meningitis		
Acute	400-800 mg/day PO x 10 to 12 wks, followed by maintenance	Acute treatment with amphotericin B x 2 weeks is preferred (*Clin Infect Dis* 2000;30:710). Alternative in patients with mild-to-moderate disease is fluconazole 400-800 mg/day x 10 to 12 weeks ± flucytosine (100 mg/kg/day x 6 weeks). Continue maintenance until immune reconstitution with CD4 >100-200/mm^3 x >6 months.
Consolidation (after Ampho induction)	400 mg PO qd x 8 weeks, followed by maintenance	
Maintenance	200 mg PO qd	

FOSAMPRENAVIR (FPV)

TRADE NAME: Europe, *Telzir* (Glaxo)

CLASS: Protease inhibitor (pro-drug of amprenavir)

FORMULATIONS, REGIMENS AND PRICE

- **Form:** 700 mg tab
- **Regimen:** Treatment-naïve patients: FPV (unboosted) 1400 mg bid; FPV/r 1400/200 mg qd or 700/100 mg bid. Treatment-experienced patients: FPV/r 700/100 mg bid.

FOOD EFFECT: Not significant

EFV: With EFV, use RTV-boosted regimens. If using qd regimen, increase RTV dose to 300 mg qd.

RENAL FAILURE: Standard dose

HEPATIC FAILURE: Child-Pugh score: 5-8, FPV 700 mg bid without RTV boosting; >8, avoid FPV

STORAGE: Room temperature, up to 25ºC or 77ºF

RESISTANCE: In trials of FPV in PI-naïve patients, the predominant mutations in patients experiencing virologic failure were 32I, 46I/L, 47V, and 54L/V/M, all mutations that cause minimal cross-resistance with other PIs. The primary PI mutations are I50V, which also confers resistance to LPV, and I84V, a multi-PI resistance mutation. Patients failing FPV/r in the SOLO trial had no PI mutations.

WARNINGS: Hepatic disease; see dose modification.

ADVANTAGES: (1) Potency comparable to LPV/r (*Lancet* 2006;368:476), (2) no food requirement, (3) may be given qd (treatment-naïve only), (4) favorable resistance profile that may preserve PI options when FPV is boosted with RTV.

DISADVANTAGE: Once-daily therapy not recommended for PI-experienced patients. GI tolerance and effect on lipids are similar to LPV/r.

PHARMACOLOGY

- **Absorption:** Not affected by food (unlike APV); bioavailability not established
- **Elimination:** APV is an inhibitor, inducer and substrate for P450 3A4
- **T½:** 7.7 h

SIDE EFFECTS

- **Skin rash:** The common adverse reaction is skin rash, seen in 12% to 33% of patients (package insert), that is sufficiently severe to result in discontinuation in <1%. FPV contains a sulfa moiety, so

caution is advised with use in patients with a history of sulfa allergy, but no increase in rashes was noted in such patients in the registration trials.

- **GI intolerance** is most common and includes nausea, vomiting, diarrhea and/or abdominal pain is reported in up to 40%, but severe in only 5% to 10%; diarrhea is much less frequent compared to NFV (NEAT and SOLO trials), GI side effects were similar to those of LPV/r in the KLEAN trial. GI intolerance rates appeared no more frequent or severe when FPV is combined with RTV 200 mg/day, although there may be individual patient exceptions.
- **Hepatotoxicity:** ALT levels are increased >5x ULN in 6% to 8%
- **Lipids:** Early studies suggested minimal effect, but the KLEAN trial indicated that lipid changes with FPV/r are similar to those with LPV/r. There appears to be no significant impact with FPV alone, but triglycerides are elevated to >750 mg/dL in 5% to 8% given RTV-boosted FPV.
- **Lipodystrophy:** Observed with FPV.

BLACK BOX WARNING: None

DRUG INTERACTIONS

- **The following drugs are contraindicated for concurrent use:** Astemizole, cisapride, dihydroergotamine, ergotamine, lovastatin, midazolam, pimozide, terfenadine, triazolam, rifampin, simvastatin, St. John's wort, flecainide, propafenone, and fluticasone.
- **The following drugs should be given concurrently with caution: Phenobarbital, phenytoin**, and **carbamazepine** have potential to decrease APV levels and various effects on anticonvulsant levels – monitor anticonvulsant levels. **Ethinyl estradiol/norethindrone** decrease APV levels; alternative birth control methods should be used. **Methadone** levels decrease 35% and APV levels are decreased. Consider alternative antiretroviral agent; if used together, Monitor for methadone withdrawal. **Bepridil** and **alprazolam** should be given with caution.
- **PIs:** See list of PIs.
- **Other drug interactions: Rifampin** decreases APV AUC by 82% and should not be used concurrently. **Rifabutin** decreases APV AUC by 15% and FPV increases rifabutin AUC by 193%; use standard FPV dose and rifabutin at 150 mg qd or 300 mg 2-3x/week. **Clarithromycin** increases APV AUC by 18%; use standard doses of both drugs. **Ketoconazole** increases APV AUC by 32% and ketoconazole AUC increases 44%; use standard doses of both drugs. FPV increases **sildenafil** AUC by 2-11x; do not exceed 25 mg/48 hours. **Vardenafil** AUC may also increase – limit dosage to 2.5 mg/24 hours (2.5 mg/72 hours with FPV/RTV).

PREGNANCY: Category C. Animal studies showed no embryo-fetal developmental abnormalities. There are inadequate data on safety and pharmacokinetics in pregnancy to recommend use (DHHS Guidelines, Oct. 10, 2006, p. 97).

FOSCARNET

TRADE NAME: *Foscavir* (AstraZeneca)

INDICATIONS AND DOSING

■ TABLE 5-15: **Dose Recommendations for Foscarnet**

Indication	Dose Regimen
CMV retinitis	Induction: 60 mg/kg IV q8h or 90 mg/kg IV q12h x 14-21 days Maintenance: 90-120 mg/kg IV qd*
CMV (other – GI)	60 mg/kg IV q8h or 90 mg/kg IV q12h x 14-21 days, indications for maintenance treatment are unclear
Acyclovir-resistant HSV	40 mg/kg IV q8h or 60 mg/kg q12h x 3 weeks
Acyclovir-resistant VZV	40 mg/kg IV q8h or 60 mg/kg q12h x 3 weeks

* Survival and time to relapse may be significantly prolonged with maintenance dose of 120 mg/day vs 90 mg/day (*J Infect Dis* 1993;168:444).

■ TABLE 5-16: **Foscarnet Dose Adjustment in Renal Failure**

CrCl (mL/min/kg)	60 mg/kg Dose	90 mg/kg Dose	120 mg/kg Dose
>1.4	60	90	120
1.4-1.3	49	78	104
1.3-1.1	42	75	100
1.1-0.9	35	71	94
0.9-0.7	28	63	84
0.7-0.5	21	57	76

Hemodialysis: 60 mg/kg post-HD (consider serum level 500-800 mcmol).

ACTIVITY: Active against herpesviruses including CMV, HSV-1, HSV-2, EBV (oral hairy leukoplakia), VZV, HHV-6, HHV-8 (KS-related herpes virus), most ganciclovir-resistant CMV, and most acyclovir-resistant HSV and VZV.

ADMINISTRATION: Controlled IV infusion using ≤24 mg/mL (undiluted) by central venous catheter or <12 mg/mL (diluted in 5% dextrose or saline) via a peripheral line. No other drug is to be given concurrently via the same catheter. Induction dose of 90 mg/kg q 12 h is given over ≥1 hour via infusion pump with adequate hydration. Maintenance treatment with 90-120 mg/kg is given over ≥2 hours by infusion pump

with adequate hydration. Many use 90 mg/kg/day for initial maintenance and 120 mg/kg/day for maintenance after re-induction for a relapse.

PHARMACOLOGY

- **Bioavailability:** 5% to 8% absorption with oral administration, but poorly tolerated
- **T½:** 3 h
- **CSF levels:** 15% to 70% plasma levels
- **Elimination:** Renal exclusively

SIDE EFFECTS

- **Dose-related renal impairment:** 37% treated for CMV retinitis have serum creatinine increase to ≥2 mg/dL; most common in second week of induction and usually reversible with recovery of renal function within 1 week of discontinuation. Monitor creatinine 2 to 3x/week with induction and every 1 to 2 weeks during maintenance. Modify dose for creatinine clearance changes. Foscarnet should be stopped for creatinine clearance <0.4 mL/min/kg. This is a toxic drug and should only be used in life threatening conditions.
- **Changes in serum electrolytes** including hypocalcemia (15%), hypophosphatemia (8%), hypomagnesemia (15%), and hypokalemia (16%). Patients should be warned to report symptoms of hypocalcemia: Perioral paresthesias, extremity paresthesias, and numbness. Monitor serum calcium, magnesium, potassium, phosphate, and creatinine, usually ≥2x/week during induction and 1x/week during maintenance. If paresthesias develop with normal electrolytes, measure ionized calcium at start and end of infusion.
- **Seizures** (10%) related to renal failure and hypocalcemia
- **Penile ulcers**
- **Miscellaneous:** Nausea, vomiting, headache, rash, fever, hepatitis, marrow suppression

DRUG INTERACTIONS: Concurrent administration with IV pentamidine may cause severe hypocalcemia. Avoid concurrent use of potentially nephrotoxic drugs such as amphotericin B, aminoglycosides, and pentamidine. Possible increase in seizures with imipenem.

PREGNANCY: Category C. No adequate studies in animals or humans. Recommend for treatment of life-threatening and site-threatening CMV infections.

FUNGIZONE – see Amphotericin B

GANCICLOVIR AND VALGANCICLOVIR

TRADE NAME (IV AND ORAL FORMS)

- Ganciclovir: *Cytovene*, IV (Roche); *Vitrasert*, ocular implant (Bausch & Lomb); and generic
- Valganciclovir: *Valcyte*, PO (Roche)

FORMS AND PRICES: Cymevene , gancyclovir 250mg, capsules 84; Cymevene, gancyclovir 500mg, vials 5

DOSE RECOMMENDATIONS: Ganciclovir, 5 mg/kg IV q 12 h x 2 wk (induction), then 5 mg/kg IV qd (maintenance); Valganciclovir, 900 mg PO q 12 h x 3 wk (induction), then 900 mg qd (maintenance).

Valganciclovir is the preferred oral formulation because it provides blood levels of ganciclovir comparable with those achieved with recommended doses of IV ganciclovir (*N Engl J Med* 2002;346:1119). Oral ganciclovir should no longer be used, and IV ganciclovir is reserved primarily for seriously ill patients and those who are unable to take oral medications. In South Africa the use of intravitreous Gancyclovir for the treatment of CMV retinitis is common. While there are intraocular implants are available, they are expensive. The cost saving of using multiple dose vials is over 75%.

CLASS: Synthetic purine nucleoside analog of guanine

ACTIVITY: Active against herpes viruses including CMV, HSV-1, HSV-2, EBV, VZV, HHV-6, and HHV-8 (KS).

INDICATIONS AND DOSE REGIMEN

- **Other forms of disseminated CMV:** Ganciclovir or foscarnet are the standard agents to treat CMV esophagitis, colitis, pneumoniitis and neurologic disease (*AIDS* 2000;14:517; *Clin Infect Dis* 2002;34:101).

PHARMACOLOGY

- **Bioavailability:** Valganciclovir – 60% absorption with food vs 6%-9% for oral ganciclovir. The valganciclovir formulation is rapidly hydrolyzed to ganciclovir after absorption.
- **Serum level:** Mean peak concentration with IV induction doses is 11.5 µg/mL (MIC_{50} of CMV is 0.1-2.75 µg/mL).
- **CSF concentrations:** 24% to 70% of plasma levels; intravitreal concentrations: 10% to 15% of plasma levels – 0.96 µg/mL *(J Infect Dis* 1993;168:1506).
- **T½:** 2.5-3.6 h with IV administration; 3-7 h with oral administration. Intracellular T½: 18 h.

- **Elimination:** IV form: 90% to 99% excreted unchanged in urine. Oral form: 86% in stool and 5% recovered in urine.
- **Renal failure:** Hemodialysis removes 50% of ganciclovir (*Clin Pharmacol Ther* 2002;72:142).

■ TABLE 5-17: **Ganciclovir and Valganciclovir Dose Modification in Renal Failure (Induction Dose)**

Creatinine Clearance			
Ganciclovir (IV Form)		**Valganciclovir† (Oral Form)**	
>80 mL/min	5 mg/kg q12h	>60 mL/min	900 mg bid
50-79 mL/min	2.5 mg/kg q12h	40-59 mL/min	450 mg bid
25-49 mL/min	2.5 mg/kg q24h	25-39 mL/min	450 mg qd
10-24 mL/min	1.25 mg/kg q24h	10-24 mL/min	450 mg qod (induction); 450 biw (maintenance)
<10 mL/min*	1.25 mg/kg tiw	<10 mL/min	Not recommended

* Hemodialysis: 1.25 mg/kg tiw; give post-dialysis.

† Maintenance dose = 50% of induction dose

SIDE EFFECTS, IV FORM

- **Neutropenia** with ANC <500/mm^3 (25% to 40%) requires discontinuation of drug in 20%. Alternative is administration of G-CSF. Discontinuation or reduced dose will result in increased ANC in 3 to 7 days. Monitor CBC 2 to 3x/week and discontinue if ANC <500/mm^3 or platelet count <25,000/mm^3.
- **Thrombocytopenia** in 2% to 8%
- **CNS toxicity** in 10% to 15% with headaches, seizures, confusion, coma
- **Hepatotoxicity** in 2% to 3%
- **GI intolerance** 2%
- **Note:** Neutropenia (ANC <500/mm^3) or thrombocytopenia (<25,000/dL) are contraindications to initial use.

GEMFIBROZIL

TRADE NAME: *Lopid* (Pfizer) or generic

FORM AND PRICE: Lopid, gemfibrozil 600mg, tablets 60, R 318.57;

CLASS: Antihyperlipidemic; fibric acid derivative (like clofibrate)

INDICATIONS AND DOSE: Elevated serum triglycerides; may increase LDL cholesterol and cholesterol levels. 600 mg bid PO >30 minutes before meal.

MONITORING: Blood lipids, especially fasting triglycerides and LDL cholesterol; if marked increases in LDL cholesterol, discontinue gemfibrozil and expect return of LDL cholesterol to pretreatment levels in 6 to 8 weeks. Gemfibrozil should be discontinued if there is no decrease in triglyceride or cholesterol level at 3 months. Obtain liver function tests and CBC at baseline, at 3 to 6 months, and then yearly. Discontinue gemfibrozil for otherwise unexplained abnormal liver function tests.

PHARMACOLOGY

- **Bioavailability:** 97%
- **T½:** 1.3 h
- **Elimination:** renal – 70%, fecal – 6%
  - Hepatic failure: Reduce dosage; use with caution
  - Renal failure: Consider reducing dose

PRECAUTIONS: Contraindicated with gallbladder disease, primary biliary cirrhosis, and severe renal failure.

SIDE EFFECTS

- **Blood lipids:** May increase LDL cholesterol and cholesterol by a mechanism that is poorly understood.
- **Gallbladder:** Gemfibrozil is similar to clofibrate and may cause gallstones and cholecystitis ascribed to increased biliary excretion of cholesterol.
- **Miscellaneous:** GI intolerance, decreased hematocrit, and/or WBC

DRUG INTERACTIONS

- **Gemfibrozil and statins** have resulted in rhabdomyolysis and renal failure; possible increased risk of myositis when used with other statins; monitor closely for evidence of myositis with concurrent use. Rosuvastatin AUC ↑ 90%; use fenofibrate instead.
- **Oral anticoagulants:** May potentiate activity of warfarin.

PREGNANCY: Category C

INDINAVIR (IDV)

TRADE NAME: *Crixivan* (Merck)

FORMULATIONS, REGIMENS, PRICE

- **Regimens:** IDV 800 mg q 8h; IDV/r, 800/100 or 800/200 mg bid
- Form and Prices: Crixivan, indinavir 400mg, capsules 18; Crixivan, indinavir 400mg, capsules 120; Crixivan, indinavir 400mg, capsules180

This drug is not recommended in the South African guidelines as a first line or second line drug. It is however used occasionally for post exposure prophylaxis

FOOD: Unboosted, take 1 hr before or 2 hrs after meal, or take with light, low-fat meal. No food restrictions for IDV/r.

FLUIDS: Must take ≥1.5 L/day

RENAL FAILURE: No restrictions

STORAGE: Room temperature, 15-30°C (59°-86°F); protect from moisture

CLASS: Protease inhibitor

INDICATIONS AND DOSE: The standard dose without RTV boosting is 800 mg q8h in fasting state (1 hour before or 2 hours after a meal), or with a light, nonfat meal. Patients should drink 6-8 glasses of fluids/day, preferably water, to prevent IDV-associated renal calculi. Most of the current limited use is RTV-boosted IDV regimens, which permit bid dosing and eliminate the food effect. Standard regimens are IDV/RTV 800 mg/100 mg bid or 800 mg/200 mg bid (increased risk of renal calculi) or 400 mg/400 mg (increased RTV side effects).

ADVANTAGES: Extensive experience with long-term follow-up

DISADVANTAGES:

PHARMACOLOGY

- **Bioavailability:** Absorption is 65% in fasting state or with only a light, nonfat meal. Full meal decreases IDV levels 77%; give 1 hour before or 2 hours after meal, with light meal or with RTV. Food has minimal effect on IDV when it is coadministered with RTV.
- **T½:** 1.5 to 2.0 h (serum)
- **C_{max}:** Peak >200 nm; 8 hours post-dose – 80 nm (95% inhibition *in vitro* at 25-100 nm). Peak levels correlate with nephrotoxicity and trough levels correlate with efficacy, but levels seem somewhat unpredictable when IDV is boosted with RTV (*J Acquir Immune Defic Syndr* 2002;29:374). Penetration into CSF is moderate (CSF: serum=0.06-0.16) but is superior to that of other PIs and adequate to

inhibit IDV-sensitive strains (*Antimicrob Agents Chemother* 2000;44:2173), since levels achieved are above the IC_{95} for most HIV isolates (*AIDS* 1999;13:1227). CSF trough levels of IDV are increased >5-fold when IDV is combined with RTV (7th CROI, San Francisco, California, 2000, Abstr. 312).

- **Dose in renal failure:** Standard dose. This also applies to hemodialysis and peritoneal dialysis (*Nephrol Dial Transplant* 2000;15:1102).

SIDE EFFECTS

- **Asymptomatic increase in indirect bilirubin** to ≥2.5 mg/dL without an increase in transaminases noted in 10% to 15% of patients. Clinically inconsequential, and rarely associated with jaundice or scleral icterus.
- **Mucocutaneous:** Paronychia and ingrown toenails, alopecia, dry skin, mouth, and eyes (common).
- **Class adverse effects:** Insulin-resistant hyperglycemia, lipodystrophy, hyperlipidemia (increased triglyceride, cholesterol, LDL levels), and possible increased bleeding with hemophilia.
- **Nephrolithiasis ± hematuria** in 10% to 28%, depending on duration of treatment, age, RTV boosting, and fluid prophylaxis (*J Urol* 2000;164:1895). The cause is crystallization of the drug with high serum levels and/or dehydration; IDV crystals can be detected in urine of up to 60% of IDV recipients. The frequency of nephrolithiasis with renal colic, flank pain, hematuria and/or renal insufficiency in the ATHENA cohort with 1219 IDV recipients was 8.3/100 patient-years.
- **Nephrotoxicity:** In a prospective study of 184 IDV recipients, routine urinalysis indicated pyuria in 35%; this was often accompanied by proteinuria, hematuria, and IDV crystals (*J Acquir Immune Defic Syndr* 2003;32:135)).
- **Alopecia:** May involve all hair-bearing areas (*N Engl J Med* 1999; 341:618)
- **GI intolerance:** Primarily nausea, with occasional vomiting, epigastric distress
- **Less common:** Increased transaminase levels, headache, diarrhea, metallic taste, fatigue, insomnia, blurred vision, dizziness, rash, and thrombocytopenia. Rare cases of fulminant hepatic failure and death. Fulminant hepatitis has been associated with steatosis and an eosinophilic infiltrate, suggesting a drug-related injury (*Lancet* 1997;349:924). Gynecomastia has been reported (*Clin Infect Dis* 1998;27:1539).

BLACK BOX WARNING: None

DRUG INTERACTIONS

- **Contraindicated for concurrent use:** Rifampin, astemizole, terfenadine, cisapride, midazolam, triazolam, ergotamines, simvastatin, lovastatin, atazanavir, St. John's wort, and pimozide.
- **Antimycobacterial agents:** Rifabutin – IDV levels decreased 32% and rifabutin levels increased 2x – reduce rifabutin dose to 150 mg/day or 300 mg 3x/week and increase IDV dose to 1000 mg tid with IDV/RTV use standard PI dose and rifabutin 150 mg qod or 150 mg 3x/wk.
- **Didanosine (buffered):** Use *Videx EC* formulation or separate doses by ≥2 hours if using buffered formulation.
- **Other interactions**
  - **Ketoconazole** and **itraconazole** increase IDV levels 70%; decrease IDV dose to 600 mg q8h.
  - **Clarithromycin** levels increase 53% – no dose change.
  - **Grapefruit juice** reduces IDV levels 26%.
  - **Oral contraceptives:** Norethindrone levels increase 26% and ethinylestradiol levels increase 24% – no dose change.
  - **Carbamazepine** markedly decreases IDV levels; consider alternative.
  - IDV increases **sildenafil** (*Viagra*) AUC 340% (*AIDS* 1999;13:F10). The maximum recommended dose is 25 mg/48 hours. **Vardenafil** AUC increased 16x IDV AUC ↓ 30% and should be limited to 2.5 mg qd or use alternative; with IDV/RTV it should be limited to 2.5 mg/3 days. **Tadalafil** AUC increased; use 5 mg initially and do not exceed 10 mg/72 hours.
  - **St. John's wort** reduces IDV AUC by 57% (*Lancet* 2000;355:547); contraindicated.
  - **Vitamin C** (≥1 gm/d): Decreases IDV C_{min} 32%

PREGNANCY: Category C. Negative rodent teratogenic assays; placental passage studies show high newborn:maternal drug levels in rats, low ratio in rabbits. Pharmacokinetic studies in PACTG 358 showed that mean levels at 30-32 wks gestation were 74% lower than at 6 wks postpartum. There is concern for the associated hyperbilirubinemia and the appropriate regimen for pregnancy is not known.

ISONIAZID (INH)

TRADE NAMES:

FORM AND PRICES: generic, Isoniazid tablets 1000; Rifinah, rifampicin/isoniazid 150/300mg, tablets 40; Rimactazid, 150/75mg, tablets 20; Rimactazid 150/75mg, tablets 60; Rimactazid, 300/150,

tablets 40; Rimactazid, 60/30 paed, tablets 40; Rimactazid 60/60 paed, tablets 80; Rimactazid, 60/60 paed, tablets 120; Rimactazid, 60/60 paed, tablets 500

INDICATIONS AND DOSES: Prophylaxis and treatment of tuberculosis

PHARMACOLOGY

- **Bioavailability:** 90%
- **T½:** 1-4 h; 1 h in rapid acetylators
- **Elimination:** Metabolized and eliminated in urine.
- **Dose modification in renal failure:** Half dose with creatinine clearance <10 mL/min in slow acetylators.

SIDE EFFECTS

- **Hepatitis:** ALT elevations are noted in 10% to 20%, clinical hepatitis in 0.6%, and fatal hepatitis in 0.02% (*Am J Respir Crit Care Med* 2003;167:603). The risk of hepatitis increases with increased age, alcoholism, prior liver disease, pregnancy, and concurrent rifampin. (defined as an ALT >5 ULN) of 0.15% in 11,141.
- **Peripheral neuropathy** due to increased excretion of pyridoxine, which is dose-related and rare (0.2%) with usual doses; it is prevented by use of concurrent pyridoxine (10-50 mg/day), which is recommended for diabetics, alcoholics, pregnant patients, AIDS patients, and malnourished patients. The usual dose is 25 mg/d. (*Pharmacotherapy* 2006;26:529).
- **Miscellaneous Reactions:** Rash, fever, adenopathy, GI intolerance. Rare reactions: Psychosis, arthralgias, optic neuropathy, marrow suppression.

DRUG INTERACTIONS

- Increased effects of warfarin, benzodiazepines, carbamazepine, cycloserine, ethionamide, phenytoin, theophylline
- INH absorption decreased with aluminum-containing antacids
- Ketoconazole: Decrease ketoconazole levels
- Food: Decreases absorption

PREGNANCY: Category C. Embryocidal in animals; not teratogenic. Large retrospective studies have shown no pattern of congenital abnormalities; small studies suggest possible CNS toxicity (*Clin Infect Dis* 1995;21[suppl 1]:S24). Pregnant women with positive PPD plus HIV infection should receive INH to begin after first trimester if possible.

LAMIVUDINE (3TC)

FORMULATIONS, REGIMENS AND PRICE

- **Forms and regimens**

  Generic lamivudine 150mg tablets 60 R 89.96

  Generic lamivudine 150mg suspension 240ml R 66.18

  Generic AZT/3TC tablets 60 R 303.66

  Trizivar AZT/3TC/ABC tablets 60 R 1,517.72

  Kivexa 3TC/ABC tablets 30 R 922.26

FOOD: No effect

RENAL FAILURE: Lamivudine – at CrCl (mL/min) level: >50 mL/min: 150 mg bid or 300 mg qd; 30-49 mL/min: 150 mg qd; 15-29 mL/min: 150 mg, then 100 mg qd; 5-14 mL/min: 150 mg, then 50 mg qd; <5 mL/min: dialysis, 50 mg, then 25 mg qd. Combivir, Trizivir, Epzicom – avoid when CrCl <50 mL/min.

HEPATIC FAILURE: No recommendation; usual dose likely

HEPATITIS B: Standard dose is 100 mg/day; coinfected patients should receive the HIV dose of 300 mg/day

CLASS: Nucleoside analog

INDICATIONS AND DOSES

- **HIV:** 3TC (or FTC) are recommended in the first line regimen in the South African guidelines. It is also recommended as first line in the DHHS, IAS-USA and BHIVA guidelines. *Epzicom*, which improve convenience and reduce co-pays.
- **Hepatitis B:** 3TC is a potent inhibitor of HBV replication (*N Engl J Med* 2004;350:1118). Several studies have verified activity with HBeAg seroconversion in 22%-29% and undetected HBV DNA in 40%-87% of patients coinfected with HBV and HIV (*J Infect Dis* 1999;180:607; *Hepatology* 1999;30:1302; *Clin Infect Dis* 2001;32: 963; *Clin Infect Dis* 2006;43:904). and improved hepatic histology (*N Engl J Med* 1998;339:61).
- **Treatment of HIV only:** Withhold NRTIs with activity vs HBV (TDF, FTC, 3TC).
- **Treatment of HIV and HBV:** Consider TDF/FTC (*Truvada*) or TDF/3TC

ADVANTAGES: Potent against HIV, well tolerated, no food effect, may be taken once daily, co-formulated with AZT (*Combivir*), AZT/ABC (*Trizivir*) and ABC (*Epzicom*); active against HBV. 3TC resistance by HIV (M184V) increases susceptibility to AZT, d4T, and TDF. Delays accumulation of TAMs, and may partially reverse their effects. 184V appears to be uniquely effective in reducing viral load as a single agent

in patients who have multiply-resistant strains.

DISADVANTAGES: Single mutation (184V) confers high level resistance; use with HBV co-infection without other agents active against HBV likely to cause HBV resistance. Discontinuation in patients with chronic HBV may cause flare of hepatitis.

RESISTANCE: The 184V mutation is associated with a >100-fold decrease in anti-HIV activity. This mutation also occurs early, often within 3 weeks with monotherapy. (These features apply to FTC as well.) The 184V mutation reduces ABC activity but it is modest and not clinically important. The 184V mutation has three possible advantages that may make it worth preserving: 1) It increases activity of AZT >d4t >TDF and always delays emergence of TAMs. 2) It reduces fitness, which may account for the activity of 3TC or FTC in salvage (*Clin Infect Dis* 2005;41:236; *J Infect Dis* 2005;192:1537). 3) There is speculation that it reduces transmissibility of HIV, a theory supported in part by the frequency of 184V mutation in failed therapy and by its infrequency in newly infected patients.

CLINICAL TRIALS: There is extensive experience with 3TC combined with AZT, TDF, d4T, and ddI, confirming antiviral potency, excellent long and short-term tolerability, but also early acquisition of the M184V resistance mutation if viral suppression incomplete.

PHARMACOLOGY

- **Bioavailability:** 86%
- **T½:** 5-7 h; Intracellular T½: 18-22 h
- **CNS penetration:** 13% (CSF: Plasma ratio=0.11). These levels exceed the IC_{50} and have been shown to clear HIV RNA from CSF (*Lancet* 1998;351:1547).
- **Elimination:** Renal excretion accounts for 71% of administered dose.

SIDE EFFECTS: Infrequent complications include headache, nausea, diarrhea, abdominal pain, and insomnia.

- **Class side effect:** Lactic acidosis and steatosis are listed as toxicities associated with the NRTI class, though it is not clear that these occur as a result of 3TC therapy. They are most often associated with d4T, AZT, and ddI (*Clin Infect Dis* 2002;34:838).
- **Hepatitis B:** In HIV-infected patients with HBV co-infection, discontinuation of 3TC may cause fulminant hepatic deterioration with increases in HBV DNA levels and increases in ALT levels (**FDA black box warning**). Monitor hepatic function and clinical course carefully for several months when 3TC is discontinued in patients with HIV/HBV co-infection. Immune reconstitution and development of HBV resistance may also cause a hepatitis B flare.

BLACK BOX WARNINGS: 1) Lactic acidosis, 2) hepatic failure with chronic HBV infection with immune reconstitution, development of HBV resistance to 3TC or discontinuation of an agent with activity vs HBV (TDF, 3TC, or FTC).

PREGNANCY: Category C. Negative carcinogenicity and teratogenicity studies in rodents; placental passage studies in humans show newborn:maternal drug ratio of 1.0. Studies in pregnant women show that lamivudine is well tolerated and has pharmacokinetic properties similar to those of nonpregnant women (*MMWR* 1998;47[RR-2]:6). Use in pregnancy is extensive; safety is well established, and when combined with AZT, efficacy in preventing perinatal transmission is also well established.

LOPINAVIR/RITONAVIR (LPV/r)

TRADE NAME: *Kaltera* (capsule) and *Aluvia* (tablets)

CLASS: Protease inhibitor (boosted with coformulated ritonavir)

PATIENT ASSISTANCE: 800-659-9050

FORMULATIONS, REGIMENS AND PRICE

- **Forms:** Aluvia, lopinavir/ritonavir 200mg/50mg, tablets 120, R 359.36; not registered in SA- section 21 only; Kaletra, lopinavir/ritonavir, solution 300ml, R 359.36; Kaletra, lopinavir/ritonavir 133.3/33.3mg, capsules 180, R 359.36;.
- **Regimens:** (400/100mg bid) For the Kaletra capsules-3 bid and for the tablets 2bid. The capsules are only stable at room temperature (18-25°C) for one month. The drug should ideally be stored in a fridge or in a cool place. The tablets are heat stable. In naïve patients, 800/100 mg can be used daily. Solution can be used it there is GIT disturbance.

FOOD: Take tabs with or without food. Take oral solution with food.

RENAL FAILURE: Standard dose

HEPATIC FAILURE: No recommendation; use with caution

STORAGE: Tabs are stable at room temperature. Oral solution is stable until date on label at 2°-8°C, and for 2 months at room temperature (25°C or 77°F).

ACTIVITY: LPV is approximately 10 times more potent than RTV against wild-type HIV. The protein binding-adjusted IC_{50} value for wild-type virus is 0.07 µg/mL. With bid dosing, the trough levels of LPV on average exceed the IC_{50} by >75-fold. LPV combined with other PIs showed an additive effect *in vitro* with IDV and APV and synergy with SQV (*Antimicrob Agents Chemother* 2002;46:2249).

ADVANTAGES: Potent antiretroviral activity; unbeaten in therapeutic trials versus other PIs, durability demonstrated with 5-year data; no evidence of PI resistance with virologic failure when used as first PI; co-formulated with RTV; frequently more active against PI-resistant virus than some other approved PIs with the exception of TPV/r and DRV/r.

DISADVANTAGES: Food requirement; need for bid dosing in PI-experienced patients. GI intolerance; hyperlipidemia and other PI-associated metabolic toxicities; limited experience in pregnant women.

PHARMACOLOGY

- **Bioavailability:** The tab formulation shows no significant difference in AUC or C_{max} whether given in a fed or fasting state. The oral solution shows AUC increase of 80% when given with a moderate-fat meal. The addition of RTV results in a significant increase in LPV concentrations, AUC, and T½ due to inhibition of the cytochrome P450 CYP3A4 isoenzymes. The mean steady-state LPV plasma concentrations are 15- to 20-fold higher than those without RTV. Because RTV activity *in vitro* is 10-fold lower than that of LPV, RTV functions primarily as a pharmacologic enhancer and not as an antiretroviral agent. Protein binding is extensive, but there is sufficient CNS penetration to exceed the 50% IC (*AIDS* 2005;19:949).
- **T½:** 5-6 h
- **Metabolism/excretion:** Metabolized primarily by cytochrome P450 CYP3A4 isoenzymes. LPV/r inhibits CYP3A4 isoenzymes, but the effect is less than that of therapeutic doses of RTV, and similar to that of IDV. Based on PK data with APV, LPV/r appears to be an inducer of CYP3A4. Less than 3% excreted unchanged in urine.
- **Renal failure:** No data are available, but usual dose is recommended. LPV/r is not removed with hemodialysis (AIDS 2001;15:662).
- **Hepatic failure:** No dose modification recommendations are available. Use with caution in end-stage liver disease.

SIDE EFFECTS: The drug is generally well tolerated, with 2% discontinuing therapy due to adverse drug reactions in phase II and III clinical trials through 48 weeks. The newer tablet formulation is better tolerated than the capsule, which is no longer available.

- **Diarrhea:** The most common adverse reactions were gastrointestinal, with diarrhea of at least moderate severity in 15% to 25%. Abdominal pain and nausea is also common and may improve with oral solution.
- **Transaminase levels:** Laboratory abnormalities through 72 weeks included transaminase increases (to >5x normal) in 10% to 12%.
- **Class adverse reactions:** Insulin resistance, fat accumulation, and hyperlipidemia. Clinical trials show triglyceride increases to >750

mg/dL in 12% to 22%, and cholesterol increases to >300 mg/dL in 14% to 22% of treatment-naïve patients receiving LPV/r. Trial M98-863, comparing LPV/r with NFV in 653 patients, showed comparable mean increases in cholesterol (about 50 mg/dL) and a mean triglyceride increase of about 100 mg/dL for LPV/r vs 25 mg/dL for NFV. In HIV-negative men given LPV/r for 10 days, the major effect was an increase in triglyceride levels averaging 83%; there was minimal effect on insulin sensitivity (*AIDS* 2004;18:641).

- Report of 7 cases of renal or parotid lithiasis (*AIDS* 2004;18:705).

DRUG INTERACTIONS: The major effect is due to the inhibition of CYP3A4 isoenzymes to prolong the half-life of drugs metabolized by the route.

- **Drugs contraindicated for concurrent use:** Astemizole, terfenadine, flecainide, propafenone, rifampin, simvastatin, lovastatin, midazolam, triazolam, cisapride, voriconazole, fluticasone, pimozide, ergot derivatives, St. John's wort, and rifapentine.
- **Drugs that require a modified dose**
  - **Rifabutin:** C_{min} increased 3-fold; reduce rifabutin dose to 150 mg 3x/week with standard LPV dose.
  - **Clarithromycin:** Clarithromycin AUC increased 77%; reduce clarithromycin dose in renal failure; use 50% clarithromycin dose with CrCl 30-60 mL/min and 25% dose with CrCl <30 mL/min.
  - **Atorvastatin:** AUC increased 5- to 6-fold; use lowest dose (10 mg/d) or use alternative, such as pravastatin or fluvastatin, or rosuvastatin.
  - **Pravastatin:** Levels increased 33%; no dose adjustment.
  - **Ketoconazole:** Levels increased by 3-fold; limit to ≤200 mg/d.
  - **Oral contraceptives:** Ethinyl estradiol AUC decreased by 42%; use additional or alternative methods.
  - **Drugs for erectile dysfunction:** Sildenafil level increase anticipated; do not exceed 25 mg/48 h. Vardenafil: no data; limit to 2.5 mg q72h. Tadalafil: Start with 5 mg dose and do not exceed 10 mg/72 h.
  - **Fluticasone:** May increase levels of fluticasone with decreased serum cortisol levels; avoid coadministration.
  - **Prednisone:** May increase prednisone level; consider dose adjustment with long-term use.
  - **Anticonvulsants:** LPV and phenytoin decreased by 33% and 31%, respectively. Carbamazepine and phenobarbital may decrease serum level of LPV. Consider TDM or use alternative anticonvulsants (i.e., valproic acid, lamotrigine, levetiracetam).

- **Atovaquone:** Levels of atovaquone may be decreased requiring dose adjustment.
- **Tenofovir DF:** TDF levels increase 34%; clinical significance unknown; dose adjustment not recommended.
- **Digoxin:** Digoxin AUC increases 81%. Monitor closely.

PREGNANCY: Category C. Placental passage shown in rats (newborn: maternal ratio=0.08). Animal carcinogenicity studies incomplete. Rodent teratogenic studies negative (but delayed skeletal ossification and skeletal variations in rats at maternally toxic doses). There are limited data in pregnancy but increased dose may be required due to anticipated reduced LPV levels in the third trimester. DHHS guidelines

■ TABLE 5-18: **Dose Adjustments for Concurrent Use of LPV/r with Other Antiretroviral Agents**

Drug	Effect on Coadministered Drug	Effect on LPV	Dose Recommendation
EFV	No change	C_{min} ↓39%	EFV 600 mg hs + LPV/r 400/100 mg bid (treatment-naïve) or 600/150 mg bid (treatment-experienced)
NVP	No change	↓ C_{min} 55%	NVP standard + LPV/r 400/100 mg bid (treatment-naïve) or 600/150 mg bid (treatment-experienced)
SQV	↑ C_{min} 3.6x	C_{min} + AUC ↑	SQV 1000 mg bid + LPV/r 400/100 mg bid*
NFV	↑25%	↓27%	Data insufficient; avoid coadministration
ATV	↑ C_{min} 45%	×	Dose: ATV 300 mg qd + LPV/r 400/100 bid
DRV	AUC ↓50%	AUC ↑37%	Avoid.
TPV	—	AUC ↓55%	Avoid.

* Shows synergy *in vitro* (*Antimicrob Agents Chemother* 2002;46:2249).

(Oct. 10, 2006) recommend LPV/r as a preferred HAART regimen along with NFV. Pharmacokinetic studies of LPV/r using the 133/33 mg formulation show only 18% had an AUC above the 10th percentile for pregnant patients in the third trimester (Stek A, Int AIDS Conf., Bangkok, 2004, Abstr. LBOrB08). The recommendation is to consider 3 tabs (600/150 mg) bid for the third trimester and change to standard dose after delivery (*Clin Pharmacokinet* 2004;43:1071; DHHS Guidelines Oct. 10, 2006, p. 96).

METRONIDAZOLE

TRADE NAME: *Flagyl* (Pharmacia & Upjohn); or generic

FORMS AND PRICES: Generic, metronidazole 200mg, tablets 21, R 2.88; Generic, metronidazole 200mg, tablets 250, R 21.64; Generic, metronidazole 400mg, tablets 10, R 1.25; Generic, metronidazole 400mg, tablets 100, R 48.27

CLASS: Synthetic nitroimidazole derivative

INDICATIONS AND DOSE REGIMENS

- **Gingivitis:** 250 mg PO tid or 500 mg PO bid
- **Intra-abdominal sepsis:** 1.5-2.0 g/day PO or IV in 2 to 4 doses
- **Amebiasis:** 750 mg PO tid x 5 to 10 days
- **Bacterial vaginosis:** 2 g x 1 or 500 mg PO bid x 7 days
- **Trichomoniasis:** 2 g x 1 or 250 mg PO tid x 7 days
- ***C. difficile* colitis:** 500 mg PO tid or 250 mg PO qid x 10 to 14 days
- **Giardiasis:** 250 mg PO tid x 5 to 10 days

ACTIVITY: Active against virtually all anaerobes (*Antimicrob Agents Chemother* 2001;45:1238), and selected enteric pathogens (*E. histolytica, Giardia*). Drug of choice for most anaerobic infections, gingivitis, *C. difficile*-associated diarrhea, amebiasis, giardiasis, and bacterial vaginosis. Mixed anaerobic infections need a companion antibiotic if aerobes are considered important because metronidazole is active against only anaerobes.

PHARMACOLOGY

- **Bioavailability:** >90%
- **Note:** Metronidazole is virtually completely absorbed with oral administration and should be given IV only if patient can take nothing by mouth.
- **T½:** 10.2 h; serum level after 500 mg dose: 10-30 µg/mL
- **Elimination:** Hepatic metabolism; metabolites excreted in urine
- **Dose adjustment in renal failure:** None
- **Liver failure:** Half-life prolonged; consider reduced daily dose in severe liver disease

SIDE EFFECTS: Most common are GI intolerance and unpleasant taste. Less common are glossitis, furry tongue, headache, ataxia, urticaria, dark urine. Seizures are rare. Prolonged use may cause reversible peripheral neuropathy; disulfiram (*Antabuse*)-type reaction with alcohol.

DRUG INTERACTIONS: Increases levels of coumadin and lithium. Mild disulfiram-like reactions noted with alcohol (flushing, headache, nausea, vomiting, cramps, sweating) are infrequent and unpredictable.

Patients should be warned, and manufacturer recommends that alcohol be avoided.

PREGNANCY: Category B. Fetotoxicity in animals. Contraindicated in first trimester, although 206 exposures during the first trimester showed no increase in birth defects. Use during the last 6 months is not advised unless essential. For trichomoniasis, CDC recommends 2 g x 1 after first trimester. Alternative agents are available for most other conditions.

MYCOBUTIN – see Rifabutin

MYCOSTATIN – see Nystatin

NELFINAVIR (NFV)

TRADE NAME: *Viracept* (Pfizer)

CLASS: Protease inhibitor

FORMULATIONS, REGIMENS AND PRICE

- **Forms:** Tabs, 250 oral powder, 50 mg/mL
- **Regimens:** 1250 mg bid (tabs); 25 cc bid (oral solution)

FOOD: Increases levels 2-3x; take with fatty food

RENAL FAILURE: Standard dose

HEPATIC FAILURE: No recommendation; use with caution

STORAGE: Room temperature, 15-30°C

ADVANTAGES: Extensive experience; well tolerated in pregnancy

DISADVANTAGES: Reduced potency compared to most other regimens; need for concurrent fatty meal; diarrhea; inability to boost levels effectively with RTV

RESISTANCE: The primary resistance mutation is D30N, which is associated with phenotypic resistance to NFV but not to other protease inhibitors (*Antimicrob Agents Chemother* 1998;42:2775). However, the L90M mutation can also occur and, unlike 30N, it confers cross-resistance to all PIs except TPV/r and DRV/r.

PHARMACOLOGY

- **Bioavailability:** Absorption with meals is 20% to 80%. Fatty meal increases absorption 2- to 3-fold.
- **T½:** 3.5-5.0 h (serum)

- **CNS penetration:** No detectable levels in CSF (*J Acquir Immune Defic Syndr* 1999;20:39)
- **Excretion:** Primarily by cytochrome P450 CYP2C19 (major) and CYP3A4 (minor). Inhibits CYP3A4. Only 1% to 2% is found in urine; up to 90% is found in stool, primarily as a hydroxylated metabolite designated M8, which is as active as nelfinavir against HIV (*Antimicrob Agents Chemother* 2001;45:1086).
- **Dose modification in renal or hepatic failure:** None. NFV is removed with hemodialysis so that post dialysis dosing is important (*AIDS* 2000;14:89). The drug is not removed by peritoneal dialysis *(J Antimicrob Chemother* 2000;45:709).
- **Dose modification with hepatic failure:** Use with caution.

SIDE EFFECTS

- **Diarrhea:** About 10% to 30% of 1,500 recipients have reported diarrhea or loose stools. . Management strategies include use of several over-the-counter, inexpensive remedies, including oat bran (1500 mg bid), psyllium, loperamide (4 mg, then 2 mg every loose stool up to 16/day), or calcium (500 mg bid).
- **Class adverse effects:** Lipodystrophy, increased levels of triglycerides and/or cholesterol, hyperglycemia with insulin resistance and type 2 diabetes, osteoporosis, and possible increased bleeding with hemophilia (*HIV Med* 2006;7:85).

DRUGS THAT SHOULD NOT BE GIVEN CONCURRENTLY: Simvastatin, lovastatin, rifampin, astemizole, terfenadine, cisapride, pimozide, midazolam, triazolam, ergot derivatives, St. John's wort, and proton pump inhibitors.

DRUGS THAT REQUIRE DOSE MODIFICATIONS

- **Oral contraceptives:** Levels of ethinyl estradiol decreased by 47%; use alternative or additional birth control method.
- **Anticonvulsants:** Phenobarbital, phenytoin, and carbamazepine may decrease NFV levels substantially; monitor anticonvulsant levels. May need to monitor NFV levels.
- **Drugs for erectile dysfunction:** Sildenafil AUC increased 2- to 11-fold; do not exceed 25 mg/48 hours. Vardenafil: limit to 2.5 mg qd. Tadalafil: Start with 5 mg dose and limit to 10 mg/72 hrs.
- **Rifabutin** levels are increased 2-fold, and NFV levels are decreased by 32%; increase NFV dose to 1000 mg tid and decrease rifabutin dose to 150 mg/day or 300 mg 3x/week.
- **Statins:** Atorvastatin levels increase 74%; start with lowest dose (10 mg/day) or use pravastatin, fluvastatin, or rosuvastatin..
- **Ketoconazole:** NFV AUC ↑35% (use standard dose).
- **Clarithromycin:** No data. Consider reducing clarithromycin dose in renal failure.

PREGNANCY: Category B. Animal teratogenic studies – negative; long-term animal carcinogenicity studies – ↑ tumors in rats given ≥300 mg/kg; placental passage – not known. Experience to establish safety in pregnancy is extensive. The pregnancy registry shows birth defects in 21/572 (3.7%) exposures (www.apregistry.com, accessed Sept. 1, 2006). The 750 tid dose produced variable levels in pregnant women that were generally lower than in non-pregnant women. The 1250 mg bid regimen produced adequate levels (*Clin Infect Dis* 2004;39:736).

NEVIRAPINE (NVP)

TRADE NAME: *Viramune* (Boehringer Ingelheim) or generic.

CLASS: Non-nucleoside reverse transcriptase inhibitor

FORMULATIONS, REGIMENS AND PRICE

- NVP is also co formulated with stavudine and 3TC in a fixed dose combination- triomune (CIPLA) For the lead in dose in this formulation, use Triomune once daily and d4T and 3TC as the other dose for two weeks
- **Forms:** Tabs, 200 mg; oral solution, 50 mg/mL (240 mL bottle); generic, nevirapine, 200mg, tablets, 60, R 171.00; generic, nevirapine 50mg/5ml, oral suspension, 240ml, R 101.46
- **Regimens:** 200 mg qd x 2 weeks, then 200 mg bid. After treatment interruption >7 days should restart with the 200 mg/d regimen. If rash appears during the lead-in period, delay dose escalation until after the rash has resolved, and rule out hepatitis. No dose escalation when switching from EFV to NVP; start with NVP 200 mg bid *(AIDS* 2004;18:572).

WARNINGS: 1) Avoid NVP as initial therapy in women with baseline CD4 count >250/mm^3 due to high rates of symptomatic hepatitis. 2) See guidelines for discontinuing NVP.

FOOD: No significant effect

RENAL FAILURE: Standard regimen

HEPATIC FAILURE: Avoid NVP in patients with moderate or severe liver disease

ADVANTAGES: Extensive experience; 2NN trial suggests antiviral potency comparable to EFV; no food effect; least expensive "third drug." A safe and effective agent for perinatal transmission prevention in a resource-limited setting.

DISADVANTAGES: High rates of serious hepatotoxicity in treatment naïve women with baseline CD4 counts >250/mm^3, high rates of rash, including TEN and Stevens-Johnson syndrome; single resistance mutation may result in loss of entire class; single dose for prevention

of perinatal transmission may cause resistance. Efficacy data for EFV is more extensive.

- **2NN:** This is the pivotal study comparing EFV and NVP. ITT analysis at 48 weeks showed similar results for NVP bid and EFV, with VL <50 c/mL in 65% and 70%, respectively. The difference was not statistically significant, but the trial did not show non-inferiority according to the FDA definition. There was more hepatotoxicity in NVP recipients (9.6% vs. 3.5%), and two deaths were attributed to NVP toxicity (*Lancet* 2004;363:1253). NVP given od caused more hepatotoxicity (13.6%) and EFV/NVP was inferior virologically compared to EFV alone.
- **Switch therapy**
  - Switch from PI-based treatment to NVP-based HAART: A review of data concluded that "a switch from a PI-based regimen to one containing NVP can be accomplished safely while maintaining virologic suppression … with no immunologic cost … and an overall benefit in the metabolic milieu" (*HIV Med* 2006;7:537). The switch is associated with good virologic control and rapid improvement in blood lipid changes and insulin resistance, but minimal change in lipodystrophy (*AIDS* 1999;13:805; *J Acquir Immune Defic Syndr* 2001;27:229). The ATHENA trial also showed good virologic control with half of the patients showing improved body shape changes (*AIDS* 2000;14:807).
  - **NVP vs EFV switch:** Retrospective analysis of 162 patients on PI-based HAART were randomized to NVP or EFV for salvage or simplification. For simplification, 36/55 (66%) maintained virologic control at 48 weeks, and the two drugs were comparable. For salvage, virologic control was achieved in 15/58 (22%) of NVP recipients and 19/49 (38%) of EFV recipients (*HIV Clin Trials* 2003;4:244).

RESISTANCE: Monotherapy is associated with rapid and high-level resistance, with primary RT mutations 103N, 100I, 181C/I, 188C/L/H, and 190A resulting in an increase in the IC_{90} of >100-fold (*J Acquir Immune Defic Syndr* 1995;8:141; *J Infect Dis* 2000;181:904). Cross-resistance with EFV, and *in vitro* it is usually seen with K103N, which is most common and causes resistance to all currently available NNRTIs. NVP resistance is important in two distinct clinical settings, both related to the relatively long half-life and the low genetic barrier to resistance mutations:

The more extensive studies involve resistance associated with **single-dose NVP for preventing perinatal transmission**, which is a common strategy in developing countries. HIVNET 012 showed this was highly effective in perinatal transmission prevention, but resistance mutations were noted using standard assays in 19% of women (*J Infect Dis* 2002;186:181). Subsequent studies using real time PCR to detect

minority species, with a detection limit of 0.2%, found that K103N was present in an additional 40% (*J Infect Dis* 2005;192:16). The frequency is clade-specific: clade C, 69%; clade D, 36%; clade A, 19% (*J Acquir Immune Defic Syndr* 2006;42:610). Resistance mutations are also observed in the infants born to exposed mothers and in strains recovered from breast milk (*J Infect Dis* 2005;192:1260). The clinical implications of these observations are unclear, but in one study, women with perinatal NVP exposure who were subsequently treated with NVP-based regimens had a poorer virologic response compared to women who had not been previously exposed to NVP (*N Engl J Med* 2004;351:217).

In clade C , according to Morris et al, 106 mutation is also a significant. In order to circumvent NVP resistance in pMTCT, there are a number of strategies. Women with CD4+ less than 350 should be offered triple therapy. In addition, women with CD4+ above 350 may be offered triple therapy is possible. Insituraions when this is not possible consider.-

- AZT from 28 weeks and
- Sd NVP + AZT/3TC and
- AZT/3TC for 7 days.

The second important application of these data pertains to **discontinuation of NVP-based HAART**. The concern is that the long half-life of NVP will result in a substantial exposure to monotherapy. Methods to deal with this theoretical concern have not been well studied, but the suggestion has been made to discontinue NVP and continue two NRTIs for 1-2 weeks or continue two NRTIs with a PI or boosted PI for 2-4 weeks before discontinuing the entire regimen.

PHARMACOLOGY

- **Bioavailability:** 93%; not altered by food, fasting, ddI, or antacids.
- **T½:** 25 to 30 h
- **CNS penetration:** CSF levels are <45% peak serum levels (CSF: plasma ratio=0.45)
- **Metabolism:** Metabolized by cytochrome P450 (CYP3A4) to hydroxylated metabolites that are excreted primarily in the urine, which accounts for 80% of the oral dose. NVP autoinduces hepatic CYP3A4, reducing its own plasma half-life over 2 to 4 weeks from 45 hours to 25 hours (*J Infect Dis* 1995;171:537).
- **Dose modification with renal or hepatic failure:** NVP is extensively metabolized by the liver, and NVP metabolites are largely eliminated by the kidney with <5% unchanged in the urine. Usual doses are recommended in renal failure (*Nephro Dial Transplant* 2001;16:192). NVP is contraindicated in severe liver disease due to hepatotoxicity.

SIDE EFFECTS

- **Hepatotoxicity:** Early hepatotoxicity usually occurs in the first 6

weeks and appears to be a hypersensitivity reaction. It may be accompanied by drug rash, eosinophilia, and systemic symptoms (DRESS syndrome). This reaction differs from "transaminitis" noted with PIs and EFV in that it (1) is symptomatic hepatitis, (2) may progress to liver necrosis and death even with early detection and drug discontinuation, (3) usually occurs in the first 16 wks, and usually in the first 6 wks, and (4) occurs primarily with high baseline CD4 counts, especially in women. The rate of symptomatic hepatitis in women with a baseline CD4 count ≥250/mm^3 is 11% compared to 0.9% in women with lower CD4 counts at baseline. Men also have an increased risk with a CD4 count ≥400/mm^3, but the rates are lower, 6.4% vs 2.3%. Chronic hepatitis B or C do not appear to be risks (*J Infect Dis* 2005;191:825). The mechanism of this reaction is not known, but the association with high CD4 counts suggests an immune mechanism and a genetic predisposition is suspected (*Clin Infect Dis* 2006;43:783). There have been at least 6 deaths in pregnant women given continuous NVP-based HAART (*J Acquir Immune Defic Syndr* 2004;36:772). Many feel that NVP should not be given to treatment-naïve women with a CD4 count >250/mm^3 (DHHS guidelines, Oct. 10, 2006). Also, the CDC issued a warning against using NVP for PEP based on reports of two HCW with severe hepatitis, including one who required a liver transplant (*Lancet* 2001;357:687; *MMWR* 2001;49:1153). This concern does not apply to the single dose of NVP given at delivery to prevent perinatal transmission. NVP recipients may also develop hepatotoxicity later in the course of treatment, a form of hepatitis that is more benign and similar to hepatitis seen with other anti-HIV drugs. This hepatitis is characterized by a elevation in transaminase levels, it is usually asymptomatic, the frequency is about 15% and is more common in those with chronic HBV or HCV. Management guidelines for the severe early form include frequent monitoring of hepatic function in the first 12-16 wks, warning the patient, and prompt discontinuation of NVP if this diagnosis is considered. Guidelines for the later asymptomatic transaminitis are unclear but many recommend discontinuation of NVP if the ALT is >5 or 10x the ULN (*Hepatology* 2002;35:182).

- **Rash:** Rash is seen in about 17%. It is usually maculopapular and erythematous with or without pruritus and is located on the trunk, face, and extremities. Some patients with rashes require hospitalization, and 7% of all patients require discontinuation of the drug, 1.7% given EFV (package insert, PDR). Frequency of severe (Grade 3-4) rash in the 2NN trial was 6% in patients with a CD4 count >200/mm^3 and 1%-2% in those with a CD4 count <200/mm^3 (*AIDS* 2005;19:463). Indications for discontinuation of an NNRTI due to rash are rash accompanied by fever, blisters, mucous membrane involvement, conjunctivitis, edema, arthralgias, or malaise. Steroids are not effective (*J Acquir Immune Defic Syndr* 2003;33:41).

Stevens-Johnson syndrome and TEN have been reported, and three deaths ascribed to rash have been reported with NVP (*Lancet* 1998;351:567). Patients with rash should always be assessed for hepatotoxicity, as the two may occur together. A review of 122 patients with NVP rashes who were switched to EFV showed EFV-associated rashes in 10 (8%), but the rate of EFV rash was 20% among those whose NVP rashes were "severe" (*HIV Med* 2006;7:378).

- **Lipodystrophy:** The D:A:D study indicates NVP increases HDL cholesterol, reduces the total:HDL cholesterol index, and shows no risk for cardiovascular events (*Drugs* 2006;66:1971).

DRUG INTERACTIONS: NVP, like rifampin, induces CYP3A4. Maximum induction takes place 2 to 4 weeks after initiating therapy.

- **Drugs that are contraindicated or not recommended for concurrent use:** Rifampin, ketoconazole, St. John's wort, rifapentine.

■ TABLE 5-19: **Dose Recommendations for NVP + PI Combinations**

PI	PI Level	NVP Level	Regimen Recommended
IDV	↓28%	No change	IDV 1000 mg q8h (NVP standard) or TPV/r
RTV	↓11%	No change	Standard doses
SQV	↓25%	No change	Recommend SQV/RTV 1000 mg/100 mg bid
NFV	↑10%	No change	Standard doses
LPV/r	LPV ↓55%	No change	LPV/r 400/100 mg bid (treatment-naïve) or 600/150 mg bid (treatment-experienced)
ATV	↓	No data	Expect ↓ATV levels. Consider ATV/RTV 300/100 mg qd. (NVP standard.) Limited data.

DRUGS THAT REQUIRE DOSE MODIFICATION WITH CONCURRENT USE

- **Oral contraceptives:** NVP decreases AUC for ethinyl estradiol by about 30% *(J Acquir Immune Defic Syndr* 2002;29:471); alternative or additional methods of birth control should be used. **Clarithromycin:** NVP reduces clarithromycin AUC by 30% but increases levels of the 14-OH metabolite, which has antibacterial activity that compensates for this reduction, so no dose adjustment is necessary. NVP levels increased 26%. Use standard doses and monitor or use azithromycin. **Ketoconazole** levels decreased 63% and NVP increases 15% to 30%; not recommended. **Voriconazole:** no data, but significant potential for decrease of voriconazole and/or increase of NVP serum level. **Rifabutin** levels are decreased by 16%; no dose alteration. **Rifampin:** NVP AUC decreases 20%-58%; there

is also concern about additive hepatotoxicity. **Phenobarbital, phenytoin, carbamazepine:** No data. Monitor anticonvulsant levels; NVP concentrations may be decreased.

PREGNANCY: Category C. NVP is the only recommended NNRTI for pregnant women, and then only if the baseline CD4 count is <250/mm^3. This is based on negative rodent teratogenicity assays, placental passage in humans showing a newborn:maternal ratio of 1.0, and pharmacokinetic studies that show no important differences for women in the third trimester compared to non-pregnant women (*Br J Clin Pharmacol* 2006;62:552). The pregnancy registry shows NVP-based HAART is associated with low rates of birth defects (9/479 or 1.9%) compared to 3.1% in untreated women (www.apregistry.com, accessed Jan. 12, 2007). Safety for the infant seems well established, but women with a baseline CD4 count >250/mm^3 should not receive NVP-based HAART based on high rates of severe hepatotoxicity and serious rash reactions as summarized above. This admonition does not apply to the single perinatal dose, which is highly effective for preventing transmission, but controversial due to the high probability of class resistance (see below).

- **Single-dose NVP given to prevent perinatal transmission:** The major findings and issues are summarized below.
  - **Efficacy:** A study from Thailand compared AZT (076 protocol) + NVP (single intrapartum dose + single infant dose) reduced perinatal transmission rates in 636 women to 1.9%; the rate with AZT alone was 6.5% (*N Engl J Med* 2004;351:217).
  - **WHO guidelines** include NVP as a preferred regimen for HIV-infected women who are pregnant or women for whom effective contraception cannot be assured in resource-limited areas (*Scaling Up Antiretroviral Therapy*, WHO, 2003). WHO guidelines to prevent perinatal transmission are: AZT (076 protocol) + NVP 200 mg at onset of labor and a single infant dose of 6 mg at 48-72 h (*N Engl J Med* 2004;351:289).
  - **Resistance:** The major concern with single-dose NVP is the high frequency of NVP resistance following exposure. This occurred in 19% in HIVNET 012 (*Lancet* 1999;354:795) and 15% in PACTG 316 (*J Infect Dis* 2002;186:181). Subsequent studies using a sensitive point mutation assay to detect K103N mutations demonstrated positive results in 42%-70% of women exposed to single-dose NVP (*J Acquir Immune Defic Syndr* 2006;42:610). The high rates decrease with follow-up at 3, 7, and 12 months (*AIDS* 2006;20:995). In HIVNET 012 these mutations were not detected at 13-18 month postpartum using standard genotypic assays (*AIDS* 2001;15:1951), but they can be shown to persist with allele-specific PCR analysis (*Proc Natl Acad Sci USA* 2006;103:7094). A subsequent study in Thailand showed patients who received a single intrapartum dose of NVP had a higher rate of virologic failure

when NVP was used therapeutically (failure rates 49% vs. 68%, $p < 0.03$; *N Engl J Med* 2004;351:229).

NORVIR – see Ritonavir

NYSTATIN

TRADE NAMES: *Mycostatin* (Bristol-Myers Squibb) or generic

FORMS AND PRICES (generic)

- **Ointment:** 100,000 U/g, 15 g at $3.00; 30 g at $7.12
- **Suspension:** 100,000 U/mL, 60 mL at $16.94; 480 mL at $116.07
- **Oral tabs:** 500,000 units at $0.69/tab

CLASS: Polyene macrolide similar to amphotericin B

ACTIVITY: Active against *C. albicans* at 3 µg/mL and other *Candida* species at higher concentrations.

INDICATIONS AND DOSES

- **Thrush:** 5 mL suspension to be gargled 4-5x/day x 14 days. Disadvantages: *Nystatin* has a bitter taste, causes GI side effects, must be given 4x/day, and does not work as well as clotrimazole troches or oral fluconazole (*HIV Clin Trials* 2000;1:47). Efficacy is dependent on contact time with mucosa.
- **Vaginitis:** 100,000 unit tab intravaginally 1-2x/day x 14 days

PHARMACOLOGY

- **Bioavailability:** Poorly absorbed and undetectable in blood following oral administration
- Therapeutic levels persist in saliva for 2 h after oral dissolution of two lozenges.

SIDE EFFECTS: Infrequent, dose-related GI intolerance (transient nausea, vomiting, diarrhea)

PEGYLATED INTERFERON

TRADE NAMES: Peginterferon alfa-2a – *Pegasys* (Roche); peginterferon alfa-2b – *Peg-Intron* (Schering-Plough)

FORMS

- Peginterferon alfa-2a (*Pegasys*) is supplied as a solution ready for injection, which requires refrigeration and is available at a fixed dose of 180 µg per 1 mL solution at R 180000.
- Peginterferon alfa-2b (*Peg-Intron*) is supplied as lyophilized powder to be reconstituted with 0.7 mL saline; several strengths are available based upon body weight.

PRODUCT: Recombinant alfa-interferon conjugated with polyethylene glycol (PEG), which decreases the clearance rate of interferon and results in sustained concentrations permitting less frequent dosing.

CONTRAINDICATIONS: Autoimmune hepatitis and hepatic failure with Child-Pugh score ≥6 before or during treatment. (Contraindications to ribavarin: 1) pregnant female, 2) male patient with pregnant partner, 3) patient with hemoglobinopathies.)

INDICATIONS: FDA indications: Treatment of compensated chronic hepatitis C not previously treated with interferon alfa. HIV-HCV co-infected patients are candidates for anti-HCV therapy if they appear at high risk for cirrhosis based on a liver biopsy showing bridging fibrosis and inflammation plus HCV RNA levels >50 IU/mL.

DOSE: Pegylated interferon (alfa 2a 180 mg or alfa 2b 1.5 mg/kg) SC/week plus ribavirin 400 mg bid. (The ribavirin dose of 800 mg/d is the dose used in clinical trials of co-infected patients, but higher doses of RBV, 800 mg/d for <40 kg, 1000 mg/d for 45-75 kg, 1200 mg/d for >75 kg) may be more effective.) Usual duration is 48 weeks regardless of genotype. With CrCl <50 mL/min consider half dose peg-interferon (*N Engl J Med* 2002;347:975).

MONITORING

- **Clinical response:** HCV RNA at 12 weeks (see pp. 425-429). Patients without a ≥2 $\log_{10}$ c/mL decrease in HCV RNA levels at 12 weeks are unlikely to achieve significant viral response, although this does not exclude the possibility of clinical benefit by other criteria (*J Acquir Immune Defic Syndr* 2006; PMID 17106276). If HCV RNA is detectable after 12 weeks, consider discontinuation. Sustained virologic response is defined as undetectable HCV RNA at 24 weeks post therapy.

- **Toxicity:** CBC and comprehensive metabolic panel at baseline, at 2 weeks, then every 6 weeks. TSH at baseline and then every 12 weeks.
- **Patients with cardiac disease:** EKG at baseline and prn.
- **Women of childbearing potential:** Urine pregnancy testing every 4 to 6 weeks.
- **Bioavailability:** Increases with duration of therapy – mean trough of peg-IFN alfa 2b with 1 µg/kg SQ at week 4=94 pg/mL, at week 48=320 pg/mL. C_{max} mean is 554 pg/mL at 15 to 44 hours and sustained up to 48 to 72 hours. Compared to non-pegylated interferon, peginterferon C_{max} is about 10x greater and AUC is 50x greater.
- **T½:** Peg-IFN alfa 2a = 77 h; Peg-IFN alfa 2b = 40 h (compared with 8 h for non-pegylated interferon).
- **Elimination:** Renal 30% (7x lower clearance than non-pegylated interferon). Eliminated primarily in the bile.

SIDE EFFECTS: Similar to those of interferon; 15%-21% in clinical trials discontinue therapy due to adverse reactions (*N Engl J Med* 2004;351:438; *N Engl J Med* 2004;351:451).

BLACK BOX WARNINGS: Depression, serious bacterial infections, autoimmune disorder, ischemic disorders.

- **Neuropsychiatric:** Depression, suicidal or homicidal ideation, and relapse of substance abuse. Should be used with extreme caution in patients with history of psychiatric disorders. Warn patient and monitor. Depression reported in 21% to 29%. Suicides reported. Active depression with suicidal ideation is a contraindication.
- **Marrow suppression:** ANC counts decrease in 70%, <500/mm^3 in 1%, platelet counts decrease in 20%, <20,000/mm^3 in 1%. Avoid or discontinue AZT. Recommendation:
- **Flu-like symptoms:** Most common; about 50% will have fever, headache, chills, and myalgias/arthralgias. May decrease with continued treatment. May be treated with NSAIDS or acetaminophen; with liver disease acetaminophen dose should be <2 g/day.
- **Thyroid:** Thyroiditis with hyperthyroidism or hypothyroidism. TSH levels should be measured at baseline and during therapy every 12 weeks.
- **Retinopathy:** Obtain baseline retinal evaluation in patients with diabetes, hypertension or other ocular abnormality.
- **Injection site reaction:** Inflammation, pruritus, pain (mild) in 47%
- **GI complaints:** Nausea, anorexia, diarrhea, and/or abdominal pain in 15% to 30%
- **Skin/hair:** Alopecia (20%), pruritus (10%), and/or rash (6%)
- **Miscellaneous:** Hyperglycemia, cardiac arrhythmias, elevated hepatic transaminase levels 2 to 5x, colitis, pancreatitis, autoimmune disorders, hypersensitivity reactions

DRUG INTERACTIONS: Avoid co-administration of marrow suppressive agents including AZT and ganciclovir. Ribavirin should not be given with ddI.

PREGNANCY: Category C. Abortifacient potential in primates. Ribavirin is a potent teratogen (Category X) and must be avoided in pregnancy and used with caution in women of childbearing potential and their male sexual partners. Breastfeeding: No data.

PENTAM – see Pentamidine (below)

PENTAMIDINE

TRADE NAME: *Pentam* for IV use; *NebuPent* for inhalation (American Pharmaceutical Partners)

FORMS AND PRICE: 300 mg vial at $98.75

CLASS: Aromatic diamidine-derivative antiprotozoal agent that is structurally related to stilbamidine

INDICATIONS AND DOSES

- ***P. jiroveci* pneumonia:** 3-4 mg/kg IV given over ≥1 hr x 21 days. The approved dose is 4 mg/kg, but some clinicians prefer 3 mg/kg. TMP-SMX is preferred (*Ann Intern Med* 1986;105:37; *AIDS* 1992;6:301).
- ***P. jiroveci* prophylaxis:** 300 mg/month delivered by a *Respirgard II* nebulizer using 300 mg dose diluted in 6 mL sterile water delivered at 6 L/min from a 50 psi compressed air source until the reservoir is dry. TMP-SMX preferred due to superior efficacy in preventing PCP, efficacy in preventing other infections, reduced cost, and greater convenience (*N Engl J Med* 1995;332:693). Aerosolized pentamidine should not be used for PCP treatment (*Ann Intern Med* 1990;113:203).

PHARMACOLOGY

- **Bioavailability:** Not absorbed orally. With aerosol, 5% reaches alveolar spaces via *Respirgard II* nebulizer. Blood levels with monthly aerosol delivery are below detectable limits.
- **T½:** Parenteral – 6 h
- **Elimination:** Primarily nonrenal but may accumulate in renal failure
- **Dose modification of parenteral form with renal failure:** CrCl >50 mL/min – 4 mg/kg q24h; 10-50 mL/min – 4 mg/kg q24h-q36h; <10 mL/min – 4 mg/kg q48h.

SIDE EFFECTS

- **Aerosolized pentamidine:** Cough and wheezing - 30% (prevented with pretreatment with beta-2 agonist).
- **Systemic pentamidine:** In a review of 106 courses of IV pentamidine, 76 (72%) had adverse reactions; these were sufficiently severe to require drug discontinuation in 31 (18%) (*Clin Infect Dis* 1997;24: 854). The most common causes of drug discontinuation were nephrotoxicity and hypoglycemia. **Nephrotoxicity** is noted in 25% to 50%. **Hypotension** is unusual (6%) but may cause death, most often with rapid infusions; drug should be infused over ≥60 minutes. **Hypoglycemia**, with blood glucose 25 mg/dL in 5% to 10%, can occur after 5 to 7 days of treatment, sometimes persisting several days after discontinuation. **Hyperglycemia** (2% to 9%) and insulin-dependent diabetes mellitus may occur with or without prior hypoglycemia. **Leukopenia and thrombocytopenia** are noted in 2% to 13%. **GI intolerance** with nausea, vomiting, abdominal pain, anorexia, and/or bad taste is common.

MONITORING

- **Aerosolized pentamidine:** This is considered safe for the patient but poses risk of TB to healthcare workers and other patients.
- **Parenteral administration:** Adverse effects are common and may be lethal..

DRUG INTERACTIONS: Avoid concurrent use of parenteral pentamidine with nephrotoxic drugs, including aminoglycosides, amphotericin B, and foscarnet and cidofovir. Amphotericin B – severe hypocalcemia.

PREGNANCY: Category C. Limited experience with pregnant women.

PRAVASTATIN

TRADE NAME: *Prava* (Bristol-Myers Squibb) or generic.

FORMS AND PRICES: Pravastatin generic, Tablets 20mg, 30,R 84.92; Pravastatin generic, Tablet 40mg, 30, R 135.44; Pravastatin generic, Tablets 80mg, 30, R 158.30

CLASS: Statin (HMG-CoA reductase inhibitor)

INDICATIONS AND DOSES: Elevated total cholesterol, LDL cholesterol, and/or triglycerides and/or low HDL cholesterol. This is often a favored statin for dyslipidemia associated with PI-based HAART due to paucity of drug interactions with PIs (*Clin Infect Dis* 2003;37:613; *Clin Infect Dis* 2006;43:645), although it may be less effective than other statins. Initial dose is 40 mg once daily. If desired cholesterol levels are not achieved with 40 mg daily, 80 mg once daily is recommended. A starting dose of 10 mg daily is recommended in patients with a history of significant hepatic or renal dysfunction. Can be administered as a

single dose at any time of the day.

MONITORING: Blood lipids at 4-week intervals until desired results are achieved, then periodically. It is recommended that transaminases be measured prior to the initiation of therapy, prior to the elevation of the dose, and when otherwise clinically indicated. Patients should be warned to report muscle pain, tenderness, or weakness promptly, especially if accompanied by fever or malaise; obtain CPK for suspected myopathy.

PRECAUTIONS: Pravastatin (and other statins) are contraindicated with pregnancy, breastfeeding, concurrent conditions that predispose to renal failure (sepsis, hypotension, etc.) and active hepatic disease. Alcoholism is a relative contraindication.

PHARMACOLOGY

- **Bioavailability:** 14%
- **T½:** 1.3-2.7 h
- **Elimination:** Fecal (biliary and unabsorbed drug) 70%; renal 20%

SIDE EFFECTS

- **Musculoskeletal:** Myopathy with elevated CPK plus muscle tenderness, weakness, or pain + fever or malaise. Rhabdomyolysis with renal failure has been reported.
- **Hepatic:** Elevated transaminase levels in 1% to 2%; discontinue if otherwise unexplained elevations of ALT and/or AST are >3x ULN.
- **Miscellaneous:** Diarrhea, constipation, nausea, heartburn, stomach pain, dizziness, headache, skin rash (eczematous plaques), insomnia, and impotence (rare)

DRUG INTERACTIONS: PIs: Concurrent use considered appropriate with PIs and NNRTIs. **RTV/SQV** decreases pravastatin AUC 50%; **EFV** decreases pravastatin AUC 40%. Prevastatin dose may need to be increased. With **DRV/r** the statin AUC increases by a mean of 81%, but up to 5-fold in individual patients; start with 10 mg qd. With **LPV/r**, the mean pravastatin AUC increase is 33%; use standard dose. Data are inadequate for **ATV**, **FPV**, **IDV**, **RTV**, **TPV**, and **NVP**; use standard dose. Possible interactions with spironolactone, cimetidine, and ketoconazole that reduce cholesterol levels and may effect adrenal and sex hormone production with concurrent use. Itraconazole increases pravastatin AUC and C_{max} 1.7x and 2.5x, respectively. Cholestyramine decrease pravastatin AUC 40%; administer pravastatin 1 h before or 4 h after. Niacin and gemfibrozil: increased risk of myopathy. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class.

PREGNANCY: Category X. Contraindicated.

PREZISTA – see Darunavir

PRIMAQUINE

TRADE NAME: Generic

FORM AND PRICE: Primaquine Available from Zeneca on special request

CLASS: Antimalarial

INDICATIONS AND DOSES: *P. jiroveci* pneumonia: Primaquine 15-30 mg (base)/day + clindamycin 600-900 mg q6-8h IV or 300-450 mg PO q6-8h. **Note:** The published experience and recommendation is for "mild to moderately severe" PCP (*Ann Intern Med* 1996;124:792; *Clin Infect Dis* 1994;18:905; *Clin Infect Dis* 1998;27:524). A meta-analysis of published reports of PCP patients who failed initial treatment showed the clindamycin-primaquine regimen was superior to all others with responses in 42 of 48 (87%) (*Arch Intern Med* 2001;161:1529).

PHARMACOLOGY

- **Bioavailability:** Well absorbed
- **T½:** 4-10 h
- **Elimination:** Metabolized by liver

SIDE EFFECTS: Hemolytic anemia in patients with G6-PD deficiency; its severity depends on drug dose and genetics of G6-PD deficiency.

PREGNANCY: Category C. Limited experience in pregnant women. There is a theoretical risk of hemolytic anemia if fetus has G6PD deficiency.

PYRAZINAMIDE (PZA)

TRADE NAME: Generic

FORM AND PRICE: Generic, PZA 500mg, Tablets 100, R 105.78; Generic, PZA 500mg, Tablets 1000, R 1,006.65.

CLASS: Derivative of niacinamide

INDICATION AND REGIMEN: Tuberculosis, initial phase of usually for 8 weeks (*MMWR* 1998;47[RR-20]; *MMWR* 2000;49:185).Treatment of latent TB with PZA + rifampin is no longer recommended due to hepatotoxicity (*MMWR* 2003;52:735). For active TB, see table below .

■ Table 5-20: **PZA Doses for Active TB**

Weight	Daily*	2x/week*	3x/week*
40-55 kg	1 gm	2.0 gm	1.5 gm
56-75 kg	1.5 gm	3.0 gm	2.5 gm
76-90 kg	2.0 gm	4.0 gm	3.0 gm

*Patients with CD4 count <100/mm^3 should receive therapy daily or 3x/week.

TREATMENT WITH RIFATER (tabs with 50 mg INH, 120 mg rifampin, and 300 mg PZA)

- <65 kg: 1 tab/10 kg/d
- >65 kg: 6 tabs/d

PHARMACOLOGY

- **Bioavailability:** Well absorbed; absorption is reduced about 25% in patients with advanced HIV infection (*Ann Intern Med* 1997;127:289).
- **T½:** 9-10 h
- **CSF levels:** Equal to plasma levels
- **Elimination:** Hydrolyzed in liver; 4% to 14% of parent compound and 70% of metabolite excreted in urine.
- **Renal failure:** Usual dose unless creatinine clearance <10 mL/min – 12-20 mg/kg/day (increased risk of hyperuricemia).
- **Hepatic failure:** Contraindicated

SIDE EFFECTS: PZA appears to be the major cause of hepatotoxicity in patients with hepatitis as a complication of TB treatment (*Am J Respir Crit Care Med* 2003;167:1472). Hepatotoxicity occurs in up to 15% who receive >3 gm/day; transient hepatitis with increase in transaminases, jaundice, and a syndrome of fever, anorexia, and hepatomegaly; rarely, acute yellow atrophy. Monitor LFTs monthly if there are abnormal baseline levels, symptoms suggesting hepatitis, or elevated levels during therapy that are not high enough to stop treatment (ALT <5x ULN). Hyperuricemia is common, but gout is rare. Nongouty polyarthralgia in up to 40%; hyperuricemia usually responds to uricosuric agents. Use with caution in patients with history of gout. Rare – rash, fever, acne, dysuria, skin discoloration, urticaria, pruritus, GI intolerance, thrombocytopenia, sideroblastic anemia.

PREGNANCY: Category C. Not teratogenic in mice, but limited experience in humans. Risk of teratogenicity is unknown, so INH, rifampin, and EMB are preferred. PZA is advocated for pregnant women if resistant *M. tuberculosis* is suspected or established and is acceptable outside the United States per WHO guidelines.

PYRIMETHAMINE

TRADE NAME: *Daraprim* (GlaxoSmithKline) or generic

FORM AND PRICE: Daraprim, pyrimethamine, Tablets 60, R 195.04

CLASS: Aminopyrimidine-derivative antimalarial agent that is structurally related to trimethoprim

INDICATIONS AND DOSE REGIMENS: Toxoplasmosis

■ Table 5-21: **Toxoplasmosis Treatment**

	Acute Phase (3 to 6 weeks)	Maintenance
First line	Pyrimethamine 200 mg x 1 then 50 mg (<60 kg) or 75 mg (>60 kg) + leucovorin 10-20 mg/d + sulfadiazine 1 g qid (<60 kg) or 1.5 g qid (>60 kg) x ≥6 weeks	Pyrimethamine at 50% acute dose and sulfadiazine at 50% acute dose + leucovorin 15 mg/day
Second line	Pyrimethamine + leucovorin + one of the following: ■ Clindamycin 600 mg PO or IV q 6 h or ■ TMP-SMX (5 mg TMP) IV or PO bid or ■ Atovaquone 1500 mg PO bid ■ Azithromycin 900-1200 mg PO qd	Pyrimethamine 25-50 mg qd + leukovorin 10-25 mg PO plus one of the following: ■ Clindamycin 300-450 mg PO q 6-8 h ■ Atovaquone 750 mg PO q 6-12 h
Other	■ Atovaquone 1500 mg PO bid + sulfadiazine 1.0-1.5 gm po q 6 h. ■ Atovaquone 1500 mg PO bid (without pyrimethamine/leukovorin)	■ Atovaquone 750 mg PO q 6-12 h (without pyrimethamine/leukovorin)

PHARMACOLOGY

- **Bioavailability:** Well absorbed
- **T½:** 54-148 h (average 111 h)
- **Elimination:** Parent compound and metabolites excreted in urine
- **Dose modification in renal failure:** None

SIDE EFFECTS: Reversible marrow suppression due to depletion of folic acid stores with dose-related megaloblastic anemia, leukopenia, thrombocytopenia, and agranulocytosis; prevented or treated with folinic acid (leucovorin).

- **GI intolerance:** Improved by reducing dose or giving drug with meals
- **Neurologic:** Dose-related ataxia, tremors, or seizures

- **Hypersensitivity:** Most common with pyrimethamine plus sulfadoxine (*Fansidar*) and due to sulfonamide component of combination
- **Drug interactions:** Lorazepam: hepatotoxicity. AZT, ganciclovir: additive bone marrow suppression.

PREGNANCY: Category C. Teratogenic in animals, but limited experience has not shown association with birth defects in humans.

RETROVIR – see Zidovudine (AZT, ZDV)

RIFABUTIN

TRADE NAME: *Mycobutin* (Pharmacia)

FORM AND PRICE: Mycobutin, rifabutin, capsules 30, R 454.72;

CLASS: Semisynthetic derivative of rifampin B that is derived from *Streptomyces mediterranei*

INDICATIONS AND DOSES

- ***M. avium* prophylaxis:** 300 mg PO qd. Efficacy established (*N Engl J Med* 1993;329:828); azithromycin or clarithromycin is usually preferred.
- ***M. avium* treatment:** Sometimes combined with clarithromycin or azithromycin and EMB using 300 mg/day, except in patients treated with PIs or NNRTIs where dose adjustment is recommended (see below).
- **Tuberculosis:** Preferred to rifamycin for use in combination with most PIs or NNRTIs (*MMWR* 2004;53:37). Usual dose for TB treatment and prophylaxis: 300 mg/day, but dose must be adjusted for concurrent use with PIs and/or NNRTIs: See Table 5-22.

ACTIVITY: Active against most strains of *M. avium* and rifampin-sensitive *M. tuberculosis*; cross-resistance between rifampin and rifabutin is common with *M. tuberculosis* and *M. avium*.

PHARMACOLOGY

- **Bioavailability:** 12% to 20%
- **T½:** 30-60 h
- **Metabolism:** Metabolized via CYP3A4 to 25-0-deacetyl-rifabutin (10% of total antimicrobial activity).
- **Elimination:** Primarily renal and biliary excretion of metabolites
- **Dose modification in renal failure:** None

SIDE EFFECTS: Common: Brown-orange discoloration of secretions; urine (30%), tears, saliva, sweat, stool, and skin. Infrequent: Rash (4%), GI intolerance (3%), neutropenia (2%).

DRUG INTERACTIONS: Rifabutin induces hepatic microsomal enzymes (cytochrome P450 3A4), although the effect is less pronounced than for rifampin. With EFV, the AUC of rifabutin decreases a mean of 37% requiring an increase in rifabutin dose to 450-600 mg/day (*Clin Infect Dis* 2005;41:1343). Drugs that inhibit cytochrome P450 and prolong the half-life of rifabutin: PIs erythromycin, clarithromycin (56% increase), and azoles (fluconazole, itraconazole, and ketoconazole). With concurrent rifabutin and fluconazole, the levels of rifabutin are significantly increased, leading to possible rifabutin toxicity (uveitis, nausea, neutropenia) or increased efficacy (*Clin Infect Dis* 1996;23;685).

COMMENTS

- Rifampin and rifabutin are related drugs, but *in vitro* activity and clinical trials show that rifabutin is preferred for *M. avium*, and rifampin is preferred for *M. tuberculosis*.
- Clarithromycin plus EMB without rifabutin may be the preferred regimen for treatment of disseminated *M. avium* infection due to the clarithromycin–rifabutin interaction.
- Drug interactions are similar for rifabutin and rifampin, although rifabutin is a less potent inducing agent of hepatic microsomal enzymes.
- Uveitis requires immediate discontinuation of drug and ophthalmology consult.
- All PIs and NNRTIs require a dose adjustment when given with rifabutin except for NVP (see Table 5-22 below).

■ TABLE 5-22: **Rifabutin Interactions and Dose Adjustments with Antiretroviral Drugs** (DHHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents, *MMWR* 2004;53:37)

Agent	AUC for		Comment
	ART Agent	Rifabutin	
Nucleosides	NC	NC	Use standard doses†
FPV	↓15%	↑193%	FPV: standard; rifabutin: 150 mg/day or 300 mg 3x/week
EFV*	NC	↓35%	EFV: standard; rifabutin: 450 mg/day or 600 mg 3x/week
NVP*	NC	NC	NVP 200 mg bid; rifabutin 300 mg/day or 300 mg 3x/week
NFV	↓32%	↑2x	NFV: 1250 mg tid; rifabutin: 150 mg/day or 300 mg 3x/week
SQV	↓40%		Not recommended without RTV
LPV/r	NC	↑3 fold	LPV/r: standard; rifabutin: 150 mg qod or 3x/week
ATV	NC	↑2.5x	ATV standard; rifabutin: 150 mg qod or 3x/week
RTV-boosted PI regimens (DRV, SQV, ATV, IDV, FPV)	—	—	PI: standard; rifabutin 150 mg qod or 150 mg 3x/wk
DRV/r	ND	ND	Rifabutin 150 mg qod

† Regimens for 2 to 3x/week should be given 3x/week in patients with a CD4 count <100 cells/mm^3 due to risk of rifamycin resistance (*Am J Respir Crit Care Med* 2001;164:1319).

NC = no change; ND = no data

PREGNANCY: Category B. Not teratogenic in rats or rabbits.

RIFAMPIN

TRADE NAME: *Rifadin* (Aventis) or generic; Combination with INH: *Rifamate*. Combination with INH and PZA: *Rifater* (Aventis)

FORMS AND PRICES: Rimactane, rifampicin 300mg, injection 1, R 124.26; Rimactane, rifampicin 450mg, tablets 100, R 208.62; Rimactane, rifampicin 600mg, tablets 100, R 389.18;

INDICATIONS AND DOSE: Tuberculosis (with INH, PZA, EMB)

- **Dose:** 10 mg/kg/day (600 mg/day max). See pp. 381-382.
- **DOT:** 600 mg 2x to 3x/week.
- **Prophylaxis (alone or in combination with PZA or EMB):** 10 mg/kg/day (600 mg/day max)
- **Antiretrovirals and TB treatment:** See Table 6-2, pp. 381-383.

Rifamycins should be included in any regimen for active TB. Options with HAART include:

- Rifampin (standard dose) + EFV. Consider increasing EFV dose to 800 mg/day.
- Rifabutin substitution with IDV, FPV, NFV, LPV/r, SQV, ATV, or any RTV-boosted regimen in which the RTV dose is ≤200 mg bid.
- Consider delay in antiretroviral therapy.

- **Treatment of latent tuberculosis:** Rifampin (600 mg/day) + PZA (20 mg/kg/day with 2 g/day max) x 2 months was advocated as a preferred regimen for HIV-infected patients with a positive PPD due to demonstrated efficacy comparable with the 12-month INH regimen and better compliance due to the abbreviated duration.
- ***Rifater* treatment**
  - <65 kg – 1 tab/10 kg/d
  - >65 kg – 6 tabs/d
- **Rifampin for:** *S. aureus* (to augment vancomycin, fluoroquinolones, or penicillinase-resistant penicillin): 300 mg PO bid

ACTIVE AGAINST: *M. tuberculosis, M. kansasii, S. aureus, H. influenzae, S. pneumoniae, Legionella*, and many anaerobes

PHARMACOLOGY

- **Bioavailability:** 90% to 95%, less with food. Absorption is reduced 30% in patients with advanced HIV infection; significance is unknown (*Ann Intern Med* 1997;127:289).
- **T½:** 1.5-5.0 h; average 2 h
- **Elimination:** Excreted in urine (33%) and metabolized
- **Dose modification in renal failure:** None

SIDE EFFECTS

- **Common:** Orange-brown discoloration of urine, stool, tears (contact lens), sweat, skin.
- **Infrequent:** GI intolerance; hepatitis (in 2.7% given INH/RIF), usually cholestatic changes in first month of treatment; jaundice (usually reversible with dose reduction or continued use); hypersensitivity, especially pruritus ± rash (6%); flu-like illness in 0.4% to 0.7% given rifampin 2x/wk with intermittent use – dyspnea, wheezing, purpura, leukopenia.
- **Rare:** Thrombocytopenia, leukopenia, hemolytic anemia, increased uric acid, and BUN. Frequency of side effects that require discontinuation of drug is 3%.

DRUG INTERACTIONS: Extensive, due to induction of hepatic cytochrome P450 (3A4, 2B6, 2C8, 2C9) enzymes Rifampin should be avoided with all **PIs** and NNRTIs except **EFV** and

possibly NVP. EFV has no significant effect on rifampin levels, but rifampin reduces EFV levels by 20% to 26%; consider EFV 800 mg hs. Limited experience suggests **NVP** at 200 bid is appropriate (*J Acquir Immune Defic Syndr* 2001;28:450; *AIDS* 2003;17:637; *AIDS Rev* 2006;8:115). Others, noting that NVP levels decrease 20%-58%, advise against the combination (DHHS Guidelines, Oct. 10, 2006. p. 85). The following drugs inhibit cytochrome P450 enzymes and prolong the half-life of rifampin: **clarithromycin, erythromycin,** and **azoles (fluconazole, itraconazole,** and **ketoconazole**).

Rifampin decreases levels of **atovaquone, barbiturates, oral contraceptives, corticosteroids, cyclosporine, dapsone, fluconazole, ketoconazole,phenytoin, theophylline, trimethoprim,** and many other drugs that are 3A4 substrates. Rifampin should not be used concurrently with **atovaquone, clarithromycin.** With **fluconazole** and **itraconazole** it may be necessary to increase the azole dose. The level of **dapsone** is decreased 7- to 10-fold – consider alternative.

PREGNANCY: Category C. Dose-dependent congenital malformations in animals. Isolated cases of fetal abnormalities noted in patients, but frequency is unknown. Large retrospective studies have shown no risk of congenital abnormalities; case reports of neural tube defects and limb reduction (*Clin Infect Dis* 1995:21[suppl 1]:S24). May cause postnatal hemorrhage in mother and infant if given in last few weeks of pregnancy. Must use with caution if used with INH and ethambutol.

RITONAVIR (RTV)

TRADE NAME: *Norvir* (Abbott Laboratories)

FORMS AND PRICES: Norvir, ritonavir 100mg, capsules 84, R 83.86; Norvir, ritonavir 400mg, solution 90ml, R 71.88.

STORAGE: Caps can be left at room temperature (up to 25ºC or 77ºF) for up to 30 days. Oral solution should *not* be refrigerated.

CLASS: PI

DOSE: Almost always used to boost other PIs. When dose is ≤400 mg/d it is subtherapeutic and should not be considered an antiretroviral agent, hence the designation "/r." The dose is 600 mg bid when used as a single PI, but this is poorly tolerated and rarely used. Administration with food improves tolerability but is not required for absorption.

- **Recommended regimens for PI-boosting** (DHHS Guidelines, October 10, 2006) appear in Table 5-23 on the following page.

■ TABLE 5-23: **RTV Boosting of PIs**

PI/r	Regimen recommended	AUC PI (-fold increase)*
ATV/r	300/100 mg qd	2.4
IDV/r	400/400 mg bid 800/100-200 mg bid	2-5
LPV/r	400/100 mg bid 800/200 mg qd	15-20
NFV/r	Not recommended	1.5
SQV/r	1000/100 mg bid	20
DRV/r	600/100 mg bid	14

*Based on data from Ogden RC and Flexner CW, eds, *Protease Inhibitors in AIDS Therapy* at 166-71, 173 (NY: M Dekker, 2001) and DHHS Guidelines (Oct. 10, 2006), pp. 87-88.

PHARMACOLOGY

- **Bioavailability:** Not well determined. Levels increased from about 4% to ≥15% when taken with meals. CNS penetration: No detectable levels in CSF.
- **T½:** 3-5 h
- **Elimination:** Metabolized by cytochrome P450 CYP3A4 >2D6. RTV is a potent inhibitor of cytochrome P450 CYP3A4>2D6, and an inducer of CYP3A4 and CYP1A2.
- **Dose modification in renal or hepatic failure:** Use standard doses for renal failure. With hemodialysis, a small amount is dialyzed: dose post-hemodialysis (*Nephron* 2001;87:186). There are no data for peritoneal dialysis, but it is probably not removed and should be dosed post-dialysis. Consider empiric dose reduction in severe hepatic disease.

SIDE EFFECTS: The most frequently reported adverse events with full dose therapy are GI intolerance (nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion), circumoral and peripheral paresthesias, and asthenia. GI intolerance is dose-related and may be severe (*J Acquir Immune Defic Syndr* 2000;23:236) and can improve with continued administration for ≥1 month. Hepatotoxicity with elevated transaminase levels is dose-related and there appears to be a modestly increased risk with hepatitis B or C co-infection (*JAMA* 2000;238:74; *J Acquir Immune Defic Syndr* 2000;23:236; *Clin Infect Dis* 2000;31:1234). Laboratory changes include elevated triglycerides, cholestrol, transaminases, CPK, and uric acid.

- **Class adverse reactions:** Insulin-resistant hyperglycemia, fat accumulation, elevated triglycerides and cholesterol, and possible increased bleeding with hemophilia. Hypercholesterolemia and triglyceridemia may be more frequent and severe with full dose RTV

compared with other PIs (*J Acquir Immune Defic Syndr* 2000;23:236; *J Acquir Immune Defic Syndr* 2000;23:261). Much of the effect on lipids is attributed to the higher levels of the concurrent PI caused by RTV, rather than by RTV per se; the effect may be due to both.

DRUG INTERACTIONS: RTV is a potent inhibitor of cytochrome P450 enzymes, including CYP3A4 and 2D6, and can produce large increases in the plasma concentrations of drugs that are metabolized by that mechanism.

- **Use with the following agents is contraindicated:** Amiodarone, astemizole, bepridil, cisapride, lovastatin, midazolam, ergot alkaloids, quinidine, simvastatin, terfenadine, triazolam, St. John's wort, rifapentine, and (with ≥400 mg/d RTV).
- **Use with caution** in patients with ↑ QTc at baseline and with drugs that can ↑ QTc (cisapride, type I and III anti-arrhythmics, erythromycin).
- **Drugs that require dose modification**

  Fluticasone (*Flonase*): RTV increased fluticasone AUC 350-fold, resulting in an 86% decrease in plasma cortisol AUC. Adrenal insufficiency reported. FDA warning: use concurrently only if benefit outweighs risk. **Clarithromycin** AUC increased 77% (*Clin Infect Dis* 1996;23:685); reduce clarithromycin dose for renal failure. **ddI, buffered form**, reduces absorption of RTV and should be taken ≥2 hours apart or use ddI EC. **Ketoconazole** levels are increased 3-fold; do not exceed 200 mg ketoconazole/day. **Itraconazole:** No data, but concern with itraconazole doses >400 mg/d; monitor itraconazole levels. **Rifampin** reduces RTV levels 35% (use standard dose RTV); limited data on combination use and concern for hepatotoxicity. **Rifabutin** levels increased 4-fold; rifabutin dose of 150 mg qod or 150 mg 3 days/week with standard RTV dose for all PI/r regimens. **Ethinyl estradiol** levels decreased by 40%; use alternative or additional method of birth control. **Theophylline** levels decreased by 47%; monitor theophylline levels. **Phenobarbital, phenytoin, and carbamazepine** interaction anticipated; carbamazepine toxicity reported. Monitor anticonvulsant levels. **Sildenafil** AUC increased 11-fold; do not use >25 mg/48 hours; **Atorvastatin** levels increase 450% with SQV/r; use lowest atorvastatin dose, or use pravastatin or fluvastatin or rosuvastatin. **Pravastatin** levels decrease 50% with concomitant SQV/RTV; may need increased pravastatin dose based on lipid response. **Lovastatin** and **simvastatin** are contraindicated.

PREGNANCY: Category B. Negative rodent teratogenic assays; placental passage studies in rodents show newborn:maternal drug ratio of 1.15 at midterm and 0.15-0.64 at late term. LPV/r and NFV are the preferred PI-based regimens. The recommended LPV/r regimen is standard dose in the first and second trimesters, and 2-3 tabs bid in the third trimester. SQV/r is an alternative regimen with *Invirase* at 1000/100 mg

bid (DHHS Guidelines, Oct. 10, 2006. p. 97).

SAQUINAVIR (SQV)

TRADE NAME: *Invirase* (hard-gel capsule) (Roche). The *Fortovase* formulation was discontinued in February 2006.

FORMULATIONS AND REGIMENS

FORMS: *Invirase:* 200 mg hard gel caps and 500 mg film-coated tabs.

REGIMENS: Give only with RTV, 1000/100 mg bid or 2000/100 mg qd. The once-daily regimen is not FDA-approved.

FOOD: Take within 2 h of a meal

RENAL FAILURE: Standard regimen

HEPATIC FAILURE: With mild hepatic disease, use standard regimen. No data for moderately severe or severe liver disease; use with caution.

STORAGE: Room temperature, 15-30°C

CLASS: PI. Note that most studies were done with the *Fortovase* formulation, which is no longer available.

- ***Invirase* vs *Fortovase* formulations of SQV:** The first PI approved by the FDA was *Invirase*, the hard-gel formulation of SQV. Later, this form was largely replaced by the *Fortovase* soft-gel formulation, which showed equivalence to IDV/r in treatment-naïve patients in MaxCMin-1 (*J Infect Dis* 2003;188:635). MaxCMin-2 compared SQV/r (*Fortovase*)) 1000/100 mg bid to LPV/r in a mixed population of treatment-experienced and -naïve patients (*Antivir Ther* 2005; 10:735). Results at 48 weeks showed no statistically significant difference in virologic outcome and a better lipid profile in SQV recipients. However, a significantly greater number in the SQV/r group discontinued treatment due to GI intolerance.

  More recently, a comparison of the *Invirase* and *Fortovase* formulations indicated that *Invirase* is better tolerated and, with RTV boosting, has better pharmacokinetic profile (*HIV Med* 2003;4:94). *Fortovase* has been discontinued and a new 500-mg hard-gel cap of *Invirase* is available to reduce the pill burden.

■ TABLE 5-24: ***Invirase* vs LPV/r in Treatment-naïve Patients**

	LPV/r *n* = 76	SQV/r *n* = 74
VL <400 c/mL	83%	80%
VL <50 c/mL	75%	69%
CD4 increase (mean)	+157/mm^3	+140/mm^3
Discontinuation due to ADR	4	2
Lipid elevation >1 grade	38%	21%

This interim analysis supports the conclusion that this SQV/r regimen appears virologically equivalent to LPV/r, possibly with less GI intolerance and hyperlipidemia (J Slim, 8th Int Congress on Drug Therapy in HIV Infection, Glasgow, 2006, Abstr. PL2.5).

RESISTANCE: Major resistance mutations selected with *in vitro* passage are L90M (most common; 3-fold in IC_{50}) and G48V (less common and 8-fold increase IC_{50}). Mutations noted in isolates with reduced susceptibility that emerged during treatment with *Invirase* include 48V and 90M and the following secondary mutations: 10I/R/V, 54V/L, 71V/T, 73S, 77I, 82A, and 84V. Treatment-naïve patients with virologic failure with SQV/r usually have no PI resistance mutations (*Antivir Ther* 2006;11:631).

PHARMACOLOGY

- **EC_{50}:** 50 ng/mL. C_{min} with SQV/r 1000/100 mg bid is usually >500 ng/mL (*J Antimicrob Chemother* 2005;56:908).
- **Bioavailability:** Absorption of SQV is not influenced by food when taken with RTV. There is essentially no CNS penetration (CSF:serum ratio is 0.02). AUC and trough levels are significantly higher in women compared to men (*J Infect Dis* 2004;189:1176).
- **Pharmacokinetics:** Current dosing recommendations are based on pharmacokinetic studies in volunteers using the *Invirase* formulation. These showed SQV/r regimens of 1000/100 mg bid and 2000/100 mg qd give desirable C_{min} and AUC values. Comparison of these two regimens showed the 2000/100 mg qd regimen gave a higher AUC (82 vs 55 mg•h/L) but lower C_{min} (0.28 vs 1.02 mg/L) than the bid regimen (*J Antimicrob Chemother* 2004;54:785).
- **T½:** 1-2 h
- **Elimination:** Metabolism is by cytochrome P450 isoenzymes CYP3A4and CYP3A5 in the liver and gut (*Clin Pharmacol Ther* 2005;78:65). 96% biliary excretion; 1% urinary excretion
- **Storage:** Room temperature.

- **Dose modification in renal or hepatic failure:** Use standard dose for renal failure. The drug is not removed by hemodialysis (*Nephron* 2001;87:186) and is unlikely to be removed by peritoneal dialysis. Consider empiric dose reduction for hepatic failure.

SIDE EFFECTS: Gastrointestinal intolerance with nausea, abdominal pain, diarrhea in 5% to 15%; headache, and hepatic toxicity;case reports of hypoglycemia in patients with type 2 diabetes (*Ann Intern Med* 1999;131:980). Class adverse effects include fat accumulation, insulin resistance, and type 2 diabetes. SQV appears to have less effect on blood lipids compared to most other PIs (*J Infect Dis* 2004;189:1056).

DRUG INTERACTIONS

- **Drugs that are contraindicated for concurrent use:** Terfenadine, astemizole, cisapride, triazolam, midazolam, rifampin, pimozide, rifabutin, ergot alkaloids, simvastatin, lovastatin, St. John's wort, flutrcasone and rifapentine.
- **Drugs that may require regimen modification**

  Omeprazole (40 mg/d) given with *Invirase*/RTV 1000/100 mg bid increased SQV AUC 80% without change in RTV AUC (*AIDS* 2006;20:1401). **Dexamethasone** may decrease SQV levels. **Phenobarbital, phenytoin**, and **carbamazepine** may decrease SQV levels substantially; monitor anticonvulsant levels or, preferably, use alternative agent. **Ketoconazole** increases SQV levels 3x; standard dose. Monitor for SQV GI toxicity if ketoconazole dose is >200 mg/day. **Itraconazole** has bidirectional interaction with SQV; may need to use reduced dose of itraconazole or to monitor levels and monitor for SQV toxicity. **Clarithromycin** increases SQV levels 177% and SQV increases clarithromycin levels 45%; reduce with renal failure. **Oral contraceptives:** No data. Recommend alternative form of contraception. **Sildenafil** AUC increased 2x; use 25 mg starting dose; **Tadalafil** – start with 5 mg dose and do not exceed 10 mg/72 h; **Vardenafil** – start with 2.5 mg dose and do not exceed 2.5 mg/72 h. **Rifampin** reduces SQV levels by 80%. A volunteer study showed marked elevations in transaminase. Rifampin + SQV/RTV should not be used (*AIDS* 2006;20:302; Roche letter to care providers, Feb. 2005). **Rifabutin** reduces SQV levels 40%. With any combination of SQV/RTV use rifabutin 150 mg qod or 150 mg 3x/wk. Monitor for efficacy of and toxicity to both drugs. **Atorvastatin** levels increase 450% with SQV/RTV; use lowest starting dose of atorvastatin, or use pravastatin, fluvastatin, or rosuvastatin. **Pravastatin** levels are reduced 50% by SQV/r; may need to increase pravastatin dose. **Methadone** – With FTV there is a 10% to 20% reduction in methadone levels; no dose adjustment. This also applies to SQV/r 1600/100 qd (*J Clin Pharmacol* 2004;44:293). **Garlic supplements** decrease SQV AUC, C_{max}, and C_{min} levels by about 50% (*Clin Infect Dis* 2002;34:234). Grapefruit juice increases SQV levels. **Other drugs**

that induce CYP3A4 (phenobarbital, phenytoin, NVP, dexamethasone, and carbamazepine) may decrease SQV levels; these combinations should be avoided if possible.

■ TABLE 5-25: **Combination Therapy with *Invirase* Plus Second PI or an NNRTI**

Drug	AUC*	Regimen*
RTV	SQV ↑20x, RTV no change	SQV 1000 mg bid + RTV 100 mg bid *or* SQV 400 mg bid + RTV 400 mg bid
IDV	IDV no change, SQV↑ ↑4 to 7x	Insufficient data. In vitro antagonism
FPV	FPV ↓32%, SQV ↓19%	Data inadequate; avoid
EFV	EFV ↓12%, SQV ↓62%	SQV 1000 mg bid + RTV 100 mg bid + EFV 600 mg hs; SQV/RTV 400/400 mg bid + EFV 600 mg qd
NVP	NVP no change, SQV ↓25%	Consider NVP standard dose plus SQV/RTV 400 mg/400 mg bid or 1000 mg/100 mg
NFV	NFV ↑20%, SQV ↑3 to 5x	FTV 800 mg tid or 1200 mg bid + NFV standard. Dose with INV not established.
LPV/r	SQV ↑3 to 5x, LPV no change	SQV 1000 mg bid + LPV/r 400/100 mg bid
ATV	ATV (RTV effect); SQV ↑60%	ATV 300 mg + SQV 1600 mg + RTV 100 mg qd. Consider ATV/SQV/RTV 300/1500-2000/100 mg qd.
DRV	DRV ↓26%, SQV no change	Avoid co-administration.
TPV	SQV AUC ↓76%	Avoid co-administration.

PREGNANCY: Category B. Studies in rats showed no teratogenicity or embryotoxicity. There is substantial variation in SQV levels in pregnancy. The PK data suggests SQV/r at 800/100 mg bid is reasonable (*Antimicrob Agents Chemother* 2004;48:430). There are no published reports of the *Invirase* formulation in pregnancy, but it should be adequate and show better GI tolerance compared to *Fortovase*. The 2006 DHHS guidelines recommend *Invirase*/RTV 1000/100 mg bid.

SPORANOX – see Itraconazole

STAVUDINE (d4T)

TRADE NAME: *Zerit* (Bristol-Myers Squibb)

CLASS: NRTI

FORMULATIONS, REGIMENS AND PRICE

FORMS: Zerit, stavudine 1mg/ml, powder for solution 200ml, R 13.22;

generic stavudine 20mg, capsules 60, R 28.79; generic, stavudine, 30mg, capsules 60, R 34.18; generic, stavudine 40mg, capsules 60, R 40.30;

REGIMENS: As per the WHO guidelines , the standard dose of Stavudine is 30mg at any weight.

FOOD: No effect

RENAL FAILURE

■ TABLE 5-26: **d4T Dosing in Renal Failure**

Wt.	CrCl (mL/min)			
	> 50	26-50	10-25	Dialysis
>60kg	40 mg bid	20 mg bid	20 mg qd	20 mg qd
<60kg	30 mg bid	15 mg bid	15 mg qd	15 mg qd

HEPATIC FAILURE: No dose recommendation

CLINICAL TRIALS: There is extensive experience with d4T combined with 3TC or ddI. **ACTG 384** showed that EFV/AZT/3TC had greater activity and less toxicity compared with EFV/ddI/d4T (*N Engl J Med* 2003;349:2293). **GS 903** compared d4T and TDF in 600 treatment-naïve patients who were randomized to receive TDF or d4T, each with 3TC and EFV. Both regimens were highly effective at 3 years, but d4T was associated with more neuropathy, hyperlipidemia, and lipodystrophy than TDF.

RESISTANCE: *In vivo* d4T resistance is mediated primarily by thymidine analog mutations (TAMs) (e.g., 41L, 67N, 70R, 210W, 215Y/F, 219Q/E), and d4T also selects for these mutations. Mutations at 44D and 118I increase resistance to AZT and d4T in the presence of TAMs (*J Infect Dis* 2002;185:8998). As with AZT, the M184V mutation increases susceptibility to d4T. The multinucleoside resistance mutations (Q151M complex and the T69-insertion mutation) result in resistance to d4T. This agent sometimes selects for the K65R mutation, though it appears to have minimal effect on d4T susceptibility.

There is increasing evidence that subtype C select for the K65R mutation, thus rendering TNF inactive in the second regimen (http://www.retroconference.org/2007/Abstracts/30137.htm)

PHARMACOLOGY

- **Bioavailability:** 86% and not influenced by food or fasting
- **T½:** Serum, 1 h. Intracellular T½: 3.5 h

- **CNS penetration:** 30% to 40% (*J Acquir Immune Defic Syndr* 1998;17:235) (CSF: plasma ratio=0.16-0.97)
- **Elimination:** Renal – 50%
- **Dose modification in severe liver disease:** No guidelines; use standard dose with caution.

SIDE EFFECTS

- **Mitochondrial toxicity:** d4T is an important cause of side effects attributed to mitochondrial toxicity, including lactic acidosis with hepatic steatosis, peripheral neuropathy, and lipatrophy. In most studies of lactic acidosis, d4T is the most frequent NRTI (*Clin Infect Dis* 2001;33:1931; *Lancet* 2000;356:1423; *Ann Intern Med* 2000;133:192). A review of reported cases for 2000 to 2001 implicated d4T in 33 of 34 (*Clin Infect Dis* 2002;31:838).
  - **Lactic acidosis and steatosis:** Decreased mitochondrial DNA to DNA ratio is a marker of mitochondrial toxicity and is relatively common without abnormal function (*Antiviral Ther* 2004;9:47). Hyperlactatemia is also relatively common and erroneously high levels are often reported due to lapses in quality control in drawing blood, transport, and lab processing. Lactic acidosis ± steatosis is reported in 1 to 14/1000 patient-years of NRTI exposure (*AIDS* 2001;15:717), but it is more common with thymidine analogues (d4T, ddI, AZT) and most common with d4T. It is important to recognize due to the potential for prolonged symptoms despite d4T withdrawal, lack of effective treatment, and possible lethal outcome. Patients present with nausea, vomiting, abdominal pain, fatigue, dyspnea, and/or weight loss, usually after 1 to 20 months of exposure (*Clin Infect Dis* 2003;36[suppl 2]:S96). Laboratory studies show elevated serum lactate (usually >5 mmol/L), sometimes combined with increased anion gap and elevated CPK, ALT, and LDH. CT scan, ultrasound, or liver biopsy may show hepatic steatosis. NRTIs should usually be stopped. In mild cases, switching to NRTIs that are less toxic to mitochondria (e.g., ABC, 3TC, FTC, TDF) may be considered, provided the patient can be closely monitored. d4T/ddI should be avoided, especially in pregnant women who have an increased risk of lactic acidosis **(FDA black box warning)**.
  - **Peripheral neuropathy:** Frequency is 5% to 15% but as high as 24% in some early trials. The presumed cause is depletion of mitochondrial DNA (*N Engl J Med* 2002;346:811). Risk appears to be substantially increased when d4T is combined with ddI or ddI plus hydroxyurea (*AIDS* 2000;14:273). Onset is usually noted at 2 to 6 months of treatment and usually resolves if d4T is promptly stopped, although the recovery is generally slow. Peripheral neuropathy due to HIV infection or alternative nucleoside analog treatment (ddI, ddC) represents a contraindication to d4T. If it is necessary to resume d4T after resolution of neuropathy, some

authorities recommend a decreased dose of 30 mg bid (12th CROI, Boston, Feb. 2005, Abstr. 851).

- **HIV-associated neuromuscular weakness syndrome:** A syndrome of ascending motor weakness is characterized by variable changes, including progressive sensorimotor polyneuropathy with areflexia and ascending neuromuscular weakness. EMG and pathology show changes in nerves, muscles or both. Of 69 cases reviewed, 61 were thought to be due to d4T, and many (36%) had onset of symptoms after d4T was stopped. Lactate levels are usually elevated (*AIDS* 2004;18:1403). The weakness was accompanied by lactic acidosis and is presumed to be a result of mitochondrial toxicity. There is an increase of peripheral neuropathy with the co-prescription of INH for TB.(AIDS:Volume 14(5)31 March 2000p 615)
- **Lipoatrophy and hyperlipidemia:** d4T is associated with lipoatrophy and hyperlipidemia (*Clin Infect Dis* 2006;43:645). The lipoatrophy is a cosmetic effect that is most obvious in the malar (cheek) area, extremities and buttocks. These effects persist for prolonged periods after d4T is discontinued, although some studies show slow but significant increase in malar fat after several months (*AIDS* 2006;20:243; *AIDS* 2004;18:1029). Serum lipid changes ascribed to d4T are most significant for triglyceride elevations but also for increased LDL cholesterol (*JAMA* 2004;292:191). Reversal of lipid effects are noted with switch to alternative NRTIs such as TDF or ABC (*J Acquir Immune Defic Syndr* 2005;38:263; *AIDS* 2005;19:15; *AIDS* 2006;20:2043). Stavudine is the most toxic drug in the National Program. It is not longer a first line drug in the WHO, DHHS or BHIVA guidelines. It may also be co-formulated with 3TC and NVP in Triomune.

- **Other clinical side effects:** Complaints are infrequent and include headache, GI intolerance with diarrhea, or esophageal ulcers.
- **Macrocytosis** with MCV >100, which is inconsequential (*J Infect* 2000;40:160).

DRUG INTERACTIONS

- **NRTIs: AZT** – Pharmacologic antagonism; avoid. **ddI** – increased risk of pancreatitis, lactic acidosis, and peripheral neuropathy.
- **Drugs that cause peripheral neuropathy** should be used with caution or avoided: ddC, ddI, ethionamide, EMB, INH, phenytoin, vincristine, glutethimide, gold, hydralazine, thalidomide, and long-term metronidazole.

PREGNANCY: Category C. The pregnancy registry shows birth defects in 12/451 (2.7%) exposures compared to overall prevalence of birth defects of 3.1% (www.apregistry.com, accessed Sept. 1, 2006). D4T is listed as an "alternate" to AZT/3TC (Oct. 10, 2006, p. 95). However, studies in pregnancy indicate good tolerability and pharmacokinetics *(J*

Infect Dis 2004;190:2167). d4T + ddI should not be given to pregnant women due to possible lactic acidosis and hepatic steatosis (*Sex Trans Infect* 2002;78:58). **(FDA black box warning.)**

SULFAMETHOXAZOLE-TRIMETHOPRIM – see Trimethoprim-Sulfamethoxazole

TENOFOVIR DISOPROXIL FUMARATE (TDF)

TRADE NAME: *Viread* (Gilead Sciences). Combination with emtricitabine (FTC): *Truvada* (Gilead Sciences). Combination with FTC and efavirenz (EFV): *Atripla* (Gilead Sciences and Bristol-Myers Squibb).

CLASS: Nucleotide analog reverse transcriptase inhibitor (NRTI)

FORMULATIONS AND REGIMENS: Tenofovir: 300 mg tab (1 PO qd); *Truvada* TDF/FTC 300/200 mg (1 PO qd); *Viread* tenofovir 300mg, tablets 30, R 199.29

FOOD: No clinically significant effect, but fatty meals increase EFV absorption by 40%. Note: EFV is supposed to be taken on an empty stomach to avoid high levels; the same applies to *Atripla*. Administration with food acceptable if tolerated.

RENAL FAILURE: See Table 5-27.

The incidence of renal pathology in the South Africa population has not been fully investigated. There is an inceased background of hypertension and diabetes as well as HIV assoiciated nephropathy. While this drug is the in the suggested first line by the WHO and the DHHS guidelines, the safely profile needs to be fully studied

■ TABLE 5-27: **TDF Dose Adjustments for Renal Failure**

CrCl	TDF	TDF/FTC (*Truvada*)
≥50	300 mg qd	1 tab qd
30-49	300 mg q 48 h	1 tab q 48 h
10-29	300 mg 72-96 h	not recommended
<10	Inadequate data; consider 300 mg/wk	not recommended
hemodialysis	300 mg/wk	not recommended

HEPATIC FAILURE: No dose change recommended

RESISTANCE: Susceptibility is decreased in patients with three or more thymidine analog mutations (TAMs) that include the 41L and 210W mutations. Susceptibility is maintained with other TAM patterns and

increased with 184V. TDF/ABC and TDF/ddI select for the 65R mutation which confers resistance to all three drugs, as well as to 3TC and FTC (Antimicrob Agents Chemother 2004;48:1413). Resistance tests in 14 patients with virologic failure in Gilead 903 showed no K65R mutations at 96 weeks. There is substantial loss of susceptibility with the T69 insertion mutation (Antimicrob Agents Chemother 2004;48:992), but it is maintained with Q151M complex. Partial phenotypic susceptibility may be maintained despite the presence at K65R when M184V is also present.

PHARMACOLOGY

- **Bioavailability:** 25% (fasting) to 40% (with food); improvement with food, especially high-fat meal
- **T½:** 12-18 h; intracellular >60 h
- **Elimination:** Renal, glomerular filtration, and active tubular secretion.

DRUG INTERACTION

- **ATV:** ATV AUC is decreased 25% and TDF AUC is increased 28%; use standard dose TDF plus ATV/r (300/100 mg) qd.
- **ddI EC:** ddI AUC is increased 50% to 60%, potentially causing increased rates of peripheral neuropathy and pancreatitis. When combining with TDF, use lower doses of ddI (e.g., *Videx EC* 250 mg qd in patients >60 kg; *Videx EC* 200 mg qd <60 kg). Other concerns are possible reduced potency of ddI/TDF based on high failure rates when combined with EFV or NVP (*AIDS* 2005;19:695; *Antivir Ther* 2005; 10:171; *AIDS* 2005;19:213). Other reports showed TDF/ddI as the NRTI backbone in HAART was associated with viral suppression but a blunted CD4 response (*AIDS* 2005;19:569; *Clin Infect Dis* 2005;41:901; *AIDS* 2005;19:1107). The CD4 effect is ascribed to failure to adjust the dose of ddI when combined with TDF (*AIDS* 2005;19:1987).

SIDE EFFECTS

- **GI intolerance:** GI intolerance reported, but it is infrequent. Flatulence occurred more often in TDF-treated patients than placebo-treated patients.
- **Nephrotoxicity:** TDF and related drugs (adefovir and cidofovir) may cause renal injury, including the Fanconi syndrome, which is characterized by hypophosphatemia, hypouricemia, proteinuria, normoglycemic glycosuria, and, in some cases, acute renal failure (*J Acquir Immune Defic Syndr* 2004;35:269; *AIDS* 2004;18:960; *Clin Infect Dis* 2003;37:e174). In the early stages this may be asymptomatic or cause myalgias; most resolve when the drug is discontinued (*J Acquir Immune Defic Syndr* 2004;35:269). Risk factors are low body weight, pre-existing renal disease (*Antimicrob Agents Chemother* 2001;45:2733), and concurrent use of nephrotoxic drugs. The incidence appears to be extremely low in patients with normal baseline renal function. Analysis of 600

participants in GS 903 with calculated creatinine clearances >60 mL/min and serum phosphorus ≥2.2 mg/dL showed no change in mean serum creatinine or phosphorus levels at week 144 (*Nephrol Dial Transplant* 2005;20:743). Another study of 1058 TDF recipients showed only 9 (0.9%) developed an otherwise unexplained increase in serum creatinine (*J Acquir Immune Defic Syndr* 2004;37:1489). Other studies show declines in creatinine clearance in some clinical cohorts (*Clin Infect Dis* 2005;40:1194). This includes the Johns Hopkins Moore Clinic database, which showed 344 TDF recipients had slightly lower creatinine clearance at 1 year compared to 314 controls given alternative NRTIs (decrease of 8 mL/min vs 4 mL/min (*Clin Infect Dis* 2005;40:1194). Conclusion is that TDF treatment may cause nephrotoxicity, but this is infrequent and usually modest in severity. Nevertheless, there are anecdotal reports of severe renal disease, including acute renal failure.

Renal function should be monitored using creatinine clearance (serum creatinine levels are too insensitive). The Cockcroft-Gault equation for males:

$$\text{CrCl (mL/min)} = \frac{\text{(Weight (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/dL)}}$$

For females, multiply this result by 0.85.

Dose adjustments are provided in the chart at "Renal Failure" in this entry (above).

Evaluation for Franconi syndrome should include serum phosphate levels, blood glucose, serum potassium, and urine glucose. Consider discontinuing TDF if there is an otherwise unexplained significant decrease in CrCl or if the serum phosphate is <1.0 mg/dL.

- **Other:** The incidence of laboratory and clinical adverse events has been similar to placebo in controlled clinical trials.

PREGNANCY: Category B. Studies in infant monkeys showed a significant reduction in growth and reduced bone porosity (*J Acquir Immune Defic Syndr* 2002;29:207). Studies in children show bone demineralization (*AIDS* 2002;16:1257). Due to concerns about bone abnormalities and limited experience it is recommended that TDF be used with caution in pregnancy.

TRICYCLIC ANTIDEPRESSANTS – see also Nortriptyline

Tricyclic antidepressants elevate mood, increase physical activity, improve appetite, improve sleep patterns, and reduce morbid preoccupations in most patients with major depression. The following principles apply:

INDICATIONS

- **Psychiatric indications:** Major depression – response rates are 60% to 70%. Low doses are commonly used for adjustment disorders including depression and anxiety. Usual therapeutic dose for depression is 50-150 mg hs for nortriptyline (*Pamelor*) and 100-300 mg hs for amitriptyline (*Elavil*).
- **Peripheral neuropathy:** Controlled trials have not shown benefit in AIDS-associated peripheral neuropathy, but clinical experience is extensive and results in diabetic neuropathy are good. If used, choice of agents depends on time of symptoms (*JAMA* 1998;280:1590). Night pain: Amitriptyline (sedating) 25 mg hs. Day pain: Nortriptyline (less sedating and less of an anticholinergic effect) 25 mg hs. Some recommend therapeutic drug monitoring for depression, but generally not for peripheral neuropathy.

DOSE: Initial treatment of depression is 4 to 8 weeks, which is required for therapeutic response. The initial dose is usually given at bedtime, especially if insomnia is prominent or if sedation is a side effect. Common mistakes are use of an initial dose that is too high, resulting in excessive anticholinergic side effects or oversedation. The dose is increased every 3 to 4 days depending on tolerance and response. Treatment of major depression usually requires continuation for 4 to 5 months after response. Multiple recurrences may require long-term treatment.

SERUM LEVELS: Efficacy correlates with serum levels of nortriptyline when used as an antidepressant. Therapeutic monitoring of drug levels allows dose titration. Target level for nortriptyline is 70-125 ng/dL.

PHARMACOLOGY: Well absorbed, extensively metabolized, long half-life, variable use of serum levels (see below).

SIDE EFFECTS: Anticholinergic effects (dry mouth, dizziness, blurred vision, constipation, tachycardia, urinary hesitancy, sedation), sexual dysfunction, orthostatic hypotension, weight gain

RELATIVE CONTRAINDICATIONS: Cardiac conduction block, prostatism, and narrow angle glaucoma. Less common side effects – mania, hypomania, allergic skin reactions, marrow suppression, seizures, tardive dyskinesia, tremor, speech blockage, anxiety, insomnia, Parkinsonism, hyponatremia; cardiac conduction disturbances and arrhythmias (most common serious side effects are with overdosage).

TRIMETHOPRIM-SULFAMETHOXAZOLE
(TMP-SMX, cotrimoxazole)

TRADE NAME: *Bactrim* (Roche), *Septra* (Monarch), or generic

FORMS AND PRICE: Generic, trimethoprim-sulphamethoxazole, tablets 20, R 3.36.

INDICATIONS AND DOSE REGIMENS

- **PCP prophylaxis:** 1 DS/day or 1 SS/day; alternative is 1 DS 3x/week. Discontinuation of PCP prophylaxis after HAART-associated immune reconstitution is safe and avoids significant toxicity (*Clin Infect Dis* 2001;33:1901; *MMWR* 2002;51[RR-8]:4). PCP prophylaxis with TMP-SMX reduces the frequency of bacterial pneumonia and other bacterial infections (*Clin Infect Dis* 2006;43:90).
- **Desensitization:** See Table 5-28, p. 219
- **PCP treatment:** 5 mg/kg (trimethoprim component) PO or IV q8h x 21 days, usually 5-6 DS/day
- **Toxoplasmosis prophylaxis:** 1 DS/day
- **Toxoplasmosis treatment:** Alternative to sulfadiazine – acute therapy (>6 weeks) TMP-SMX 5 mg/kg (TMP) PO or IV bid x ≥6 weeks, then maintenance at half dose (*Eur J Clin Microbiol Infect Dis* 1992;11:125; *Antimicrob Agents Chemother* 1998;42:1346; *Cochrane Database Syst Rev* 2006;19:CD005420).
- ***Isospora:*** 1 DS PO qid x 10 days; may need maintenance with 1-2 DS/day. IDSA recommendation: TMP-SMX 1 DS bid x 7 to 10 days, then 1 DS 3x/week or 1 *Fansidar* every week indefinitely.
- ***Salmonella:*** 1 DS PO bid x 5 to 7 days; treat >14 days if relapsing.
- ***Nocardia:*** 4-6 DS/day x ≥6 months
- **Urinary tract infections:** 1-2 DS/day x 3 to 14 days
- **Prophylaxis for cystitis:** ½ SS tab daily
- **Malaria prophylaxis:** TMP-SMX is effective prophylaxis for PCP and has proven highly effective for preventing malaria (*Lancet* 2006;367:1256). Initial results in malaria-endemic areas shows TMP-SMX prophylaxis for PCP does not select for TMP-SMX resistant malaria (*Ann J Trop Med Hyg* 2006;75:375).

ACTIVITY: TMP-SMX is effective in the treatment or prophylaxis of infections involving *P. jiroveci*, most methicillin-sensitive *S. aureus*, nearly all community-associated MRSA (USA 300 strains), *Legionella*, *Listeria*, and common urinary tract pathogens. Some studies show increasing rates of mutations in the dihydropteroate synthase gene of *P. jiroveci* that are associated with increased resistance to sulfonamides and dapsone (*J Infect Dis* 1999;180:1969); a meta-analysis found that this mutation is associated with prolonged exposure to sulfonamides, but the clinical significance of these mutations in terms of reduced response is unclear (*Emerg Infect Dis* 2004;10:1760). In clinical trials, clinical outcome has not been worse with DHPS mutation when these patients were treated with TMP-SMX (*Lancet* 2001;358:545; *Emerg Infect Dis* 2004;10:1721; *Proc Am*

Thorac Soc 2006;3:655). Current rates of resistance of *S. pneumoniae* to TMP-SMX are about 15% to 30% (*Antimicrob Agents Chemother* 2002;46:2651; *N Engl J Med* 2000;343:1917), but their significance is doubted (*Proc Am Thoracic Soc* 2006;3:655).

PHARMACOLOGY

- **Bioavailability:** >90% absorbed with oral administration (both drugs)
- **T½:** Trimethoprim, 8-15 h; sulfamethoxazole 7-12 h
- **Elimination:** Renal; T½ in renal failure increases to 24 hours for trimethoprim and 22 to 50 hours for sulfamethoxazole
- **Renal failure:** CrCl >30 mL/min – usual dose; 10-30 mL/min – one-half to two-thirds dose; <10 mL/min – manufacturer recommends avoidance, but one-third to one-half dose may be used for PCP.

SIDE EFFECTS: Noted in 10% of patients without HIV infection and about 50% of patients with HIV. The gradual initiation of TMP-SMX noted above results in a 50% reduction in adverse reactions (*J Acquir Immune Defic Syndr* 2000;24:337), suggesting that it is not a true hypersensitivity reaction. The prevailing opinion is that these side effects are usually due to toxic metabolites ascribed to altered metabolism of TMP-SMX with HIV infection. The presumed benefit from gradual initiation is to permit time for enzyme induction.

- **Most common:** Nausea, vomiting, pruritus, rash, fever, neutropenia, and increased transaminases. Many HIV-infected patients may be treated despite side effects (GI intolerance and rash) if symptoms are not disabling; alternative with PCP prophylaxis is dose reduction usually after drug holiday (1 to 2 weeks) and/or "desensitization" (see below). The mechanism of most sulfonamide reactions is unclear, and cause of increased susceptibility with HIV is also unclear.
- **Rash:** Most common is erythematous, maculopapular, morbilliform, and/or pruritic rash, usually 7 to 14 days after treatment is started. Less common are erythema multiforme, epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria, and Schönlein-Henoch purpura.
- **GI intolerance** is common with nausea, vomiting, anorexia, and abdominal pain; rare side effects include *C. difficile* diarrhea/colitis and pancreatitis.
- **Hematologic side effects** include neutropenia, anemia, and/or thrombocytopenia. The rate of anemia is increased in patients with HIV infection and with folate depletion. Some respond to leucovorin (5-15 mg/day), but this is not routinely recommended.
- **Neurologic** toxicity may include tremor, ataxia, apathy, aseptic meningitis, and ankle clonus (*Am J Med Sci* 1996;312:27).
- **Hepatitis** with cholestatic jaundice and hepatic necrosis has been

described.

- **Hyperkalemia** in 20% to 50% of patients given trimethoprim in doses >15 mg/kg/day (*N Engl J Med* 1993;328:703)
- **Interstitial nephritis** is more commonly a pseudo-elevation of serum creatinine of ≥17.6% without affecting GFR (*Chemotherapy* 1981;27:229).

PROTOCOL FOR ORAL DESENSITIZATION OR "DETOXIFICATION" (Tables 5-28 and 5-29)

- **Rapid desensitization** (*Clin Infect Dis* 1995;20:849): Serial 10-fold dilutions of oral suspension (40 mg TMP, 200 mg SMX/5 mL) given hourly over 4 hours (see Table 5-28, below).
- **Note:** A prospective trial showed no difference in outcome with desensitization compared with rechallenge (*Biomed Pharmacother* 2000;54:45)

■ TABLE 5-28: **Rapid TMP-SMX Desensitization Schedule**

Time (hour)	Dose (TMP/SMX)	Dilution
0	0.004/0.02 mg	1:10,000 (5 mL)
1	0.04/0.2 mg	1:1,000 (5 mL)
2	0.4/2.0 mg	1:100 (5 mL)
3	4/20 mg	1:10 (5 mL)
4	40/200 mg	(5 mL)
5	160/800 mg	Tablet

■ TABLE 5-29: **8-Day TMP-SMX Desensitization Schedule**

Day	Dilution
1	1:1,000,000
2	1:100,000
3	1:10,000
4	1:1,000
5	1:100
6	1:10
7	1:1
8	Standard suspension – 1 mL 40 mg SMX – 8 mg TMP
≥9	1 DS tab/day

- **8-day protocol:** Serial dilutions prepared by pharmacists using oral suspension (40 mg TMP, 200 mg SMX/5 mL). Medication is given 4 times daily for 7 days in doses of 1 cc, 2 cc, 4 cc, and 8 cc using the following dilutions:

DRUG INTERACTIONS: Increased levels of oral anticoagulants, phenytoin, and procainamide. Risk of megaloblastic anemia with methotrexate.

PREGNANCY: Category C. Teratogenic in animals. No congenital abnormalities noted in 35 children born to women who received TMP-SMX in first trimester. A systematic CDC literature review to July 2005 showed most cases of exposure of pregnant women to TMP-SMX did not cause hyperbilirubinemia and there were no cases of kernicterus. There was "mixed evidence linking first trimester exposures to cleft lips, neural tube defects, cardiovascular defects, and urinary tract defects "(*AIDS Rev* 2006;8:24). The conclusion is that the risk is small and TMP-SMX is considered safe for pregnant women in developing countries as currently recommended by the WHO. In the U.S., recommendation is to use TMP-SMX with caution due to possible kernicterus, although no cases of kernicterus have been reported (*Clin Infect Dis* 1995;21[suppl 1]:S24).

VIDEX – see Didanosine

VIRACEPT – see Nelfinavir

VIRAMUNE – see Nevirapine

ZALCITABINE (ddC)

This drug has been discontinued.

ZERIT – see Stavudine

ZIDOVUDINE (AZT, ZDV)

TRADE NAME: *Retrovir*, *Combivir* (AZT/3TC), *Trizivir* (AZT/3TC/ABC) (GlaxoSmithKline), and generic

CLASS: Nucleoside analog

FORMULATIONS, REGIMENS AND PRICE

- **Forms**
  - AZT – 100 and 300 mg tabs; 10 mg/mL IV solution; 10 mg/mL oral solution.
  - AZT/3TC – 300/150 mg tabs (*Combivir*)
  - AZT/3TC/ABC – 300/150/300 mg tabs (*Trizivir*)
  - Generic, zidovudine 100mg, capsules 100, 115.85; Retrovir, zidovudine 20ml, IV solution 5, R 319.46; Generic, zidovudine

250mg, capsules 60, R 231.34; Generic, zidovudine 300mg, Tablets 60, R 252.81; Generic, zidovudine, Syrup 200ml, R 70.26

- **Regimens:** AZT – 300 mg bid or 200 mg tid; AZT/3TC or AZT/3TC/ABC – 1 tab bid.
- **Food:** No effect
- **Renal failure:** CrCl <15 mL/min – 100 mg tid or 300 mg qd. AZT/3TC (*Combivir*) and AZT/3TC/ABC (*Trizivir*): not recommended with CrCl <50 mL/min
- **Hepatic failure:** AZT, *Combivir:* standard dose. *Trivizir* contra-indicated with severe liver disease.
- **ACTG 076 protocol:** Intrapartum regimen is 2 mg/kg IV over 1 h, then 1 mg/kg/h until delivery.

CLINICAL TRIALS: FDA-approved in 1987 based on a controlled clinical trial showing significant short-term benefit in preventing AIDS-defining opportunistic infections and death (*N Engl J Med* 1987;317:185). Early studies (ACTG 019, 076, 175, Concord, etc.) became sentinel reports. Despite 15 years of use, resistance in recently transmitted strains is only about 2%-10%% (*N Engl J Med* 2002;347:385). AZT is commonly paired with 3TC (*Combivir*), or ABC/3TC (*Trizivir*) as the nucleoside components of HAART regimens. Potency of these regimens is well established. ACTG 384 showed that AZT/3TC/EFV was superior to ddI/d4T/EFV (*N Engl J Med* 2003;349:2293), but Gilead 934 showed TDF/FTC/EFV was superior to AZT/3TC/EFV in terms of viral suppression to <50 c/mL (80% vs 70%), rates of toxicity, CD4 response at 48 weeks (+90/mm^3 vs +58/mm^3), and adverse reactions requiring discontinuation (4% vs 9%; *N Engl J Med* 2006;354:251). Follow-up at 96 weeks demonstrated greater loss of limb fat and more M184V mutations in patients in the AZT/3TC arm (*J Acquir Immune Defic Syndr* 2006;43:535).

RESISTANCE: The thymidine analog mutations (TAMs) are 41L, 67N, 70R, 210W, 215Y/F, and 219Q/E. A total of 3 to 6 mutations result in a 100-fold decrease in sensitivity. About 5% to 10% of recipients of AZT + ddI as dual nucleoside therapy develop the Q151M complex, and a larger number have the T69S insertion mutation, both of which confer high-level resistance to AZT, ddI, ddC, d4T, 3TC and ABC. The M184V mutation that confers high-level 3TC resistance delays resistance or improves susceptibility to AZT unless there are multiple TAMs. It may also prevent the emergence of multinucleoside mutations, which are now very uncommon. Analysis of patients with early HIV infection indicates that 2% to 10% have genotypic mutations associated with reduced susceptibility to AZT (*N Engl J Med* 2002;347:385).

PHARMACOLOGY

- **Bioavailability:** 60%; high-fat meals may decrease absorption. CSF levels: 60% serum levels (CSF:plasma ratio=0.3-1.35) (*Lancet*

1998;351:1547).

- **T½:** 1.1 h; Renal failure: 1.4 h; intracellular: 3 h
- **Elimination:** Metabolized by liver to glucuronide (GAZT) that is renally excreted.
- **Dose modification in renal failure or hepatic failure:** Excreted in urine as active drug (14% to 18%) and GAZT metabolite (60% to 74%). In severe renal failure (CrCl <18 mL/min), AZT half-life is increased from 1.1 to 1.4 hours and GAZT half-life increased from 0.9 to 8.0 hours. Dosing recommendation: GFR >15 mL/min – 300 mg bid; GFR <15 mL/mm – 300 mg/day; hemodialysis and peritoneal dialysis – 300 mg/day. No dose modification with liver disease.

SIDE EFFECTS

- **Subjective:** GI intolerance, altered taste (dysgeusia), insomnia, myalgias, asthenia, malaise, and/or headaches are common and are dose related (*Ann Intern Med* 1993;118:913). Most patients can be managed with symptomatic treatment.
- **Marrow suppression:** Related to marrow reserve, dose and duration of treatment, and stage of disease (*J Viral Hepatol* 2006;13:683). Anemia may occur within 4 to 6 weeks, and neutropenia is usually seen after 12 to 24 weeks. Marrow examination in patients with AZT-induced anemia may be normal or show reduced RBC precursors. Severe anemia should be managed by discontinuing AZT or giving erythropoietin concurrently (see pp. 360 and 214). With neutropenia, an ANC <750/mm^3 should be managed by discontinuing AZT or giving G-CSF concurrently.
- **Myopathy:** Rare dose-related complication possibly due to mitochondrial toxicity. Clinical features are leg and gluteal muscle weakness, elevated LDH and CPK, muscle biopsy showing ragged red fibers, and abnormal mitochondria (*N Engl J Med* 1990;322:1098); response to discontinuation of AZT occurs within 2 to 4 weeks.
- **Macrocytosis:** Noted within 4 weeks of starting AZT in virtually all patients and serves as crude indicator of adherence.
- **Hepatitis** with reversible increases in transaminase levels, sometimes within 2 to 3 weeks of starting treatment.
- **Class adverse reaction:** Lactic acidosis, often with steatosis, is a complication ascribed to all nucleoside analogs but primarily to d4T, ddC, and, to a lesser degree, ddI and AZT. This complication should be considered in patients with fatigue, abdominal pain, nausea, vomiting, and dyspnea. Laboratory tests show elevated serum lactate, CPK, ALT and/or LDH, and reduced serum bicarbonate ± increased anion gap. Abdominal CT scan or liver biopsy may show steatosis. This is a life-threatening complication. Pregnant women and obese women appear to be at increased risk. NRTIs should be stopped or there should be a change to NRTIs that are unlikely to

cause mitochondrial toxicity such as TDF, ABC. Lipoatrophy, also most commonly associated with d4T or d4T + ddI, also occurs with AZT therapy. In ACTG 384, lipoatrophy was observed in both the ddI + d4T and AZT + 3TC arms, but its onset was slower in the AZT + 3TC-treated patients.

- **Fingernail discoloration** with dark bluish discoloration at base of nail noted at 2 to 6 weeks.
- **Carcinogenicity:** Long-term treatment with high doses in mice caused vaginal neoplasms; relevance to humans is not known.

DRUG INTERACTIONS: Use with caution with ribavirin. Additive or synergistic against HIV with ddI, ddC, ABC, alpha interferon, and foscarnet *in vitro*; antagonism with ganciclovir and d4T. AZT and d4T should not be given concurrently due to *in vitro* and *in vivo* evidence of antagonism. Clinical significance of interaction with ganciclovir is unknown. Methadone increases levels of AZT 30% to 40%; AZT has no effect on methadone levels (*J Acquir Immune Defic Syndr* 1998;18:435). Marrow suppression usually precludes concurrent use with ganciclovir. Other marrow-suppressing drugs should be used with caution: TMP-SMX, dapsone, pyrimethamine, flucytosine, interferon, adriamycin, vinblastine, sulfadiazine, vincristine, amphotericin B, and hydroxyurea. Probenecid increases levels of AZT, but concurrent use is complicated by a high incidence of rash reactions to probenecid.

PREGNANCY: Category C. Advocated for pregnant women beyond first trimester to prevent vertical transmission. Recent studies suggest use in first trimester may be associated with an increased risk of hypospadias (7/752 vs 2/895; *P*=0.007) (*J Acquir Immune Defic Syndr* 2006;PMID 17159659). Prior studies showed AZT was positive in the rodent teratogen assay at near-lethal doses. Studies in humans show newborn:maternal ratio of 0.85. Prolonged high doses to pregnant rodents were complicated by the development of squamous epithelial vaginal tumors in 3% to 12% of female offspring (*Fund Appl Toxicol* 1996;32:148) but relevance to humans is questioned because the dose used in rodents was 10 to 12x higher and AZT in humans is largely metabolized, whereas unmetabolized AZT is excreted in urine of mice. A report from France found evidence of mitochondrial toxicity with neurologic consequences in 12 infants exposed to AZT *in utero* (*Lancet* 1999;354:1084). Subsequent reviews of ACTG 076 infants and several other cohorts with data on 20,000 infants exposed to AZT failed to show any neurologic, immunologic, oncologic, or cardiac complications (*N Engl J Med* 2000;343:759; *N Engl J Med* 2000;343:805; *AIDS* 1998;12:1805; *JAMA* 1999;281:151; *J Acquir Immune Defic Syndr* 1999;20:464). An expert NIH panel concluded that the risk of perinatal transmission exceeded the hypothetical concerns of transplacental carcinogenesis. Nevertheless, they advised that pregnant women be warned of this risk. The Pregnancy Registry now has enough reports to

detect a 2-fold increase in birth defects. The prevalence with AZT was was 43/1459 live births (2.9%) compared to 3.1% in the general U.S. population (www.apregistry.com, accessed Aug. 30, 2006).

Extensive study and experience have clearly documented the efficacy and safety of AZT for reducing perinatal transmission (*N Engl J Med* 1994;331:1173) due to reduction in maternal viral load (*N Engl J Med* 1996;335:1621) and to other factors that are less well understood. More recent studies show that rates of perinatal transmission are far lower with HAART than with AZT monotherapy (0-2% vs 8.8%) (*J Acquir Immune Defic Syndr* 2002;29:484). The October 2006 DHHS recommendations are for HAART if the maternal viral load is >1,000 c/mL or the CD4 count is <350/mm^3, and consideration of AZT monotherapy if the CD4 cell count is >350/mm^3 and the viral load is <1000 c/mL. AZT/3TC is the preferred NRTI backbone for HAART in pregnant women (DHHS Guidelines, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the U.S., Oct. 10, 2006, p. 95).

ZITHROMAX – see Azithromycin

ZOVIRAX – see Acyclovir

6 Management of Infections
(Pathogens are listed alphabetically)

Recommendations are based largely on Benson C., et al., Treating Opportunistic Infections Among HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR* 53(RR15):1 (December 17, 2004), available online at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5315a1.htm.

Candida spp.
Thrush (Oral Candidiasis)

PRESENTATION: Most common is pseudomenbraneous candidiasis: white painless plaques on the buccal or pharyngeal mucosa or tongue surface that can easily be scraped off, typically in patients with a risk factor: CD4 <250 cells/mm^3, antibiotics, chronic steroids, etc. If lab confirmation is necessary, use KOH prep. Culture is best used for speciation and sensitivity testing (*Medicine* 2003:82:39) but not for diagnosis due to high rates of colonization.

TREATMENT: INITIAL INFECTION

- **Preferred regimen**
  - Clotrimazole oral troches 10 mg 5x/day *(HIV Clin Trials* 2000;1:47) until lesions resolve, usually 7-14 days.
  - Nystatin 500,000 units (4-6 mL) gargled 4-5x day or 1 to 2 flavored pastilles 4-5x/day x 7-14 days.
  - Fluconazole 100 mg/day PO x 7-14 days.
- **Alternative regimens for refractory infections**
  - Itraconazole 200 mg/day oral suspension swished and swallowed; take on empty stomach.
  - Amphotericin B 1-5 mL qid, swish and swallow.
  - Amphotericin B IV 0.3 mg/kg/day.
  - Other azoles with increased activity versus fluconazole-resistant *Candida*: itraconazole (see above), voriconazole (note interaction with EFV), ravuconazole (experimental) or posaconazole (*Antimicrob Agents Chemother* 2006;50:917).
- **Comments**
  - Tolerability: Nystatin has a bitter taste, many GI side effects, must

be taken 4x to 5x, daily and is significantly less effective than fluconazole for rates of response and relapse. Clotrimazole is easier to take and more effective (*HIV Clin Trials* 2000;1:47).

- Fluconazole is preferred over itraconazole and ketoconazole due to more predictable absorption and fewer drug interactions (*HIV Clin Trials* 2000;1:47; *Am J Med* 1998;104:33; *J Antimicrob Chemother* 2006;57:384).
- *In vitro* azole resistance is most common with prolonged prior azole exposure and late-stage HIV infection with CD4 count <50 cells/mm^3 (*Clin Infect Dis* 2000;30:749).
- Azole drug interactions: Fluconazole increases NVP AUC 100%. Voriconazole AUC decreases 77% with EFV and 40% with RTV in doses of 200 mg/day.

RESPONSE: Most respond within 7-14 days, except with extensive prior azole exposure and CD4 count <50/mm^3 (*Clin Infect Dis* 2000;30:749; *Clin Infect Dis* 1997;24:28).

MAINTENANCE

- **Indications:** Multiple recurrences, especially if severe and refractory to treatment. Optimal prevention is immune reconstitution and avoidance of steroids and antibacterials. Dapsone may be preferred in place of TMP-SMX. Maintenance or secondary prophylaxis is not usually recommended
- **Preferred regimens**
  - Fluconazole 100 mg/day PO or 200 mg 3x week.
  - Topical clotrimazole or nystatin prn.
  - Itraconazole solution 100-200 mg/day on empty stomach.
- **Comments**
  - Immune reconstitution is highly effective (*AIDS* 2000;14:979).
  - Potential problems with use of continuous or intermittent fluconazole include azole resistance, drug interactions, and cost. Risks for azole resistant *Candida* infections are prolonged azole exposure (although this was not shown in ACTG 323), use of TMP/SMX prophylaxis for PCP, and low CD4 cell count (*J Infect Dis* 1996;173:219). Most authorities try to avoid continued use of fluconazole except where necessary, such as in cases of cryptococcal meningitis (*Clin Infect Dis* 2000;30:749), recurrent *Candida* esophagitis, or severe and refractory oropharyngeal candidiasis (*J Infect Dis* 1998;27:1291), but supporting data are inconsistent, and the largest controlled trial is not supportive.
  - The differential diagnosis includes
    - Herpes simplex ulcers
    - CMV ulcers

- TB
- Aphthous ulcers.

Esophagitis

PRESENTATION: Symptoms include diffuse retrosternal pain, dysphagia, and odynophagia, usually without fever. Thrush is usually present, and the CD4 count is <100/mm^3. Cases with typical features are usually treated empirically; rapid response to standard treatment strongly supports this diagnosis.

TREATMENT: INITIAL INFECTION

- **Preferred regimen:** Fluconazole 100-400 mg/day PO or IV x 14-21 days.
  - Itraconazole solution 200 mg PO x 14-21 days.
- **Alternative regimens**
  - Amphotericin B IV 0.3-0.7 mg/kg/day.
  - Amphotericin lipid formulations: 3 to 5 mg/kg/day.
- **Comments**
  - Fluconazole is preferred over ketoconazole and itraconazole due to more predictable absorption.
  - Relapse rate within 1 year is high in absence of either immune reconstitution or maintenance therapy.
  - Resistance: See oropharyngeal candidiasis, below.

RESPONSE: Most (85-90%) patients respond within 7-14 days (*Clin Infect Dis* 2004;39:842). For refractory cases: 1) Perform endoscopy to establish diagnosis ± fungal culture for *in vitro* sensitivity tests, or 2) Change therapy: increase fluconazole dose.

MAINTENANCE: Only with relapsing disease

- **Preferred regimen:** Fluconazole 100-200 mg/day PO.
- **Comment:** Consider maintenance therapy in patients with recurrent esophagitis.

Vaginitis (*MMWR* 2006;55:21)

DIAGNOSIS: Typical symptoms are mucosal burning and pruritis combined with a creamy yellow-white discharge. Examination shows erythema and yellow-white adherent discharge; 10% KOH prep or gram stain show yeast or pseudohyphae. Most cases are in immunocompetent women. Culture is rarely necessary except to detect a non-*albicans* species (rare) or fluconazole resistance (also rare).

TREATMENT

- **Preferred regimens:** Intravaginal azoles, usually 3-7 days
  - Clotrimazole 1% cream 5 g/day x 7 to 14 days* 100 mg vaginal tab/day x 7 to 14 days, 100 mg vaginal tab bid x 3 days, 500 mg vaginal tab x 1.
  - Miconazole 2% cream 5 g/day x 7 days* 100 mg vaginal supp/day x 7 days*, 200 mg supp/day x 3 days.*
  - Ticonazole 6.5% ointment 5 g x 1*, 0.4% cream 5 g/day x 7 days, 0.8% cream 5 g/day x 3 days 80 mg supp/day x 3 days.
  - Nystatin 100,000 units/day x 14 days

* Available over-the-counter

- **Preferred systemic azoles**
  - Fluconazole 150 mg PO x 1.
  - Itraconazole 200 mg PO bid or 200 mg qd x 3 days
  - Gentian violet is a cheap alternative but is often not acceptable to most women.

- **Comments**
  - Treatment is identical for women with and without HIV infection.
  - Clotrimazole, tioconazole, and miconazole are available over the counter. Self-administration advised only if prior diagnosis and typical symptoms.
  - Azole-resistant strains of *Candida* are rare causes of vaginitis.
  - Severe disease: Topical azole x 7-14 days or oral fluconazole 150 mg PO x 2 separated by 72 hours.
  - Pregnancy: Topical azole only.
  - Probiotic treatment with lactobacilli for prevention shows unconvincing evidence of efficacy (*J Antimicrob Chemother* 2006;58:266).

RESPONSE: Uncomplicated vaginitis (90% of all cases) responds rapidly. Complicated cases are prolonged or refractory, account for 10% of cases and are treated for >7 days.

MAINTENANCE (with 4 episodes/year): Clotrimazole 500 mg supply vaginal tablet every week, or fluconazole 100-150 mg PO every week or ketoconazole 200 mg PO every week or itraconazole 400 mg every month or 100 mg every week, all x 6 months. (Based on recommendations for women without HIV infection.)

Clostridium difficile

FREQUENCY: Analysis of 44,778 HIV-infected persons followed for a mean of 2.6 years showed *C. difficile* was by far the leading bacterial agent of diarrhea (*Clin Infect Dis* 2005;41:1621). Another report indicated *C. difficile* accounted for 36% of HIV-infected patients with acute diarrhea (*Diag Microbiol Infect Dis* 2002;44:325).

CLINICAL FEATURES: Watery diarrhea, fecal WBCs variable; fever, hypoalbuminemia, and leukocytosis are common. Nearly all patients have recent (within 2 weeks of onset) exposure to antibacterial agents, especially fluoroquinolones, extended spectrum cephalosporins, and clindamycin; less commonly – macrolides, TMP-SMX, narrow-spectrum betalactams, and rifampin. Antiretrovirals, antivirals, antifungals, dapsone and INH are not implicated. May occur with any CD4 count; low CD4 count may be associated with increased risk or with more severe disease.(*N Engl J Med* 2005;353: 2442,2433,2503).

DIAGNOSIS: Stool toxin assay: tissue culture (gold standard)or EIA (most commonly used, only 70-75% sensitive) preferred

TREATMENT (*N Engl J Med* 2002;346:334; *Ann Intern Med* 2006;145:758)

- Metronidazole 500 mg PO tid x 10 to 14 days (preferred)
- Vancomycin 125 mg PO qid x 10 to 14 days
- Antiperistaltic agents such as loperamide (*Imodium*) or atropine/ diphenoxylate (*Lomotil*) are contraindicated.

RESPONSE: Fever usually resolves within 24 hours and diarrhea resolves in an average of 5 days. About 20% to 25% have relapses at 3 to 14 days after treatment stops. Virtually all respond to treatment unless ileus is present; relapse post-therapy in 15% to 20% (*N Engl J Med* 2002;346:334).

Cryptococcus neoformans

Cryptococcal Meningitis

PRESENTATION The usual portal of entry is the lung, and many have pneumoniitis. The usual presentation is subacute meningitis with fever, headache, and malaise in a patient with a CD4 count <100/mm^3. Some patients are asymptomatic and many have non-meningeal sites of involvement, especially the skin, with vesicular or papular lesions that may resemble molluscum. CSF analysis should be performed whenever there is evidence of cryptococcal infection. The diagnosis of cryptococcal meningitis is usually easy, with positive blood cultures in 50% to 70%, positive serum cryptococcal antigen in >95%, positive CSF culture in >95%, positive CSF cryptococcal antigen in >95%, and

positive India ink in 60% to 80%. CSF usually shows elevated opening pressure (>200 mm H_2O in 75%) increased protein (50-150 mg/dL) and mononuclear pleocytosis (5-100 mg/dL) (*N Engl J Med* 1992;329:83; *N Engl J Med* 1997;337:15).

TREATMENT (*Clin Infect Dis* 2006;42:1289)

- **Preferred regimen:** Amphotericin B 0.7 mg/kg/day IV ("induction phase"), then fluconazole 400 mg/day x 8 weeks or until CSF is sterile ("consolidation phase"), then maintenance therapy, fluconazole 200 mg/day ("suppressive phase"). Discontinue treatment when CD4 count is 200 cells/mm^3, initial therapy is completed, and the patient is asymptomatic (*Clin Infect Dis* 2003;36:1329).
- **Elevated intracranial pressure:** With focal neurologic signs or obtundation, obtain CNS imaging before LP to define lesions that contraindicate LP.
  - Occasional patients have very high pressure (>400 mm H_2O) and may require a lumbar drain or a ventricular-peritoneal shunt.
  - Elevated pressure persists: Lumbar drain or V-P shunt.
- **Alternative regimens** (induction and consolidation stages)
  - Fluconazole 400-800 mg/day PO + 5-FC 100 mg/kg/day PO x 6 to 10 wks.
  - Consolidation: Itraconazole 200 mg PO bid
- **Comments**
  - Repeat LP is indicated only to control elevated intracranial pressure or if there is failure to respond with new symptoms after 2 weeks of therapy.
  - Management of increased intracranial pressure is critical (*Clin Infect Dis* 2000;30:47). Increased intracranial pressure accounts for >90% of deaths in first 2 weeks and 40% of deaths in weeks 3-10 (*Clin Infect Dis* 2000;30:47). **Failure to manage elevated intracranial pressure is the most common and most dangerous mistake in management** (*Clin Infect Dis* 2005; 40:477).
  - Patients with renal failure receiving fluconazole should have fluconazole blood levels monitored; 2 h post-dose level should be <100 mg/mL.
  - Serum cryptococcal antigen is not useful in following response to treatment; CSF antigen with comparative titers may be (*HIV Clin Trials* 2000;1:1).
  - A trial of chronic suppressive therapy with fluconazole versus weekly amphotericin showed relapse rates at 1 year were 2% and 19%, respectively (*N Engl J Med* 1993;326:793). Another study found relapse rates of 4% with fluconazole versus 23% with itraconazole (*Clin Infect Dis* 1999;28:291).

- Resistance: Amphotericin B resistance is rare or hard to demonstrate (*Antimicrob Agents Chemother* 1993;37:1383; *Clin Microbiol Rev* 2001;14:643; *Antimicrob Agents Chemother* 1999;43:1463). Resistance develops rapidly with flucytosine monotherapy (*Lancet* 2002;359:1135). Fluconazole resistance is rare (*Antimicrob Agents Chemother* 1999;43:1856; *Antimicrob Agents Chemother* 2001;45:420).

RESPONSE: Mortality rate with the recommended 3-phase regimen is 5%, and CSF cultures at 2 weeks are sterile in 60% (*N Engl J Med* 1997;337:15). The major early concern is elevated intracranial pressure, which can lead to cranial nerve deficits or herniation. Management of elevated intracranial pressure with lumbar drainage is critical *(Clin Infect Dis* 2000;30:47). Most deaths are associated with increased intracranial pressure (*Clin Infect Dis* 2000;30:47). CSF culture at 2 weeks is negative in 70% (*Clin Infect Dis* 2000;30:710). A repeat LP at 2 weeks is indicated if there are new symptoms or signs. The relapse rate with fluconazole therapy (phase 3) is 2% (*N Engl J Med* 1992;326:796). Serum cryptococcal antigen is usually not useful in following response to treatment; CSF antigen may be (*HIV Clin Trials* 2000;1:1).

Long-term follow-up of 82 HIV-infected patients with cryptococcal meningitis in the HAART era who survived >3 months had a relapse rate of 0.9/100 patient-years. The serum cryptococcal antigen assay became negative by 48 months in 71% (*AIDS* 2006;20:2183).

TREATMENT FAILURE: Treatment failure is defined as failure to achieve clinical response in 2 weeks. Recommendations are to (1) continue the same treatment, (2) use higher doses of fluconazole in combination with flucytosine.

IMMUNE RECONSTITUTION: In a review of 21 cases, 3 were the initial manifestation of cryptococcal infection and 18 complicated treatment of cryptococcal meningitis with concurrent initiation of HAART (*Clin Infect Dis* 2005;40:1049). The frequency of the latter was 18/59 (30%). The main differential diagnosis issue was the distinction between cryptococcal meningitis due to immune reconstitution inflammatory syndrome (IRIS) or relapse. Factors favoring IRIS were: 1) stopping fluconazole therapy when starting HAART before immune-reconstitution has occurred; 2) they had a good response to HAART (median CD4 increase of 94 cells/mm^3 vs 4 cells/mm^3, plus median VL change of –2.3 $\log_{10}$ c/mL vs –0.15 $\log_{10}$ c/mL); 3) greater inflammatory response (mean CSF WBC 56/mL vs 12 mL) and a lower mortality (9% vs 38%). Other characteristic features of IRIS cryptococcal meningitis are onset at 2-8 months after initial treatment and negative CSF cultures (*AIDS* 2005;19:1043). Non-meningeal IRIS manifestations of cryptococcosis are lymphadenitis, necrotizing pneumonia, cerebritis,

mediastinitis, spinal cord lesions, cerebral cryptococcomas, and cutaneous abscesses (*AIDS Read* 2006;16:199; *Scand J Infect Dis* 1998;30:615; *AIDS* 2004;18:349). **Management recommendations** are to continue HAART and fluconazole; a brief course of corticosteroids may be necessary and may result in prompt response (*Neurology* 2006;67:383) Anti-inflammatory agents have shown impressive results in patients with IRIS presenting as cryptococcal lymphadenitis (*J Infect Dis* 1998;30:615).

MAINTENANCE

- **Preferred regimen:** Fluconazole 200 mg/day PO.
- **Alternative regimens**
  - Amphotericin B 1.0 mg/kg/week or twice weekly for patients with multiple relapses on azoles.
  - Fluconazole: May increase maintenance dose to 400 mg/day.
  - Itraconazole 200 mg caps PO qd (for patients who failed fluconazole or could not tolerate it).
- **Comments**
  - Fluconazole maintenance (150 mg/day) is superior to amphotericin B maintenance (*N Engl J Med* 1992;326:793) and superior to itraconazole at a dosage of 200 mg/day PO (*Clin Infect Dis* 1999; 28:291).
  - Immune reconstitution: Discontinue treatment (secondary prophylaxis) when CD4 cell count is 200/mm^3 .

Pulmonary, Disseminated, or Antigenemia

DIAGNOSIS: Positive cultures of blood, urine, and/or respiratory secretions virtually always indicate cryptococcal disease and mandate lumbar puncture to exclude meningitis. Serum antigenemia suggests cryptococcosis, especially with titer >1:8; this test should be confirmed with positive culture.

TREATMENT

- **Preferred regimen:** Fluconazole 200-400 mg/day PO indefinitely unless immune reconstitution is achieved.
- **Alternative regimen:** Itraconazole 200 mg PO bid as caps with meal or 200 mg/day bid oral suspension on empty stomach indefinitely unless immune reconstitution is achieved.
- **Comments**
  - Goal of treatment is to prevent meningitis.
  - Refractory lung and bone lesions may require surgery.
  - Non-meningeal sites include lungs, skin, joints, eye, adrenal gland, GI tract, liver, pancreas, prostate, and urinary tract.

- Antigenemia: Obtain chest x-ray, LP, urine and blood culture. If no focus identified and antigenemia at >1:8 confirmed, treat with fluconazole (*Clin Infect Dis* 1996;23:827).

MAINTENANCE (Need for maintenance therapy with non-meningeal cryptococcosis is not established.)

- **Preferred regimen:** Fluconazole 200 mg/day PO.
- **Alternative regimens:** Itraconazole 200 mg/day as caps with meal + acidic drink or 100-200 mg/day oral suspension on empty stomach or amphotericin B 0.6-1 mg/kg IV weekly or twice a week.

Cryptosporidium parvum

Cryptosporidiosis (See *Clin Microbiol Rev* 1999;12:554; *Clin Infect Dis* 2001;32:331; *N Engl J Med* 2002;346:1723)

PRESENTATION: Typical symptoms are acute, subacute, or chronic profuse watery diarrhea often associated with cramps, nausea, and vomiting; about one-third have fever (*Ann Intern Med* 1996;124:429; *Clin Infect Dis* 2003;36:903). Stool assays with acid fast stain, IFA, or EIA are sensitive, specific, and nearly equal in diagnostic utility to watery stools (*N Engl J Med* 2002;346:1723). IFA is preferred for formed stool. A single specimen is adequate with severe diarrhea. Repeat sampling is recommended for less severe disease. Patterns of disease with AIDS: 1) asymptomatic carriage (4%); 2) self-limited diarrhea <2 months (29%); 3) chronic diarrhea >2 months (60%); 4) fulminant diarrhea with >2 k/day (8%) *(N Engl J Med* 2002;346:1723). The chronic and fulminant form are seen almost exclusively with CD4 counts <100 cells/mm^3. A serologic survey of stored sera in 78 HIV-infected men in San Francisco suggests rates of seroconversion and infection are much higher than usually reported, about 250/1000 patient years (*J Infect Dis* 2006;194:1428).

TREATMENT

- **Preferred regimens**
  - HAART with immune reconstitution is the only treatment that controls persistent cryptosporidiosis. Resolution usually occurs with CD4 >100/mm^3 and may improve with only minor increases.
  - Symptomatic treatment: Fluids (sports rehydration beverages such as *Gatorade*, bouillon, oral rehydration; see comments below), nutritional supplements and anti-diarrheal agents: *Lomotil*, loperamide, paregoric, bismuth subsalicylate (*Pepto-Bismol*), and deodorized tincture of opium.
- **Comments**
  - Antimicrobials: More than 95 drugs have been tried, and none have been consistently successful. (*N Engl J Med* 2002;346:1723; *Lancet* 2002;360:1375). This includes paromomycin, azithromycin,

and nitazoxanide. One randomized trial of paromomycin (a nonabsorbable aminoglycoside) showed a modest but statistically significant improvement in symptoms and oocyte shedding (*Clin Infect Dis* 2000;31:1084); another randomized trial showed no benefit (*J Infect Dis* 1995;170:419).

- Oral rehydration (severe diarrhea): NaCl 3.5 g (¾ tsp), $NaHCO_3$ 2.5 g (1 tsp baking soda), KCl 1.5 g (1 cup orange juice or bananas) in 1 liter water. Packets of pre-mixed salts available.

RESPONSE: Cryptosporidiosis in patients with CD4 count >100 cells/mm^3 usually resolves spontaneously after 2 to 8 weeks, as it does with immunocompetent hosts. For AIDS patients with fulminant or chronic, persistent cryptosporidiosis, the goal is immune reconstitution: even modest elevations in CD4 count may result in resolution of symptoms and pathogen elimination (*J Acquir Immune Defic Syndr* 1998;12:35; *J Acquir Immune Defic Syndr* 2000;25:124).

Cytomegalovirus (CMV)

CMV Retinitis

PRESENTATION: May be asymptomatic or present with floaters, field defects, scotomata, or decreased acuity. CD4 count is usually <50/mm^3. Funduscopic exam shows perivascular yellow-white retinal infiltrates ± intraretinal hemorrhage. Blood cultures, CMV load determinations, and antigen assays are often not helpful due to lack of specificity for CMV disease *(J Clin Microbiol* 2000;323:563). The diagnosis is usually made by funduscopic exam by an experienced ophthalmologist.

TREATMENT

- **Preferred regimens**
  - Vision-threatening lesion: Intraocular ganciclovir implant (*Vitrasert*) every 6-8 months + valganciclovir 900 mg PO bid with food x 14-21 days, then 900 mg/day. *Vitrasert* may be implanted with outpatient surgery, but vitreal hemorrhage is more common with local anesthesia (*Retina* 2004;24:41).
  - Peripheral lesions: Oral valganciclovir (above doses). Some would not treat small peripheral lesions if immune recovery is anticipated but risk of immune reconstitution uveitis.
- **Alternative regimens for peripheral lesions**
  - Ganciclovir 5 mg/kg IV q12 h x 14 to 21 days, then valganciclovir 900 mg PO qd
- **Comments**
  - Some would not treat small peripheral lesions if immune recovery is anticipated, but risk of immune reconstitution uveitis may be

greater in absence of anti-CMV therapy (*Arch Ophthalmol* 2003;121:466; *J Infect Dis* 1999;179:179; *Am J Ophthalmol* 2000;130:49).

PROGRESSION OR RELAPSE

- **Preferred regimens**
  - Intraocular ganciclovir implant if not used previously (even with relapse on ganciclovir, since intraocular levels are high with implant), plus systemic treatment with ganciclovir, foscarnet, cidofovir or valganciclovir, with drug selection based on anticipated or measured CMV resistance.
  - Induction dose of the same agent (ganciclovir 10 mg/kg/day, foscarnet 180-240 mg/kg/day, or valganciclovir 900 mg bid). Switching to alternative drug for first relapse is generally not advocated unless resistance is suspected (see below) or toxicity is the reason.
  - Late relapse: switch to alternative agent (see below).
- **Comments**
  - Relapse is expected in the absence of immune recovery.
  - Early relapse (<3 months) is usually not due to drug-resistant CMV; late relapse (>6 months) usually is.
  - Time to relapse varies with definition, use of retinal photographs, and treatments summarized above. Subsequent relapses occur more rapidly.

RESPONSE: The goal of treatment is to stop visual loss. Treatment usually stops progressive blindness, but does not reverse prior changes.

MAINTENANCE

- **Immune reconstitution:** Discontinue maintenance therapy when the CD4 cell count is >100-150/mm^3 for 6 months, there is no evidence of active disease, and there will be regular ophthalmologic exams. Restart prophylaxis when CD4 count is <50-100 cells/mm^3. Relapses occur when the CD4 count decreases to <50 cells/mm^3 (*AIDS* 2000;14:173). Safety of these recommendations has been demonstrated (*AIDS* 2001;15:23), but rare patients have relapses with CD4 counts >100 cells/mm^3 x 3 months due to lack of CMV-specific immunity (*J Infect Dis* 2001;183:1285; *HIV Clin Trials* 2005;6:136).

IMMUNE RECOVERY VITRITIS

- Clinical features: Inflammation in the anterior chamber and/or vitreous, usually at 4 to 12 weeks after initiating HAART (*Arch*

Ophthalmol 2003;121:466; *Am J Ophthalmol* 2000;129:634). Incidence is highly variable, from 0.11/person-years to 0.86/person-years (*Am J Ophthalmol* 2000;129:634; *J Infect Dis* 1999;179:697). Lower rate may be due to better CMV suppression before HAART started. CMV PCR on aqueous humor and vitreous is usually negative (*Ophthalmalgia* 2004;218:43), and CMV viremia is not found (*HIV Clin Trials* 2005;6:136). Treatment usually includes continued HAART, anti-CMV agent and local steroids such as intravitreal injection of 0.1 mL triamcinolone 0.4% soln (*Ophthalmol Surg Lasers Imaging* 2003;34:398).

- **Preferred regimen:** Systemic or periocular corticosteroids. About 50% respond. The fellow eye must be carefully examined to exclude CMV disease before stating HAART. This is to prevent CMV retinitis flare up with immune reconstitution.

CMV Extraocular Disease – Gastrointestinal (Usually esophagitis or colitis)

DIAGNOSIS: CMV esophagitis is characterized by fever, odynophagia ± retrosternal pain that is often well localized in patients with a CD4 count <50/mm^3. The diagnosis is established by endoscopic visualization of shallow ulcers in the distal esophagus and biopsies showing characteristic intranuclear and intracytoplasmic inclusions. CMV colitis is characterized by fever, abdominal pain, weight loss, and diarrhea in patients with a CD4 count <50/mm^3. Major complications include hemorrhage or perforation. The diagnosis is established by endoscopic evidence of mucosal ulcers and biopsies showing typical intranuclear and intracytoplasmic inclusions.

TREATMENT

- **Preferred regimens**
  - Ganciclovir 5 mg/kg IV bid x 3 to 4 weeks.
  - Indication for maintenance therapy: relapse on or after therapy.
- **Comments**
  - All patients with symptomatic CMV esophagitis should be treated; indications to treat CMV colitis are less clear due to poor response.
  - Duration of treatment is usually 21-28 days or until signs and symptoms have cleared.
  - Patients should undergo ophthalmoscopic screening.

RESPONSE: CMV esophagitis usually responds within 1 to 2 weeks with decrease in fever and odynophagia. Patients with colitis respond poorly – abdominal pain and diarrhea may not improve or may improve only modestly; viral shedding is markedly reduced.

CMV Neurological Disease

DIAGNOSIS: CMV neurologic disease includes dementia, ventriculoencephalitis and ascending polyradiculomyelopathy. *Dementia* presents with: 1) lethargy, confusion, and fever and 2) CSF with mononuclear cells and elevated protein. Patients with *polyradiculomyelopathy* present with: 1) progressive leg paresis, then bladder and bowel dysfunction; 2) CSF showing polymorphonuclear cells and increased protein. *Encephalitis* presents with (1) rapidly progressing delirium, cranial nerve defects, ataxia, and nystagmus; (2) CSF with increased protein and a mononuclear pleocytosis; (3) MRI showing periventricular enhancement. The diagnosis of CMV CNS disease is established by a compatible clinical syndrome plus detection of CMV, usually by PCR, in CSF or brain. The sensitivity of CSF PCR is 80% with specificity of 90% (*Clin Infect Dis* 2002;34:103). Brain biopsy with histopathology or culture is diagnostic. With radiculomyelopathy CSF shows PMNs.

TREATMENT

- **Preferred regimen**
  - Immune reconstitution is most important.
- **Alternative regimen:** Ganciclovir 5 mg/kg IV bid x 3 to 6 weeks, then maintenance with ganciclovir IV or valganciclovir PO.
- **Comments**
  - Treatment does not significantly prolong survival, and irreversible damage is often present when treatment is started (*Neurology* 1996;46:444; *Clin Infect Dis* 2002;34:103).

RESPONSE

- CMV encephalitis: A trial of ganciclovir + foscarnet for CMV encephalitis showed a median survival of 94 days vs 42 days in historic controls (*AIDS* 2000;14:517).
- CMV polyradiculopathy: Improvement occurs within 2 to 3 weeks (*Neurology* 1993;43:493).
- Induction therapy may need to be continued for several months in severe cases with CMV neurologic disease (*Clin J Infect Dis* 1993; 17:32). Maintenance therapy is lifelong. It is unclear if valganciclovir is adequate for induction.
- **IRIS:** A case of CMV ventriculitis due to immune reconstitution inflammatory syndrome (IRIS) with onset after 3 weeks of HAART has been reported; the patient responded to foscarnet therapy (*J Neurol Neurosurg Psychiatry* 2005;76:888).

CMV Pneumonitis

DIAGNOSIS: Symptoms include fever, cough, dyspnea, and interstitial infiltrates. Minimum diagnostic criteria include all of the following (*Clin Infect Dis* 1996;23:76): 1) pulmonary infiltrates; 2) characteristic intracellular inclusions in lung tissue; and 3) absence of another pulmonary pathogen.

INDICATIONS TO TREAT: CMV pneumonitis in patients with histologic evidence of CMV disease plus failure to respond to treatment of other pathogens. Isolation of CMV from respiratory secretions is not diagnostic; true CMV pneumonitis is uncommon.

TREATMENT: Ganciclovir 5 mg/kg IV bid > 21 days.

- **Comments**
  - Response to ganciclovir is >60% (*Clin Infect Dis* 1996;23:76).
  - Indications are unclear for long-term maintenance therapy.

Entamoeba histolytica (*Clin Infect Dis* 2001;32:331)

DIAGNOSIS: Stool always shows blood with invasive disease; fecal leukocytes are usually not present. O&P examination x 3 has 85% to 95% sensitivity.

TREATMENT

- **Preferred regimens:**
  - Metronidazole 500-750 mg PO or IV tid x 7-10 days
  - Tinidazole 2 gm PO qd x 3 days
- **Comments:** Pathogen distinction: *E. histolytica* is responsible for amebiasis – dysentery and liver abscesses. *E. dispar* accounts for over 90% of stool isolations.

RESPONSE: Cure rate with metronidazole x 10 days is 90%; second agent is given to assure elimination of intraluminal encysted organism.

Haemophilus influenzae

TREATMENT

- **Preferred regimen:** Cephotaxime
- **Alternative regimens**
  - TMP-SMX
  - Cephalosporins, 2nd and 3rd generation
  - Fluoroquinolones
- **Comments**
  - Standard therapy is usually adequate (*Clin Infect Dis* 2000;30:461).

- *H. influenzae* vaccine is not recommended for adults because most infections involve non-encapsulated strains that are not covered by the vaccine.

Hepatitis viruses – see pp. 421-429

Herpes simplex (*MMWR* 2006;55[RR-11]:16)

PRESENTATION: Orolabial and genital HSV are similar in presentation, diagnosis, and management, except for anatomical site of infection. The usual presentation starts with a sensory prodrome at the involved site, followed by rapid evolution of lip/genital papule ∅ vesicle ∅ ulcer ∅ crust. Lesions with advanced AIDS are more severe, more likely to disseminate, more likely to be refractory to therapy and more likely to have acyclovir-resistant HSV. The diagnosis is made on the basis of appearance. With atypical presentation or lesions that do not respond to therapy, the diagnosis can be confirmed by swabs of lesions submitted for viral culture, HSV antigen detection and/or Tzanck prep. The Tzanck prep show has a sensitivity of 60-80%.

TREATMENT (*MMWR* 2006;55[R11]:16)

- **Preferred regimen**

2006 CDC Recommendations for Treatment of HSV in HIV-infected Persons

	Acute	Episodic	Suppression
Acyclovir	400 mg tid x 7-10 d	400 mg tid x 5-10 d	400-800 mg bid
Fanciclovir	250 mg tid x 7-10 d	500 mg bid x 5-10 d	500 mg bid
Valacyclovir	1 gm bid x 7-10 d	1 gm bid x 5-10 d	500 mg bid

- Severe disease: Acyclovir 5 mg/kg IV q8h until lesions regress, then use oral regimen above and continue until lesions heal.
- Genital, pregnancy: Herpetic lesions at onset of labor is indication for cesarean section to prevent neonatal herpes. Safety of acyclovir, famciclovir, and valacyclovir is not clearly established; the most experience is with acyclovir, which appears safe and is advocated for pregnancy with first episode, or severe recurrent HSV. Acyclovir is often advocated in late pregnancy for women with recurrent HSV since it reduces the need for cesarean section. Severe HSV infections during pregnancy should be treated with IV acyclovir. Histology can also be considered in non-responding ulcers.
- Severe disease with pneumonitis, esophagitis, disseminated infection, or hepatitis: Acyclovir 5-10 mg/kg IV q8h for 2 to 7 days or until improvement.
- Encephalitis: Acyclovir 10 mg/kg IV q8h x 14 to 21 days.
- Acyclovir orally must be continued for another ten day at 400mg tds.

RESPONSE: Early treatment shortens duration of mucocutaneous lesions, reduces systemic symptoms, and reduces viral shedding (*Arch Int Med* 1996;156:1729); it does not change probability of recurrence (*Med Letter* 1995;37:117). With refractory disease plus HIV infection, suspect acyclovir resistance (*N Engl J Med* 1991;325:551). Acyclovir-resistant strains are resistant to famciclovir, valacyclovir, and (usually) ganciclovir. Treatment options are topical cidofovir (*J Infect Dis* 1997;17:862, *N Engl J Med* 1993;327:968) (*J Acquir Immune Defic Syndr* 1996;12:147). IRIS herpes simplex has been described with erosive genital lesions (*HIV Med* 1999;1:10; *Clin Infect Dis* 2006;42:418).

SUPPRESSION

- **Indication:** 6 recurrences/year; alternative is to treat each episode. (See below for HSV suppression to prevent HIV transmission.)
- **Suppressive regimens:** Acyclovir 800 mg bid, famciclovir 500 mg bid, or valacyclovir 1 g qd.
- **HIV PREVENTION:** HSV-2 infection is associated with a 2- to 4-fold increase in HIV transmission, according to 30 epidemiologic studies (*J Acquir Immune Defic Syndr* 2004;35:435). HIV shedding is increased during HSV reactivation, including subclinical reactivations. HSV suppression with antiviral agents reduces the frequency and severity of HSV recurrences; it also reduces HSV shedding. Studies from the Rakai district of Uganda show HSV infection is associated with higher levels of HIV, presumably due to chronic immune stimulation, and a 1.7- to 5-fold increase in rates of HIV transmission (*N Engl J Med* 2000;342:921; *J Infect Dis* 2003;188:1492; *J Infect Dis* 2005;191:1403). Similar conclusions are supported by studies in the United States (*Clin Infect Dis* 2006;43:347). These data prove a role for HSV suppression in reducing rates of HSV transmission, and suggest a role in reducing rates of HIV transmission, acquisition, and progression.
- **Comments**
  - Acyclovir, famciclovir, and valacyclovir are clinically equivalent (*Sex Transm Dis* 1997;24:481; *J Infect Dis* 1998;178:603; *JAMA* 2001; 144:818; *Br J Dermatol* 2001;144:188).
  - Allergy to acyclovir is rare but will contraindicate use of famciclovir and valacyclovir. Desensitization has been described (*Ann Allergy* 1993;70:386).
  - Acyclovir registry for exposure in pregnancy does not indicate risk (*Birth Defects Res A Clin Mol Teratol* 2004;70:201).
  - Prophylactic acyclovir beginning at 36 weeks gestation reduces the risks of genital HSV recurrence at delivery. Cesarean section is indicated for active genital lesion at time of delivery (*Obstet Gynecol* 2003;102:1396; *Am J Obstet Gynecol* 2003;188:836).
  - Control of HSV genital ulcers appears to be an important factor in

reducing HIV transmission and HIV acquisition (*J Acquir Immune Defic Syndr* 2004;35:435; *J Infect Dis* 2003;187:19; *J Infect Dis* 2003;187:1513).

- Suppressive therapy may decrease the rate of HIV progression (*J Infect Dis* 2002;186:1718).

Herpes Zoster

PRESENTATION: About 95% of healthy adults are seropositive for VZV and about 5% of healthy adults develop zoster. Risk factors are advanced age and immunosuppression. The risk with HIV infection is 15x to 25x greater compared to the general population. Patients at all CD4 strata are at increased risk, and HAART has had minimal effect on incidence. Nevertheless, incidence increases with each incremental decrease in CD4 count (*J Acquir Immune Defic Syndr* 2005;38:111; *J Acquir Immune Defic Syndr* 2004;37:1604). The usual presentation is a painful prodrome in the region of a dermatome that then evolves within days to a characteristic dermatomal vesicular (OR = 2.4) and CD4 50-200 cells/mm^3 (OR = 2.7 vs CD4 <50 cells/mm^3), and 18% had post-herpetic neuralgia (*J Acquir Immune Defic Syndr* 2005;40: 169).The diagnosis is usually made on the basis of clinical presentation, Tzanck prep is about 60% sensitive. PCR is experimental and probably most useful with CSF. Most cases include pain syndromes, often severe and sometimes requiring narcotics for pain relief. There are no residual defects except post-herpetic neuralgia and scarring.

- **Major complications:**
  - Progressive outer retinal necrosis is associated with rapid vision loss (*Ophthalmology* 1994;101:1488; *AIDS* 2002;16:1045). Most patients have CD4 counts <50/mm^3, the disease is characterized by dermatomal zoster and multifocal retinal opacification. Immediate evaluation by an ophthalmologist and high-dose IV acyclovir plus foscarnet are required.
  - Acute retinal necrosis with peripheral necrotizing retinitis and vitritis and a high rate of vision loss is sometimes due to retinal detachment. This may be seen with any CD4 count.
  - Neurologic VZV syndromes seen rarely in AIDS patients include transverse myelitis, encephalitis, and vasculitic stroke. Caution is necessary in the interpretation of CSF findings, since a mononuclear pleocytosis, with increased protein and positive VZV PCR, may also characterize uncomplicated shingles.
  - Post-herpetic neuralgia

TREATMENT

- **Preferred regimens**

  Dermatomal zoster (localized)

- Acyclovir 800mg 5 times per day.
- Famciclovir 500 mg PO tid or valacyclovir 1 g PO tid x 7 to 10 days.
- Severe cutaneous or visceral disease: Acyclovir 10 mg/kg IV q 8 h followed by valacyclovir, 1 gm PO tid until all lesions are cleared.
- Acute retinal necrosis: Acyclovir 10 mg/kg IV q 8 h followed by valacyclovir.
- Progressive outer retinal necrosis: Acyclovir 10 mg/kg IV q 8 h plus foscarnet 60 mg/kg IV q 8 h.
- Suspected resistance: Foscarnet IV 120-200 mg/kg/d.

Pain control

- Gabapentin, tricyclics, carbamazepine, lidocaine patch, narcotics (effective and underutilized).
- Chicken pox: IV acyclovir 30 mg/kg/day x 7 to 10 days until afebrile, then valacyciclovir 1 g tid or famciclovir 500 mg po tid.

- **Comments**
  - Post-herpetic neuralgia is uncommon in persons <55 years, including AIDS patients.
  - Comparative trial of oral acyclovir vs valacyclovir showed slight advantage of valacyclovir (*Antimicrob Agents Chemother* 1995;39: 1546).

RESPONSE: Antiviral therapy of zoster reduces the duration of lesions, reduces the number of new lesions, and reduces systemic complaints, but the benefits are modest and largely limited to those receiving therapy within 24 hours of onset (*N Engl J Med* 1991;325:1539). For most patients the main concern is pain, including post-herpetic neuralgia, especially in older patients. **IRIS** has been reported, presenting with transverse myelitis, iritis, keratitis, and typical dermatomal lesions (*AIDS* 2004;18:1218; *Clin Infect Dis* 2006;42:418; *Medicine* 2002;81:213).

PREVENTION

- **Indication:** Exposure to chickenpox or shingles plus no history of either and, if available, negative anti-varicella IgG. Preventive treatment must be initiated within 96 hours of exposure and preferably within 48 hours.
- **Preferred regimen:** Varicella zoster immune globulin (VZIG) 5 vials (6.25 mL) within 96 hours of exposure.
- **Alternative regimen:** Acyclovir 800 mg PO 5x/day x 3 weeks.

Isospora belli
Isosporiasis

PRESENTATION: The usual presentation is watery diarrhea ± fever, abdominal pain, vomiting, and wasting. The diagnosis requires detection of oocysts in stool with acid-fast stain, which is specific and reasonably sensitive, but several stool specimens may be required. There are no commercial antigen detection methods.

TREATMENT

- **Acute Infection**
  - Preferred regimen: TMP-SMX 1 DS PO bid (or equivalent IV) x 10 days (CDC/IDSA 2004)
  - Alternative regimen: Pyrimethamine 50-75 mg/day PO + leucovorin acid 5-10 mg/day x 10 days
  - Ciproflaxin 500 mg PO bid x 10 days
  - Other fluoroquinolone
  - Support: Fluid and nutritional management; HAART
- **Comment**
  - Immunocompetent patients usually have self-limited diarrhea lasting 2 to 3 weeks. AIDS patients may have severe or persistent diarrhea and are usually treated. Duration of therapy is not well defined.
  - The response with TMP-SMX is rapid, but relapses are common with CD4 counts <200/mm^3 (*N Engl J Med* 1989;320:1044; *Ann Intern Med* 2001;132:885)
  - Pyrimethamine may be as effective as TMP-SMX, but experience is less extensive (*Ann Intern Med* 1988;109:474).

RESPONSE: AIDS patients usually respond to TMP-SMX within 2-3 days (*N Engl J Med* 1986;315:87; *N Engl J Med* 1989;320:1024). Stool examination may show continued shedding after clinical response.

SUPPRESSIVE THERAPY

- **Preferred regimen:** TMP-SMX 1-2 DS/day or 3x/week.
- **Alternative regimens**
  - Pyrimethamine 25 mg + sulfadoxine 500 mg/week PO (1 *Fansidar*/week).
  - Pyrimethamine 25 mg + folinic acid 5 mg/day.
- **Duration:** Consider discontinuation of TMP-SMX when CD4 >200/mm^3 for 3 months.

JC Virus

Progressive Multifocal Leukoencephalopathy (PML)

DIAGNOSIS: Most healthy persons (70-80%) harbor JC virus as a latent virus in marrow, spleen, tonsils, etc. (*Neurol Res* 2006;28:299). PML is the only disease caused by JC virus and occurs most frequently as a devastating neurologic syndrome with insidious onset and progression over weeks or months. Common features are 1) cognitive dysfunction, dementia, seizures, aphasia, cranial nerve deficits, ataxia, hemiparesis; 2) CSF that shows no cells and normal protein; 3) no fever; 4) CD4 count that is usually <100/mm^3 but may be >200/mm^3 in up to one-third; 5) a head CT or MRI that shows hypodense white matter disease and 6) a course that is inevitably progressive over weeks or months (*Clin Infect Dis* 2003;36:1047; *Clin Infect Dis* 2002;34:103; *Lancet* 1997;349:1534). A definitive diagnosis requires compatible clinical history and MRI findings plus a brain biopsy positive by DFA stain for JC virus and typical inclusions in oligodendrocytes. PCR in CSF for JCV has a sensitivity of 75-80%, specificity of 90% to 99% (*J Neurol Neurosurg Psychiatry* 2000;69:569).

TREATMENT

- **Preferred regimen:** There is no effective treatment. With HAART some patients improve, some stabilize, and some progress, but HAART should always be initiated in patients not already receiving it.
- **Comments**
  - Positive PCR plus typical clinical and MRI findings constitute presumptive PML. If PCR is negative, consider brain biopsy depending on probability of a treatable alternative diagnosis.
  - Prognosis: Median survival after PML diagnosis is 2 to 4 months (*J Acquir Immune Defic Syndr* 1992;5:1030; *N Engl J Med* 1998; 338:1345; *Clin Infect Dis* 2002;34:103). It is longer, up to a mean of 8-9 months, with HAART (*J Neurovirol* 1999;5:421).
  - Treatment trials: No antiviral therapy is clearly effective, including cidofovir, interferon alfa, amantadine, cytarabine, adenosine, foscarnet, ganciclovir, and cytosine arabinoside (*AIDS* 2002;16: 1791; *J Neurovirol* 2001;7:364; *J Neurovirol* 2001;7:374; *J Neurovir* 1998;4:324; AIDS 2002;16:1791; *N Engl J Med* 1998;338:1345; *AIDS* 2000;14:517).

RESPONSE: The average survival is 6-9 months, but there is great individual variation, with survival up to 19 years and spontaneous improvement without therapy (*Ann Neurol* 1998:44:341). There is no specific treatment for PML with verified merit, although HAART has been associated with increased survival. In one study of 31 PML patients given HAART, 18 survived. Of these, 8 improved, 6 were worse, and 4 remained stable (*J Neurovirol* 1999;5:421). Similar variations have been noted by others (*J Infect Dis* 2000;182:1077;

AIDS 1999;13:1881; *Clin Infect Dis* 2000;30:95; *J Acquir Immune Defic Syndr* 2004;37:1268).

IRIS involving PML appears to be mediated by JC virus-specific CD4 T lymphocytes. Histology may show diffuse mononuclear perivascular inflammatory infiltration throughout the cortex with positive JCV *in situ* hybridization (*J Neurol Neurosurg Psychiatry* 2003;74:1142). This is associated with contrast enhancement on MRI (*AIDS* 1999;13:1426). IRIS may be associated with either clinical improvement or severe PML disease and death (*Acta Neuropathol* 2005;109:449). Management of severe reactions may include high-dose corticosteroids, or on rare occasions, may require discontinuation of HAART (*Acta Neuropathol* 2005;109:449; *Neurology* 2006;67:1692).

Microsporidia

Microsporidiosis (*Clin Infect Dis* 2001;32:331)

PRESENTATION: Microsporidia are a broad group of microbes related to fungi that were implicated in 20-50% of AIDS-related chronic diarrhea in the pre-HAART era. The frequency now is much lower. The usual presentation is watery diarrhea in patients with a CD4 count <100/mm^3. The diagnosis is usually established by stool studies with light microscopy of stool specimens using calcofluor white, Chromatope 2R, or Uvitex 2B to detect spores (*N Engl J Med* 1992;326:161; *Ann Trop Med Parasitol* 1993;87:99; *Adv Parasitol* 1998;40:351). These tests have sensitivity and specificity of about 100% and 80%, respectively (*J Clin Microbiol* 1998;36:2279). Microsporidia refers to a large group of microbes, of which only two are known to cause diarrhea: *Enterocytozoon* (*Septata*) *intestinalis*, which accounts for about 10-20% of microsporidiosis cases, and *E. bieneusi*, which accounts for 80-90%. Non-intestinal manifestations of microsporidiosis include encephalitis, ocular infections, myositis, sinusitis, and disseminated infection (*Clin Infect Dis* 1994;19:517; *Adv Parasitol* 1998;40:321).

TREATMENT

- **Preferred regimens**
  - Optimal therapy: HAART with virologic control and CD4 count increase to >100/mm^3.
  - *E. intestinalis*: Albendazole 400 mg PO bid until CD4 >200/mm^3. (See first item in comments below.)
  - Symptomatic treatment with nutritional supplements and anti-diarrheal agents (diphenoxylate/atropine, loperamide, etc.).
  - Disseminated disease: Itraconazole 400 mg PO qd plus albendazole 400 mg PO bid (*Trachipleistophora* or *Brachiola*)

- **Comments**
  - Extraintestinal: *E. bellum* – sinusitis and disseminated disease; *E. cuniculi* – CNS, conjunctiva, renal, lungs; *T. hominis* – myositis; *Braciola* – myositis.
  - Albendazole is recommended for disseminated (non-ocular) microsporidiosis caused by any microsporidia other than *E. bienuesi* (CDC/IDSA 2004).
  - Albendazole efficacy: Established only for infections involving *E. intestinalis*, which causes 10% to 20% of cases.
  - Anecdotal success: Reported with itraconazole, fluconazole, nitazoxanide, nitrofurantoin, atovaquone, and metronidazole (*Infect Dis Clin North Am* 1994;8:483).
  - Immune reconstitution with CD4 >100/mm^3: Best therapy, especially for the 80% to 90% of cases involving *E. bieneusi* (*Lancet* 1998;351:256; *AIDS* 1998;12:35; *J Clin Microbiol* 1999;37:421; *J Acquir Immune Defic Syndr* 2000;25:124).

RESPONSE: Symptoms resolve with CD4 count increase to >100/mm^3.

Malaria

PRESENTATION: Malaria presents with fever and anemia. Neurological signs are present in cerebral malaria. Renal failure may be present in "black water fever. Among adult men and women who are not pregnant, HIV may increase the risk of malaria, especially in those with advanced immune-suppression. In non-endemic areas malaria transmission, HIV-infected adults may be at increased risk of developing severe malaria. HIV-infected adults with low CD4 cell counts may also be more susceptible to treatment failure of anti-malarial drugs. Furthermore, acute malaria episodes temporarily increase viral replication and hence HIV viral load.

DIAGNOSIS: Usually made by microscopy of thick and thin blood smear. Bedside dipstick tests using monoclonal antibodies for histidine-rich protein-2 appear to be of comparable accuracy to blood smears in diagnosis of P. falciparum and require less training than microscopy.

Treatment of uncomplicated Plasmodium falciparum malaria

Recommended Drug	Dose in Adults
Sulphadoxine-pyrimethamine*	3 tablets PO as a single dose, >65kg = 4 tablets
OR	
Quinine (oral)	2 tablets (600 mg quinine salt) 8 hrly x 7 days or until blood smear is negative
OR	
Artemisinin (500mg tablets)	20 mg/kg on day 1 (500-100mg) then 500mg for five days
Halofantrine**	500 mg 6hrly for 3 doses. Repeat after one week

* ITreatment of complicated Plasmodium falciparum malaria

IF: Parasitaemia > 5% Hb < 6 g/dl Spontaneous hypoglycaemia Major organ dysfunction eg. cerebral malaria, respiratory distress, renel failure etc.

Recommended Drug	Dose in Adults
Quinine (intravenous)	Quinine 10 mg/kg in 5 -10 ml/kg 5% dextrose IV over4 hours and repeat 8 hrly until able to take oral medication. (Max 1800 mg per day). Treat for 7 days and change to oral as soon as possible
Quinine (oral) - if able to take oral medication and not vomiting	600 mg (2 tablets) 8 hrly x 7 days
Sulfadoxine- pyrimethamine	3 tablets PO as a single dose

MAINTENANCE: Emphasis must be placed on avoidance of mosquitoes and mosquito bites.

Chemoprophylaxis for malaria.

Mefloquine	1 tablet = 250 mg for adults. 250 mg (1 tablet) every 7 days, starting 1 week before entering the area, once weekly while in the area, and once weekly for 4 weeks after leaving the area.
Doxycycline	1 tablet = 100 mg 100 mg once daily, starting 1- 2 days before entering the area, continuing daily while in the area, and daily for 4 weeks after leaving the area. Don't use for longer than 3 months.

Molluscum Contagiosum

CAUSE: A poxvirus

PRESENTATION: Clinical presentation is with flesh-colored, pink, or whitish dome-shaped papules with central umbilication (dimpling). It can occur anywhere on the body, except palms and soles. Most common areas are the face (beard area), neck, and genitals. Lesions are usually <5 mm in diameter; occasionally lesions are >1 cm (giant molluscum). The diagnosis may be confirmed by KOH preparation, Tzanck smear, or biopsy that shows intraepidermal molluscum bodies.

TREATMENT: An individual lesion may be treated with curettage, cryotherapy, electrocauterization (*Sex Transm Infect* 1999;75[suppl 1]:S80), chemical cauterization (trichloroacetic acid, cantharidin, podophyllin, topical cidofovir. Lesions usually disappear in patients responding to HAART (*Eur J Dermatol* 1999;9:211).

Mycobacterium avium Complex

Disseminated MAC

PRESENTATION: MAC is a ubiquitous mycobacterium found in environmental sources that is acquired by ingestion or inhalation. It is a relatively common cause of chronic pulmonary disease in otherwise healthy adults and of disseminated infection without pulmonary involvement in patients with AIDS. The incidence of disseminated MAC in patients with a CD4 count <100/mm^3, no HAART, and no MAC prophylaxis is 20-40%. With HAART and MAC prophylaxis, this is reduced to 2%.

- These is an increase incidence of rash associated with the co-prescription of efavirenz and clarithromycin. The options are to use azithromycin or to use a PI based regimen.
- Anemia is common the usual symptoms in AIDS patients are fever, night sweats, weight loss, diarrhea, and abdominal pain typically occurring in patients with a CD4 count <50/mm^3 (*Lancet Infect Dis* 2004;4:557). The diagnosis is established by culture of MAC from a non-pulmonary, normally sterile site; blood cultures are 90% to 95% sensitive using Bactec bottles but usually require 7 to 14 days. The diagnosis rarely requires biopsy of liver, bone marrow, or lymph nodes. Sputum and stool are insensitive and nonspecific culture sources (*J Infect Dis* 1994;168:1045; *J Infect Dis* 1994;169:289).
- Pulmonary MAC (uncommon in HIV-infected patients): Infiltrate on x-ray and culture with ≥2+ growth and ≥1 positive AFB stain (*Am J Respir Crit Care Med* 1997;155:2041).

TREATMENT

- **Preferred regimens**

- Clarithromycin 500 mg bid PO + ethambutol (EMB) 15 mg/kg/day PO.

  Consider adding a third drug with CD4 count <50/mm^3, high MAC load or absence of effective HAART: rifabutin 300 mg/day PO.
- Start HAART simultaneously or within 1-2 weeks.

- **Alternative regimen:** Azithromycin 500-600 mg/day + ethambutol 15 mg/kg/day PO.
- Alternative "third drugs" are 1) levofloxacin 500 mg PO qd; 2) ciprofloxacin 500-750 mg PO bid; 3) Amikacin 15 mg/kg/d IV.

RESPONSE: Decrease in fever and in quantitative blood cultures is expected in 2 to 4 weeks. Obtain blood cultures if there is no clinical improvement within 4 to 8 weeks. Treatment failure is defined by positive blood cultures at 4 to 8 weeks. Sensitivity tests should be performed and treatment should include at least two new drugs that show *in vitro* activity. Antibiotics to consider include ethambutol, rifabutin, ciprofloxacin, levofloxacin, and amikacin. Optimal HAART is always important (*Clin Infect Dis* 2000;31:1245; *Clin Infect Dis* 1998;27:1278). Care should be taken to distinguish MAC treatment failure from both MAC bacteremia and MAC IRIS, in which blood cultures are negative (discussed below).

- **Comments**
  - With severe disease use a 3-drug combination, but the best third drug is unclear. Studies with rifabutin as a third drug suggest improved survival and reduced resistance (*Clin Infect Dis* 1999;28:1080). Alternative third drugs are levofloxacin, ciprofloxacin, or amikacin, but data supporting benefit are sparse (*N Engl J Med* 1996;335:377; *Clin Infect Dis* 1997;25:621; *J Infect Dis* 1993;168:112).
  - **Failure:** ≥2 new drugs; benefit of continuing clarithromycin or azithromycin if resistant *in vitro* is not known.
  - **Macrolide resistance:** resistance to clarithromycin and azithromycin is unusual even in patients who develop MAC during use of these drugs for prophylaxis (*Clin Infect Dis* 1994;18:S237; *Ann Intern Med* 1994;121:905).
  - **Clarithromycin drug interactions:** Clarithromycin AUC is increased with concurrent IDV (50%), RTV (75%), FPV (18%), LPV/r (77%), ATV (94%), NVP (26%), and SQV (177%). The clarithromycin dose should be reduced 50% or should be avoided when used with ATV due to increased levels and concern for prolonged QTc; dose adjustments for the other drugs listed require no clarithromycin dose adjustment except when LPV/r or RTV are used with renal failure. With EFV, clarithromycin levels are decreased 39% – monitor response or use alternative drug (DHHS

guidelines 11/04) (*N Engl J Med* 1996;335:428).

- **Rifabutin dose:** 300-600 mg/day, but should not exceed 300 mg/day if given with clarithromycin or fluconazole. Note interactions with PIs and NNRTIs.
- ***In vitro* susceptibility:** Most useful for macrolides in patients with prior macrolide exposure (*N Engl J Med* 1996;335:392; *Clin Infect Dis* 1998;27:1369; *J Infect Dis* 2000;181:1289). Threshold for clarithromycin sensitivity is 32µg/mL and for azithromycin is 256µg/mL using Bactec radiometric susceptibility testing.
- **Clarithromycin vs azithromycin:** In a comparative trial for MAC bacteremia, clarithromycin was superior in time to negative blood cultures (*Clin Infect Dis* 1998;27:1278; see also *Antimicrob Agents Chemother* 1999;43:2869). Nevertheless, another large trial using azithromycin 600 mg/day vs clarithromycin 500 mg bid, each combined with EMB, showed comparable results (*Clin Infect Dis* 2000;31:1254).
- **3-drug combination:** Comparison of clarithromycin/EMB vs clarithromycin/EMB/rifabutin showed no clinical benefit to 3-drug regimen but a decreased rate of clarithromycin resistance (*Clin Infect Dis* 1999;28:1080).
- **ASA or NSAID** often effective for symptom relief.
- **Immune reconstitution:** Discontinue maintenance therapy when CD4 count >100 cells/mm^3 x 6 months + ≥12 months treatment and asymptomatic.

MAC Immune Reconstitution Inflammatory Syndrome (IRIS)

CHARACTERISTIC FEATURES: 1) Host and timing factors: most common in the first 8 months (usually at 1-3 months) after initiating HAART with baseline CD4 <50/mm^3 and a good CD4 response to >100/mm^3 and VL response (*Lancet* 1998;351:252; *J Acquir Immune Defic Syndr* 1999; 20:122; *Ann Intern Med* 2000;133:447; *Clin Infect Dis* 2004;38:1159). 2) The most common presentation is fever and a focal inflammatory lesion, usually cervical adenitis, but others include mediastinal adenitis, mesenteric adenitis, pericarditis, osteomyelitis, skin abscesses, bursitis, CNS infections, hepatic granuloma, osteomyelitis, thoracic spine abscess, psoas abscess, peritonitis, cholestatic liver disease, etc. (*Ann Intern Med* 2000;133:447; *Clin Infect Dis* 2004;38:461; *Clin Infect Dis* 2004;38:1159; *Clin Infect Dis* 2005;41:1483; *Medicine* 2002;81:213; *Lancet Infect Dis* 2005;5:361). A review of 43 cases of MAC IRIS found an incidence of 3% among HAART recipients with three main clinical presentations: peripheral lymphadenitis, thoracic disease, and intra-abdominal disease. The median CD4 count from pre-HAART baseline and at IRIS presentation were 20 cells/mm^3 and 120 cells/mm^3, respectively. There was no difference in outcome with or without

treatment directed at MAC, and 8 of 9 responded to prednisone (*Clin Infect Dis* 2005;41:1483).

TREATMENT

- Continue HAART
- Continue MAC therapy
- Treat IRIS with NSAIDs; severe cases may need prednisone 20-60 mg/d, with slow taper guided by symptoms.

Mycobacterium tuberculosis (TB)

EPIDEMIOLOGY AND CLINICAL FEATURES: The risk of active TB with latent infection is increased 100-fold by HIV infection; primary TB is also common and accounts for one-third of cases (*MMWR* 2003;52RR-10:1). HIV promotes TB at all CD4 strata (*J Infect Dis* 2005;19:150), but clinical features vary according to CD4 count. With CD4 count >350/mm^3 lung lesions are "typical," with upper lobe infiltrates ± cavitation. With CD4 count <50/mm^3 extrapulmonary TB is far more common with pleuritis, pericarditis, meningitis, and disseminated disease; chest x-rays typically show lower and middle lobe and miliary infiltrates, usually without cavitation. TB is associated with increased VL and more rapid progression of HIV infection (*Am J Respir Crit Care Med* 1995;151:129; *Am J Respir Crit Care Med* 1993;148:1293).

DIAGNOSIS: The standard test for pulmonary TB is morning expectorated sputa x 3 days for AFB smear and culture. Induced sputa and bronchoscopy are used if there is no sputum production. Sensitivity of AFB smear is about 50%, is similar for patients with and without AIDS, and is not better with induced sputum or bronchoscopy specimens compared with expectorated sputum (*Chest* 1992;101:1211; *Chest* 1992;102:1040; *Am J Respir Crit Care Med* 2000;162:2238). Specificity of the smear depends on prevalence of MAC in local water (*J Clin Microbiol* 1998;36:1046), but most positive AFB smears of respiratory specimens in patients with AIDS indicate TB even in areas where MAC is common (*Clin Infect Dis* 1998;19:334). Nucleic acid amplification (Gen-Probe *Amplified MTB Test*; Roche *Amplicor MTB Test*) is more sensitive than AFB smear (80% vs 50%), is specific for *M. tuberculosis*, is 95% sensitive in AFB-smear positive cases, and hastens mycobacterial identification with culture and smear, but the tests are expensive. Current recommendation is that they be used with positive AFB smear or negative AFB smear plus high level of suspicion (*Am J Respir Crit Care Med* 2001;164:2020; *MMWR* 2000;49:593). With miliary TB, sputum cultures are positive in only 25%, but multiple other specimens are AFB smear or culture positive, including blood in 50% to 60%. All positive cultures should be tested for sensitivity to the 5 first-line drugs: INH, rifampin, ethambutol, PZA, and streptomycin. PPD skin tests have high rates of false-negative results that correlate inversely with CD4 count – up to 65% false-negatives in AIDS patients

with active TB (*J Infect Dis* 1992;166:194). Positive cultures for *M. tuberculosis* approach 100% for sensitivity and 97% for specificity (*Clin Infect Dis* 2001;31:1390).

TREATMENT:

- **Initiation of HIV treatment:** Do not initiate treatment of both TB and HIV simultaneously due to overlapping drug toxicities, drug interactions, adherence requirements, and the risk of immune reconstitution (IRIS). The CDC/ATS recommendation is to: 1) continue antiretroviral therapy that was previously started; 2) avoid initiating treatment of both and always treat TB first with HAART introduced at 4-8 weeks. The possible exception is patients with advanced HIV with CD4 counts <50/mm^3, though such patients frequently experience an increase in CD4 count with treatment of TB alone. WHO guidelines are:
  1. **CD4 <200/mm^3:** Start ART at 2 to 8 weeks after TB treatment with EFV-based HAART
  2. **CD4 200 to 350/mm^3:** Consider ART. If given, start after initial TB phase using EFV-based HAART (with EFV dose of 600 or 800 mg/d) or PI-based HAART with rifabutin in place of rifampin and appropriate dose adjustment (see Table 6-2e).
  3. **CD4 >350/mm^3:** Defer ART
- **Unique issues with HIV coinfection**
  - Atypical TB presentation with low CD4 count: more non-cavitary, lower- and mid-lobe involvement and extrapulmonary disease
  - TB incidence is increased 100-fold with HIV; HIV viral loads are higher and HIV disease progresses more rapidly with active TB (*Am J Resp Crit Care Med* 1995;151:129). The increased risk of TB begins within 1 year of HIV transmission.
  - IRIS is reported in 11%-45% of patients who receive HAART within 6 weeks of starting TB treatment (*Int J Tuberc Lung Dis* 2006;10:946).
  - One report shows a high rate of morbidity and mortality in the first month of TB treatment in patients with a CD4 count <100/mm^3 at baseline (*J Infect Dis* 2004;190:1670).
  - Other differences in anti-TB therapy: 1) optimal duration is unclear; 2) CD4 <100/mm^3 – continuation phase should be daily or 3x/week; 3) rifapentine is contraindicated.
  - In a large trial of steroids for pleural TB in coinfected patients in Kampala, prednisone (50 mg/d x 2 wks, then taper over 6 wks) was not associated with an increase in OIs or a decrease in CD4 cell count response (*J Infect Dis* 2004;190:869).
- **XDRTB:** There is a great concern for the sudden epidemic of

"extensively drug-resistant" tuberculosis (XDRTB) in KwaZulu, Natal in S. Africa (*Br Lancet* 2006;368:1575). These strains are resistant to INH and rifampin (MDRTB) but also are resistant to 3 of the 6 second line classes (*MMWR* 2006;55:301). Most occur in HIV-infected patients and are rapidly fatal (*Science* 2006;313:1554; *Br Med J* 2006;333:559).

- **Immune reconstitution inflammatory syndrome (IRIS):** May occur in absence of HIV co-infection but more common with HIV and thought to be due to immune reconstitution.
  - Characterized by worsening of symptoms and x-ray changes, with high fever, lymphadenopathy, expanding CNS lesions, large effusions (*Arch Intern Med* 2002;162:97; *Chest* 2001;120:193). Rule out other causes, especially TB treatment failure and lymphoma.
  - Severe reaction: Prednisone 20-60 mg/d with slow taper guided by symptoms, then taper. Continue TB and HIV therapy. (See above regarding corticosteroids.) Mild to moderate reaction: Treat symptomatically with non-steroidals.
  - IRIS includes pulmonary disease (pneumonitis, effusions, lymphadenitis), ARDS, cerebritis, meningitis, parotitis, epididymitis, ascites, adenopathy (*Lancet Infect Dis* 2005;5:361; *Am J Respir Crit Care Med* 1998;158:157; *Chest* 2001;120:193).
  - Risks for TB IRIS: HAART within 6 weeks of starting TB treatment, low baseline CD4 count, high baseline VL, good CD4 and HIV response, and extrapulmonary disease (*Int. J Tuberc Lung Dis* 2006;10:946).
- Risks for MDRTB: 1) previous history of TB, 2) exposure to MDRTB, 3) failure to respond to standard treatment, or 4) prior residence in a country with high rates of MDRTB
- **Infection control:**

  Procedures at high risk (induced sputum, aerosolized pentamidine, bronchoscopy): airborne precautions and specialized rooms

  Hospitalized patients with suspected AFB smear-positive pulmonary or laryngeal TB:
  - Room: code compliant with airborne precautions and AFB isolation room until 1) TB treatment plus clinical and bacterial response, as shown by 3 consecutive AFB-negative smears on different days, or 2) TB is excluded. Note: patients with smear-positive TB should receive 2 weeks of anti-TB treatment before additional AFB smears are obtained.
  - Patient discharge criteria: 1) Symptoms, especially cough, resolved or near resolution; 2) treatment given for TB strain known or likely to be sensitive to drugs used; 3) patient likely to adhere to regimen;

Recommended standard treatment regimens for adults (8 years and older)

1. New case (a patient who has never been treated for TB in the past or who has taken anti-tuberculosis drugs for less than four weeks). Treatment regimens have an initial (or intensive) phase lasting 2 months and a continuation phase usually lasting 4 months. During the intensive phase consisting of 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol), there is rapid killing of tubercle bacilli. Infectious patients become rapidly non-infectious (within approximately 2 weeks). Symptoms abate. The vast majority of patients with sputum smear-positive TB become smear negative within 2 months. In the continuation phase fewer drugs (isoniazid, rifampicin) and are necessary but for a longer time. The sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse.
2. Re-treatment cases: Previously treated patients include all TB patients who were treated as new cases for more than one month in the past and are now smear or culture positive (failure, relapse, return after default). They have a higher likelihood to have drug resistance, which may have been acquired through inadequate prior chemotherapy.

   The re-treatment regimen has an initial phase of 3 months - two months with 5 drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin), one month with 4 drugs ((isoniazid, rifampicin, pyrazinamide, ethambutol) and a continuation phase of 5 months with 3 drugs (isoniazid, rifampicin, ethambutol). Three drugs (rifampicin, Isoniazid, Ethambutol) are given throughout the treatment period. This regimen can cure patients excreting bacilli still fully sensitive to the drugs and those excreting bacilli resistant to isoniazid and or streptomycin. Under proper case management conditions, MDR-TB cases are those most at risk of failure in the re-treatment regimen.

Standard code for TB treatment regimen

Each antituberculosis drug has an abbreviation:

- R (Rifampicin),
- H (Isoniazid),
- Z (Pyrazinamide),
- E (Ethambutol) and S
- (Streptomycin).

A TB treatment regimen consists of two phases: an initial phase and continuation phase. The number before a phase is the duration of that phase in months. Letters in parentheses indicates fixed dose combinations of those drugs. A subscript number (i.e. 3) after a letter or let-

ters in parentheses indicates the number of doses of that drug per week. If there is no subscript number, treatment is daily.

Regimen 1: New cases, age above 8 years and adults

New smear-positive patients, new smear-negative patients and extra-pulmonary TB.(R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol)

Pre-treatment body weight	RHZE (150,75 400,275), Two months initial phase given FIVE a week
30-37 kg	2 tabs
38-54 kg	3 tabs
55-70 kg	4 tabs

Formulation of the RH for the continuation phase is determined by the formulation

Regimen 2: Re-treatment cases

Previously treated TB patients after cure, after completion, default and failure.(R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol)

Pre-treatment body weight	Two months initial phase		Third month initial phase
	RHZE (150,75 400,275)	Streptomycin	RHZE (150,75 400,275)
30-37 kg	2 tabs	050.5	2 tabs
38-54 kg	3 tabs	0.75	3 tabs
55-70 kg	4 tabs	1	4 tabs
>71 kg	5 tabs	1	5 tabs

Formulation of the RH for the continuation phase is determined by the formulation

The South African TUBERCULOSIS Control Programme

- Keep strictly to the correct dose and the duration of treatment.
- Cure of the new PTB patients depends on taking Regimen 1 for 6 months.
- Cure of re-treatment PTB patients depends on taking Regimen 2 for 8 months.

Patient must take treatment 5 days a week, Monday to Friday. No treatment is necessary on Saturday and Sunday. In hospitals, treatment is given for seven days a week.

Intermittent therapy (3 times a week), if used, may be given in the continuation phase only.

No trials of therapy should be given.

Side effects of the main anti- TB drugs and their management

1.Isoniazid (H)

ADVERSE EFFECTS:

- Peripheral neuropathy (tingling and numbness of the hands and feet).
- Hepatitis, more often in patients older than 35 years (rare).
- Generalised skin rash (occurs rarely).
- Fever.
- Joint pains.

MANAGEMENT:

- Mild itching: continue drug treatment, reassure the patient, give calamine lotion and if necessary antihistamine.
- Fever and generalised skin rash: stop all drugs and give antihistamine.
- Neuropathy: give 10 mg -25 mg of pyridoxine, daily.
- Drug induced hepatitis: stop anti-TB treatment, do liver function tests. If there is a loss of appetite, jaundice and liver enlargement, do not give treatment for at least 1 week or until the liver functions have returned to normal. In most patients INH can usually be given later without the return of hepatitis.

Isoniazid inhibits the breakdown of epileptic drugs i.e. phenytoin and carbamazepine. Dosages of these drugs may need to be reduced during the treatment period.

2.Rifampicin (R)

ADVERSE EFFECTS:

- Gastro-intestinal: nausea, anorexia and mild abdominal pain, diarrhoea occurs less frequently.
- Cutaneous reactions: mild flushing and itchiness of the skin.
- Hepatitis: This is uncommon unless the patient has a history of liver disease or alcoholism.
- Serious side effects like influenza syndrome and shock may occur in patients who take the medicine intermittently instead of daily. Stop the treatment and refer the patient.

- The patient should be warned that rifampicin colours the urine, sweat and tears pink (urine looks orange-pink).

DRUG INTERACTIONS:

Rifampicin stimulates liver enzymes, which may the break down other drugs more rapidly than normal, e.g. oral anticoagulants (warfarin), oral diabetic drugs, digoxin, phenobarbitone and other anti-epileptics.

CONTRACEPTION:

The dose of contraceptives should be increased in patients on rifampicin. Depo provera 150mg should be given 8 weekly instead of 12 weekly. Nur-Isterate 200mg should be given 6 weekly instead of 8 weekly. Combined oral contraceptives with at least 0.05mg of ethinyloestradiol should be prescribed. The pill free interval should be shortened from 7 to 4 days. Intra Uterine Contraceptive Devices (IUCDs) may be recommended. WARN the patient that the effect of rifampicin may last up to 2 months after the treatment is stopped.

3.Streptomycin (S)

ADVERSE EFFECTS:

- Cutaneous hypersensitivity, rash and fever.
- Ototoxicity (damage to eighth cranial nerve). Damage to the vestibular (balancing) apparatus is shown by dizziness, sometimes with vomiting. Unsteadiness is more marked in the dark.
- Deafness.
- Anaphylaxis. Streptomycin injection may be followed by tingling around the mouth, nausea and occasioally by sudden collapse. Treat as for any anaphylactic reaction and do not give streptomycin again.patient either has TB and should be treated, or \• Deafness in unborn children. Streptomycin should be avoided during pregnancy because it crosses the placenta.

CONTRA-INDICATIONS:

Do not give to patients with existing renal disease, as it will impair renal function more. Older people (>65 years) have reduced renal function and should not be given streptomycin.

MANAGEMENT:

- Skin reactions: treat as for allergic skin reactions.
- Damage to vestibular apparatus: treatment must be stopped immediately.
- Ringing in the ears or loss of hearing: if the drug is stopped immediately, the symptoms will usually clear over weeks, if not, the

damage will be permanent.

- Do not give streptomycin to patient above 65 years, to pregnant women or to young children.

4.Ethambutol (E)

ADVERSE EFFECTS:

- Progressive loss of vision caused by retrobulbar neuritis, usually manifests first as loss of colour vision and usually presents after the patient has been on treatment for at least two months. This is usually caused by excessive doses of ethambutol.
- Skin rash.
- Joint pains.
- Peripheral neuropathy.

MANAGEMENT:

If the patient complains about visual disturbance, stop treatment immediately. Skin rashes and joint pains usually respond to symptomatic treatment.

CONTRA-INDICATION:

Ethambutol should not be given to children under the age of 8 years who are unable to tell you that they are losing their sight. The patient should be warned about the possible changes in vision and informed to report any changes in the eyesight.

5.Pyrazinamide (Z)

ADVERSE EFFECTS:

- Liver damage: Anorexia, mild fever, tender enlargement of the liver and spleen may be followed by jaundice.
- Arthralgia: This is common and mild. The pain affects both large and small joints, the level of uric acid is increased and gout may occur.
- Skin rash on sun exposed areas.

MANAGEMENT:

- Hepatotoxicity: Do not give the drug again if severe hepatitis occurs. Arthralgia: Treatment with aspirin is usually sufficient. Allopurinol may be required for the treatment of gout.
- Pyridoxine (Vitamin B6) It is unnecessary to give pyridoxine routinely. The use of alcohol during drug therapy should be discouraged or restricted. However, pyridoxine should be added for TB patients who are alcohol abusers, pregnant, diabetic or epileptic. The protective

dose is 10-25 mg daily. This dose should never be exceeded in pregnancy.

Symptom-based approach to management of drug side Drug(s) responsible Management

Minor: Continue anti-TB drugs		
Anorexia, nausea, abdominal pain	Rifampicin	Give tablets last thing at night
Joint pains	Pyrazinamide	Aspirin
Burning sensation in feet	Isoniazid	Pyridoxine 25mg daily
Orange / red urine	Rifampicin	Reassurance

Major: Stop drugs responsible		
Skin itching / rash (anaphylactic reaction)	Streptomycin	Stop streptomycin treat as for hypersensitivity reaction
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystamus)	Streptomycin	Stop streptomycin if severe
Jaundice (other causes excluded)	Most anti-TB drugs	Stop anti-Tb drug until jaundice resolves, then reintroduce one by one
Vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	Most anti-TB drugs	Stop anti-TB drugs, urgent liver function tests
Visual impairment	Ethambutol	Stop ethambutol
Generalised reaction, including shock and purpura	Rifampicin	Stop rifampicin

■ TABLE 6-1: **Dose Adjustments for PI/NNRTIs When Used with Rifampin and Rifabutin (*MMWR* 2004;53:37)**

PI or NNRTI	Rifampin
EFV 800 mg hs	standard
Rifampin is contraindicated with all boosted PIs, and NVP: use rifabutin	
PI or NNRTI	**Rifabutin**
IDV 1000 mg q8h; with IDV/r – standard dose	150 mg/day or 300 mg 3x/week*
ATV, ATV/r, SQV/r, FPV, FVP/r, NFV-standard dose	150 mg/day or 300 mg 2x to 3x/week*

* Intermittent treatment of active TB should be >3x/week with CD4 <100 cells/mm^3.

TABLE 6.2: Treatment of Tuberculosis in Special Populations

■ TABLE 6-2a: **Extrapulmonary TB**

Standard 4 drug initial phase followed by INH/RIF for 4-7 months except for CNS. TB which is treated 9-12 months.		
Site	**Duration**	**Steroids**
Lymph nodes disseminated, pleural, genitourinary, peritoneal pleural	6 months	No
Bone or joint	6-9 months	No
Pericarditis	6 months	Recommended
CNS TB	9-12 months	Recommended

■ TABLE 6-2b: **Pregnancy and Breastfeeding**

Regimen:	INH/RIF/EMB x 9 months or standard treatment with INH/RIF/EMB/PZA x 2 months, then INH/RIF x 4 months. The issue is safety of PZA, for which there is no evidence of adverse effects in pregnancy, but inadequate experience to assure safety. PZA is recommended in WHO guidelines but not U.S. guidelines.

■ TABLE 6-2c: **Renal Insufficiency**

Drug	Dose with creatinine cl. < 30 cc/min or hemodialysis
INH	Standard; increased risk of hepatotoxicity – monitor ALT
RIF	Standard
RZA	25-35 mg/kg 3x/week; see comment above regarding limited experience
EMB	15-25 mg/kg 3x/week
Levofloxacin	750-1000 mg 3x/week
Cycloserine	250 mg qd or 500 mg 3x/week
Ethionamide	Standard
PAS	Standard
Aminoglycosides	12-15 mg/kg 2-3x/week

■ TABLE 6-2d: **Hepatic Insufficiency**

Regimen excluding INH:	RIF/PZA/EMB x 6 months
Regimen excluding PZA:	INH/RIF/EMB x 2 months, then INH/RIF x 7 months
Regimen for severe liver disease:	■ RIF/fluoroquinolone/cycloserine/aminoglycoside x 18 months or ■ Streptomycin/EMB, fluoroquinolone/another second-line drug x 18 to 24 months

■ TABLE 6-2e: **Drug-resistant Tuberculosis**

Drug Resistance	Regimen
INH	RIF/PZA/EMB ± fluoroquinolone x 6-9 months or 6 months post sputum conversion, whichever is longer
INH/RIF	Fluoroquinolone/PZA/EMB/aminoglycoside or capreomycin ± alternative agent x 24 months and >6 months post sputum conversion
RIF	INH/PZA/EMB ± fluoroquinolone x 12 months or INH/PZA/STREP x 9-12 mo
INH/RIF and EMB	Fluoroquinolone/aminoglycoside/2 alternative agents and PZA or EMP (if active)

MONITORING

- **Baseline:** LFTs (ALT/AST, alkaline phosphotase, bilirubin), creatinine or BUN, platelet count, and CBC; PZA – uric acid, EMB – visual acuity.
- **Clinical monitoring:** Clinical assessment monthly. Warn of symptoms of hepatitis to discontinue therapy and obtain medical care – nausea, vomiting, dark urine, malaise, fever >3 days.
- **Laboratory monitoring:** LFTs with symptoms of hepatitis; some recommend routine tests at 1 and 3 months, especially if prior liver disease, older age, or alcoholism. Sputum smear and culture should be done ≤ monthly until two consecutive are negative. Some recommend chest x-ray at 2 months and at the termination of therapy.
- **Hepatotoxicity:** If ALT/AST ≥5x ULN, discontinue INH, rifampin + PZA, and give an alternative such as EMB, streptomycin + quinolone. When LFTs normal, reintroduce primary drugs one at a time (*Ann Intern Med* 1993;119:400). Options are: 1) standard therapy with more frequent monitoring; 2) RIF, EMB + PZA x 6 months; 3) INH + RIF + EMB x 2 months, then INH + RIF x 7 months. With severe liver disease consider RIF + EMB with fluoroquinolone first 2 months.
- Pregnancy

RESPONSE: Response to therapy is similar to that in patients without HIV except: 1) Drug interactions between anti-TB and HIV drugs and

2) the greater risk of paradoxical reactions with IRIS. Most patients become afebrile within 7 to 14 days; persistence of fever beyond this time suggests resistance or another cause of fever (*Clin Infect Dis* 1992;102:797). Sputum culture becomes negative ≤2 months in 85% (*N Engl J Med* 2001;345:189). Persistence of positive cultures at ≥4 months suggests nonadherence or drug resistance. IRIS must be distinguished from therapeutic failure.

Progressive Multifocal Leukoencephalopathy (PML), see JC Virus

*Pneumocystis jiroveci (P. carinii)**

(*N Engl J Med* 2004;350:2487)

Pneumonia (PCP)

CLINICAL FEATURES: Subacute onset and progression of exertional dyspnea, nonproductive cough, fever, and chest pain over days or weeks. P.E. typically shows fever, tachycardia, increased respiration rate ± rales.

LAB: Hypoxemia with reduced pO_2 or alveolar-arterial O_2 difference (A-a gradient), demonstrated at rest or post-exercise in mild cases. LDH is usually >500 mg/dl. X-ray usually shows bilateral, symmetrical interstitial infiltrates, but may be normal in up to 20% of cases (*Am J Roentgenol* 1997;169:967). Atypical findings include nodules, blebs, and cysts. Pneumothorax is relatively common and suggests this diagnosis. Thin-section CT scan shows ground glass attenuation, and gallium scan shows increased lung uptake in patients with a negative chest x-ray. A negative thin-section CT scan does not exclude PCP.

DIAGNOSIS: Standard specimens are induced sputum; sensitivity averages 56% in meta-analysis of 7 reports (*Eur Respir J* 2002;20:982) or BAL with sensitivity of >95%. Some labs prefer immunofluorescent stains, which may give a higher yield (*Eur Respir J* 2002;20:982).

* *P. carinii* has been renamed *P. jiroveci* but the eponym PCP is retained (*Emerg Infect Dis* 2002;8:891).

TREATMENT

- **Preferred regimens**
  - Trimethoprim 15-20 mg/kg/day + sulfamethoxazole 75-100 mg/kg/day PO or IV x 21 days in 3 to 4 divided doses (typical oral dose is 2 DS tid). May treat for only 14 days if mild disease and rapid response.

- Adjunctive corticosteroids: Patients with moderately severe or severe disease (PO_2 <70mm Hg or A-a gradient >35 mm Hg) should receive corticosteroids (prednisone 40 mg PO bid x 5 days, then 40 mg qd x 5 days, then 20 mg/day to completion of treatment) starting as early as possible. IV methylprednisolone can be given as 75% of prednisone dose. Efficacy of corticosteroids for hypoxemia is established (*N Engl J Med* 1990;323:1451; *N Engl J Med* 1990;323:1500). Cochrane library review found that use of steroids was associated with an OR of 0.56 for overall mortality according to criteria discussed above (*Cochrane Database Syst Rev* 2006;3:CD006150). The rationale for the use of steroids is that PCP prognosis correlates better with inflammatory markers than with number of organisms (*Expert Rev Mol Med* 2005;7:1). Side effects of steroids include CNS toxicity, thrush, cryptococcosis, *H. simplex* infection, tuberculosis, and other OIs (*J Acquir Immune Defic Syndr* 1995;8:345).

- **Alternative regimens**
  - TMP 15 mg/kg/day PO + dapsone 100 mg/day PO x 21 days (*Ann Intern Med* 1996;124:792; *N Engl J Med* 1990;320:323:776).
  - Pentamidine 3-4 mg/kg/day IV infused over ≥60 min x 21 days; usually reserved for severe cases (*Ann Intern Med* 1986;105:37; *Ann Intern Med* 1990;113:203; *Ann Intern Med* 1994;121:174).
  - Clindamycin 600-900 mg IV q6h-q8h or 300-450 mg PO q6h + primaquine* 15-30 mg/day base PO x 21 days (*Clin Infect Dis* 1994;18:905; *Clin Infect Dis* 1998;27:524; *Arch Intern Med* 2001;161:1529).
  - Atovaquone 750 mg suspension PO bid with meal x 21 days (*N Engl J Med* 1993;328:1521; *Ann Int Med* 1994;121:154).

- **Comments**
  - The use of 15 mg/kg/day of TMP appears to be as effective as 20 mg/kg/day and better tolerated (*N Engl J Med* 1993;328:1521; *Ann Intern Med* 1996;124:792).
  - ACTG 108 showed TMP-SMX, TMP-dapsone and clindamycin-primaquine to be equally effective for mild-moderate PCP (*Ann Intern Med* 1996;124:792).
  - Adverse reactions to TMP-SMX have been noted in 25% to 50%, primarily rash (30% to 55%), fever (30% to 40%), leukopenia (30% to 40%), azotemia (1% to 5%), hepatitis (20%), thrombocytopenia (15%), and hypokalemia (TMP) (*J Infect Dis* 1995;171:1295; *Lancet* 1991;338:431). Most can be "treated through," using antihistamines for rashes, antipyretics for fever, and antiemetics for nausea.
  - Opinions vary regarding initiation of HAART during treatment of PCP. Some report better short-term survival (*J Infect Dis* 2001; 183:1409); others report paradoxical worsening, due possibly to

IRIS (*Am J Respir Crit Care Med* 2001;164:841). Immune reconstitution with acute respiratory failure has been described (*Am J Respir Crit Care Med* 2001;164:847).

- Geographic clustering of cases suggests person-to-person spread (*Am J Respir Crit Care Med* 2000;162:1617; *Am J Respir Crit Care Med* 2000;162:1622; *N Engl J Med* 2000;19:1416; *Emerg Infect Dis* 2003;9:132). However, isolation from other vulnerable patients is not generally advocated.

- **Prophylaxis:**

RESPONSE: Response to therapy is slow – usually 5 to 7 days. Preferred therapy (TMP-SMX) should not be changed based on an assumption of clinical failure until 4-8 days. Drug toxicity is common and may be mistaken for therapeutic non-response (*Ann Intern Med* 1996;124:972). The mortality rate of untreated PCP is 100%; for PCP with hospitalized patients given standard regimens it is 15% to 20%, (*AIDS* 2003;17:73). One meta-analysis suggested that primaquine-clindamycin is the most effective salvage regimen (*Arch Int Med* 2001;161:1529). **IRS PCP** has been reported with progression of pneumonia including ARDS (*Clin Infect Dis* 2002;35:491; *Am J Respir Crit Care Med* 2001;164:847). It must be remembered that PCP disease is largely the product of the inflammatory response and severe disease is treated with steroids.

Pseudomonas aeruginosa

DIAGNOSIS: Clinically compatible case plus recovery of the organism from a normally sterile source. Caution is necessary in interpreting growth of *P. aeruginosa* in contaminated respiratory tract specimens (sputum, bronchoscopy, etc.), especially in patients with prior antibiotics use or when the organism is recovered in low numbers.

TREATMENT

- **Preferred regimen:** Aminoglycoside + antipseudomonal beta-lactam (ceftazidime, cefoperazone, cefepime, ticarcillin, imipenem, piperacillin).
- **Alternative regimen:** Monotherapy with antipseudomonas beta-lactam, (ceftazidime, cefepime, piperacillin), carbapenem (imipenem, meropenem), ciprofloxacin, aminoglycoside.
- **Comments**
  - Antibiotic selection requires *in vitro* susceptibility data.
  - Risks: Reverse risk factors when feasible – neutropenia, corticosteroids, CD4 <50/mm^3.
  - The frequently quoted adage that *P. aeruginosa* requires "double coverage" is debatable. Like other pathogens, it requires an

agent active *in vitro* and, for pulmonary infections, an agent that penetrates alveolar lining fluid. Use of monotherapy with a fluoroquinolone usually results in persistent disease with a fluoroquinolone-resistant strain.

Salmonella spp.

PRESENTATION: The predominant strains in the U.S. are *S. enteriditis* and *S. typhimurium*.

TREATMENT (*Clin Infect Dis* 2001;32:331)

- **Preferred regimen:** Ciprofloxacin 500-700 mg PO bid or 400 mg IV bid; total treatment is 7 to 14 days, for cases that are mild and nonbacteremic; at least 4 to 6 weeks with advanced AIDS (CD4 <200/mm^3) ± bacteremia. Other fluoroquinolones (moxifloxacin and levofloxacin) should be equally effective.
- **Alternative regimen:** TMP 5-10 mg/kg/day/SMX IV or 1 DS bid x >2 weeks or ceftriaxone 1-2 g/day IV ≥2 weeks (see duration above).
- **Comments**
  - Immunocompetent hosts with salmonellosis often do well without antibiotic treatment. Most experts recommend antibiotics for all HIV-infected patients based on high rates of bacteremia (CDC/IDSA recommendations).
  - Relapse is common. Eradication of *Salmonella* carrier state has been demonstrated only with ciprofloxacin.
  - AZT is active against most *Salmonella* strains and may be effective prophylaxis (*J Infect Dis* 1999;179:1553).
  - Drug selection requires *in vitro* susceptibility data, especially for ampicillin. TMP-SMX preferred if sensitive. Ciprofloxacin resistance is reported (*N Engl J Med* 2001;344:1572) but is rare.

Staphylococcus aureus

PRESENTATION: Staphylococcal infection syndromes most commonly encountered with HIV infection include:

- **Furunculosis:** Furunculous Community acquired MRSA is not common in South Africa. The most common infections associated with this strain are soft tissue infections, especially furuncles, and cellulitis. Rare but very serious variants are necrotizing pneumonia, necrotizing fasciitis, and pyomyositis.
- **Pyomyositis:** This is classically an infection of muscle caused by *S. aureus*, usually MSSA (Methicillin Sensitive Staph Aureus), and sometimes called "tropical pyomyositis" due to high rates in tropical countries. Most cases present with fever and focal pain; the

diagnosis is usually made by CT scan (*Radiographics* 2004;24:1029) and treatment consists of drainage plus antibiotics selected by *in vitro* sensitivity tests (*Am J Med* 2004;117:420; *J Rheumatol* 2001;28:802). Some patients respond to antibiotics without surgery (*Am Surg* 2000;66:1064).

TREATMENT

- **Preferred regimens**
  - **Parenteral:** Methicillin-sensitive *S. aureus* (MSSA): Antistaphylococcal betalactam (nafcillin, oxacillin, cefazolin, ceftriaxone); alternatives should be selected by *in vitro* tests. Clindamycin, fluoroquinolone, and TMP-SMX are usually active.

    Oral: Cephalexin 500 mg qid, dicloxacillin 500 mg qid, clindamycin 300 mg tid, or fluoroquinolone.
  - **Nosocomial** methicillin-resistant *S. aureus* (MRSA): Vancomycin 1 g IV q12h). Alternatives include linezolid 600 mg bid IV or PO or daptomycin 4 mg/kg/day IV.
  - **Community-acquired MRSA:** Often sensitive to TMP-SMX, clindamycin or doxycycline as well as vancomycin or linezolid. For serious infections it may be appropriate to use combinations of these or to combine with rifampin (*MMWR* 2003;52:993).
- **Management recommendations:** 1) Culture and sensitivity tests. 2) Furuncles require surgical drainage. 3) If antibiotics are used, the recommendation is TMP-SMX or doxycycline; clindamycin is appropriate if the strain is sensitive to erythromycin or the D test is negative. 4) Infection control requires covering wounds and good hand hygiene.
- **Comments**
  - Fluoroquinolones: Use of quinolone requires *in vitro* sensitivity results. Resistance is 10% for MSSA and 90% for nosocomial MRSA.
  - Tricuspid valve endocarditis: nafcillin + gentamicin (MSSA) x 2 weeks (*Ann Intern Med* 1988;109:619), but abbreviated courses are generally not advocated for HIV-infected persons.
  - For tricuspid valve endocarditis due to MSSA, nafcillin/oxacillin is preferred to vancomycin (*Clin Infect Dis* 2001;33:120).

Streptococcus pneumoniae

PRESENTATION: The rate of community-acquired pneumonia (CAP) is increased 8-fold with HIV infection (*Am Rev Respir Dis* 1993;148:1523) and the rate of *S. pneumoniae* bacteremia is increased 150- to 300-fold (*JAMA* 1991;265:3275). Rates of both CAP and pneumococcal bacteremia correlate with CD4 cell counts. Patients with pneumococcal bacteremia also have an 8-25% probability of recurrent

bacteremia within 6 months (*JAMA* 1991;265:3275; *J Infect Dis* 2002;185:1364). Most of the recurrent cases involve new strains of *S. pneumoniae* and thus do not represent relapses. The clinical features of pneumococcal pneumonia and pneumococcal bacteremia are not unique in patients with HIV infection. Standard diagnostic tests in CAP patients who are hospitalized include x-rays and studies for a microbial etiology including blood culture, Gram stain + culture of respiratory secretions, and urinary antigen assay for *S. pneumoniae.*

TREATMENT

- **Preferred regimens:** Penicillin, amoxicillin, cefotaxime, ceftriaxone (see Comments), or fluoroquinolone (suspected or established penicillin resistance): Levofloxacin, moxifloxacin, or telithromycin (Ketek).
- **Alternative regimens:** Macrolide.
- **Comments**
  - Penicillin-resistant strains: Strains highly resistant to penicillin should be treated with fluoroquinolones quinolones (levofloxacin, or moxifloxacin). TMP-SMX is now considered inadequate for empiric use due to high rates of resistance. Fluoroquinolone resistance is uncommon (<2%) but increasing (*N Engl J Med* 2002;346:747; *Emerg Infect Dis* 2002;8:594).

RESPONSE: Most patients respond well with clearance of bacteremia in 24 to 48 hours and clinical improvement in 1 to 3 days. Patients with pneumococcal pneumonia may transition from IV to oral antibiotics when they are clinically better, vital signs and blood gases are improved, and they can take pills. HIV-infected patients with pneumococcal bacteremia usually respond well to treatment and actually have better survival rates than bacteremic patients without HIV infection (*Mayo Clin Proc* 2004;79:604).

Toxoplasma gondii

Toxoplasmic encephalitis

PRESENTATION: Toxoplasmosis in patients with HIV infection nearly always represents reactivation of latent cysts, almost always in patients with a CD4 count <100/mm^3. Seroprevalence in the U.S. is about 15% but often 50-75% in some European countries and developing nations. The usual clinical presentation is fever, headache, confusion, and/or focal neurologic deficits. The diagnosis is based on 1) CNS imaging, 2) evidence of *T. gondii* by serology and PCR of CSF, and 3) response to therapy. Typical features are ≥2 ring enhancing lesions on MRI, fever, focal neurologic defect, and positive anti-*T. gondii* IgG (>90%). CSF *T. gondii* PCR is 50% sensitive and >96% specific (*Clin Infect Dis* 2002;34:103).

TREATMENT: ACUTE INFECTION (≥6 weeks)

- **Preferred therapy:** Pyrimethamine 200 mg PO x 1, then:

  Sulfadiazine 4 - 8 g/day orally plus pyrimethamine 100 - 200 mg loading dose, then 50 - 100 mg/day orally plus folinic acid 15 mg/ day for at least 6 weeks. Sulphadiazine, unfortunately, is not readily available in South Africa. There are a number of reports which now have shown that cotrimoxazole (TMP 15 mg/kg/day + SMX 75 mg/kg/day) orally or IV is useful in the treatment of toxoplasmosis.

- **Prophylaxis for HIV-infected patients:** Indications for chemoprophylaxis
  - Patients with prior evidence of exposure to toxoplasmosis (positive IgG serology for T. gondii).
  - CD4 count < 100 cells/mm3.
- **Agents:**

Preferred:	Cotrimoxazole	(TMP-SMX) 1 DS PO per day
Alternatives:	Cotrimoxazole	(TMP-SMX) 1 SS PO per day
		OR

  Dapsone 50 mg PO daily plus pyrimethamine 75 mg/week PO

- **Alternative regimens**
- **Comments**
  - Pyrimethamine + sulfadiazine is preferred; pyrimethamine + clindamycin is less effective but better tolerated (*Clin Infect Dis* 1996;22:268). All other regimens listed have been less well studied.
  - Atovaquone regimens: May wish to confirm serum level ≥18 µg/mL due to variable absorption.
  - Alternative regimens: Azithromycin, *AIDS* 2001;15:583; Clarithromycin, *Antimicrob Agents Chemother* 1991;35:2049; Atovaquone, *Clin Infect Dis* 2002;34:1243; TMP-SMX: *Antimicrob Agents Chemother* 1998;42:1346.

IMMUNE RECONSTITUTION: Discontinue maintenance therapy when CD4 count >200 cells/mm^3 x 6 months, initial therapy completed + asymptomatic.

PROPHYLAXIS:

RESPONSE: Clinical response expected in 1 week in 60% to 80% and MRI response expected in 2 weeks. Failure to achieve these goals should prompt consideration of alternative diagnosis, especially primary CNS lymphoma, tuberculous, or brain abscess. Stereotatic biopsy is usually required, and yields a definitive diagnosis in 98% of cases (*Clin Infect Dis* 2000;30:49).

Treponema pallidum

Syphilis

PRESENTATION

- **Stages**
  - Primary: genital ulcer
  - Secondary (2 to 8 weeks): macular, papular, or maculopapular rash that is generalized including palms and soles, generalized lymphadenopathy ± constitutional symptoms or aseptic meningitis
  - Tertiary: Cardiac, neurologic, ocular, auditory, or gummatous
  - Latent: Early latent <1 year; late latent >1 year or duration unknown
- **Diagnosis: Primary syphilis** – darkfield and DFA test of exudate. **Late syphilis** (secondary, tertiary and latent) – non-treponemal test (VDRL or RPR) + treponemal test (FTA-ABS). Non-treponemal test titers correlate with disease activity. The RPR and VDRL responses may be atypical with HIV infection, but treponemal tests appear no different in persons with and without HIV infection. Changes in RPR or VDRL titers are significant if ≥4-fold (2 dilutions). The diagnosis of **neurosyphilis** is made by CSF exam that shows mononuclear pleocytosis (>5 WBC/mL), mild elevation of protein, and/or positive VDRL. The CSF VDRL is specific but not sensitive; the CSF FTA-ABS is sensitive but not specific. There is often great difficulty in establishing this diagnosis due to the high rate of false negative CSF VDRLs and the pleocytosis (5-15 monos/mL) that can be attributed to HIV. If neurosyphilis cannot be excluded, the patient should be treated for it (*MMWR* 2004;53[RR-15]:28).

INDICATIONS FOR LP: (1) Neurologic, ocular, or auditory signs or symptoms; (2) treatment failure; and (3) late latent syphilis. Some authorities recommend LP in all patients with HIV infection and latent syphilis.

- **MANAGEMENT:**
  - **Primary, secondary, and early latent syphilis:** Benzathine penicillin 2.4 million units IM x 1.

    Some authorities advocate 3 weekly doses of 2.4 million units benzathine penicillin IM for HIV-infected patients.
  - **Follow-up:** Clinical evaluation and serology at 3, 6, 9, 12, and 24 months. If symptoms persist or recur, or if there is a 4-fold increase in titer of nontreponemal test, CSF exam and retreatment. If titer does not decrease within 6-12 months, strongly consider CSF exam and retreatment. Retreatment: 2.4 million units benzathine penicillin q mo x 3 if CSF negative.
  - **Penicillin allergy** – must monitor closely because data supporting efficacy of alternate treatments is limited.

- Doxycycline 100 mg PO bid x 14 days
- Ceftriaxone 1 gm IV or IM qd x 8-10 days
- Azithromycin 2 gm PO x 1 (*N Engl J Med* 2005;353:1236)
- **Late latent syphilis (syphilis > 1 year) and syphilis of unknown duration:** Treatment is based on CSF analysis.

  Early latent syphilis is established by 1) documented seroconversion or ≥4-fold increase in titer of nontreponemal test; 2) unequivocal symptoms of primary or secondary syphilis; 3) sex partner with documented primary or secondary or early latent syphilis; or 4) positive tests from a person whose only exposure was within 12 months.

  - **CSF normal:** Benzathine penicillin 2.4 million units IM weekly x 3. Follow-up and retreatment as described above for primary, secondary, and early latent syphilis.
  - **CSF abnormal:** Treat for neurosyphilis. Note that CSF mononuclear pleocytosis and elevated protein may be due to HIV.
- **Neurosyphilis:** Clinical signs and symptoms: cognitive dysfunction, motor or cranial nerve deficits, ophthalmic or auditory symptoms, signs or symptoms of meningitis.
  - Preferred: Aqueous crystalline penicillin 18-24 million units/day delivered as 3-4 million units IV q 4 h or continuous infusion for 10-14 days.
  - Alternative: Procaine penicillin 2.4 million units IM qd plus probenecid 500 mg PO qd x 10-14 days.
  - Penicillin allergy: Ceftriaxone 2 gm/day IV or IM qd x 10-14 days. Concern for cross-allergy: skin test for penicillin sensitivity; desensitize if positive.
  - Follow-up: LP q 6 months until CSF cell count normal; VDRL and protein respond more slowly. Re-treat if cell count has not decreased at 6 months or CSF not normal at 2 years. Note that HIV infection is associated with delayed response (*Clin Infect Dis* 2004;38:1001).

■ TABLE 6-3: **Treatment of Syphilis in Patients with HIV Infection**

Form	Treatment	Follow-up VDRL/RPR	Expectation	Management
Primary, secondary, and early latent	Benz PCN 2.4 mil IM x 1	Month 3, 6, 9, 12, and 24	1) 4-fold ¬ in titer by 6-12 mo; 2) No 4-fold ? in titer 3) Symptoms and signs resolve	■ LP: Neg – Re-treat with Benz PCN 2.4 mil U IM weekly x 3 ■ LP: Pos – Treat for neurosyphilis
Late latent	Benz PCN 2.4 mil IM weekly x 3	Month 3, 6, 9, 12, and 24	1) 4-fold ¬ in titer by 6-12 mo; 2) No 4-fold ? in titer 3) Symptoms and signs resolve	■ LP: Neg – Re-treat with Benz PCN 2.4 mil U IM weekly x 3 ■ LP: Pos – Treat for neurosyphilis
Neuro-syphilis	Aq PCN 18-24 mil U/d x 10-14 d	CSF exam q 6 mo until cell count normal	CSF WBC ¬ at 6 months and CSF normal at 2 yrs	If CSF cell count not ¬ at 6 mo *or* CSF not normal at 2 yrs, re-treat

*CSF WBC (attributed to syphilis) not decreased at 6 months; CSF changes positive at 2 years; persistent signs or symptoms of neurosyphilis; VDRL titer in CSF increased ≥4x at 6 months or titer ≥1:16 fails to decrease 2x at 6 months or 4x at 12 months.

■ TABLE 6-4: **Penicillin Allergy Skin Test and Desensitization (*MMWR* 2002;51[RR-6]:28)**

Penicillin Skin Test:

- Reagents: Benzylpenicilloyd poly-L-lysine (*Pre-Pen*) + minor determinant if available. If minor determinant is not available, use *Pre-Pen* only.
- Positive control for epicutaneous test is commercial histamine (1 mg/mL).
- Negative control is diluent, usually saline.
- Sequence: Epicutaneous test ∅ Positive (wheal >4 mm at 15 min) = penicillin allergy; negative histamine control + negative prick test = unreliable; positive histamine test + negative prick test = do intradermal test.
- Epicutaneous (prick) test: Drops on forearm pierced with #26 needle without blood wheal >4 mm at 15 min is positive.
- Intradermal test: 0.02 mL intradermal injection forearm with #26 or #27 needle; at 15 min a wheal >2 mm larger than negative controls and the initial wheal = positive

Desensitization:

- Indication: Positive skin test.
- Route: Oral or IV; oral is safer and easier.
- Site: Hospital setting.
- Time: Requires 4 hours.
- Schedule: Administer every 15 minutes using the following amount in 30-mL aliquots for oral administration.

Dose	Units/mL	mL	Units	Dose	Units/mL	mL	Units
1	1,000	.10	100	**8**	10,000	1.20	12,000
2	1,000	.20	200	**9**	10,000	2.40	24,000
3	1,000	.04	400	**10**	10,000	4.80	48,000
4	1,000	.80	800	**11**	80,000	1.00	80,000
5	1,000	1.60	1,600	**12**	80,000	2.00	160,000
6	1,000	3.20	3,200	**13**	80,000	4.00	320,000
7	1,000	6.40	6,400	**14**	80,000	8.00	640,000

7 Systems Review
(Complications are listed by organ system)

Cardiopulmonary Complications

Dilated Cardiomyopathy (*N Engl J Med* 1998;339:1153)

CAUSE: Unknown,

FREQUENCY: 6% to 8% for symptomatic cardiomyopathy in longitudinal studies in the pre-HAART era (*Eur Heart J* 1992;13:1452; *Clin Immunol Immunopathol* 1993;68:234). Rates of left ventricular diastolic dysfunction with routine echo are much higher and correlate with stage of immunosuppression (*Heart* 1998;80:184). Rates have decreased during the HAART era (*Am Heart J* 2006;151:1147).

SYMPTOMS: CHF, arrhythmias, cyanosis, and/or syncope

DIAGNOSIS: Echocardiogram showing ejection fraction <50% normal ± arrhythmias on EKG, not otherwise explained.

TREATMENT (*Am J Cardiol* 1999;83:1A)

- **HAART:** Use non-AZT-containing regimen if possible.
- **ACE inhibitor:** Enalapril 2.5 mg bid; titrate up to 20 mg bid. Alternatives: Captopril 6.25 mg tid up to 50 mg tid or lisinopril 10 mg/day titrated up to 40 mg/day
- **Persistent symptoms:** Add diuretic: hydrochlorothiazide 25-50 mg/day, furosemide 10-40 mg/day (up to 240 mg bid) or spironolactone 25 mg/day (up to 50 mg bid)
- **Refractory:** Consider digoxin 0.125-0.25 mg/day
- **Other options:** Treat hypertension, treat hyperlipidemia, discontinue EtOH, discontinue cocaine, discontinue AZT; some recommend supplemental carnitine, and/or selenium if deficient.

Cardiovascular Disease Associated with Antiretroviral Agents

Pulmonary Hypertension (see *Adv Cardiol* 2003;40:197)

CAUSE: Possible genetic predisposition (*Ann NY Acad Sci* 2001;946:82)

FREQUENCY: Infrequent (0.5%); does not correlate well with CD4

count. Histology is similar to primary pulmonary hypertension (*Chest* 1991;100:1268).

SYMPTOMS: Major symptom is exertional dyspnea. Other symptoms are exertional chest pain, syncope, cough, hemoptysis, and fatigue.

DIAGNOSIS: X-ray shows enlarged pulmonary trunk or central pulmonary vessels (early), massive right ventricular and right atrial enlargement (late). Echo shows dilated right atrium and ventricle ± tricuspid insufficiency. Doppler echo shows pulmonary arterial systolic BP >30 mm Hg. The best test is cardiac catheterization to show increased pulmonary artery pressure, increased right atrial pressure, and normal pulmonary capillary pressure. Lung scan and pulmonary function tests are normal.

TREATMENT (usually progressive despite treatment)

- **HAART:** Some reports show impressive improvement with HAART (*Clin Infect Dis* 2004;38:1178), but others dispute this (*Clin Infect Dis* 2004;39:1549).
- **Iloprost:** 2.5-5 mcg inhalations 6-9x/day (*Eur Repir J* 2004;23:321).
- **Epoprostenol** infusions at 8-24 ng/kg/min (*Am J Respir Crit Care Med* 2003;167:1433)
- **Diuretics**
- **Oral anticoagulant**
- **Sildenafil** 25 mg/day. Increase by 25 mg every 3 to 4 days up to 25 mg qid (*AIDS* 2001;15:1747; *AIDS* 2002;16:1568; *N Engl J Med* 2000;343:1342). Note drug interactions with antiretroviral agents.

DERMATOLOGIC COMPLICATIONS

Cryptococcosis (*Clin Infect Dis* 2000;30:652)

CAUSE: Disseminated cryptococcosis, usually from a pulmonary portal of entry

PRESENTATION: Nodular, papular, follicular, or ulcerative skin lesions; may resemble molluscum. Usual locations are face, neck, scalp.

DIAGNOSIS: Serum cryptococcal antigen assay is usually positive. Skin biopsy with Gomori methenamine silver stain shows typical encapsulated, budding yeast, and positive culture. Perform LP in any patient with a positive serum cryptococcal antigen or culture for *C. neoformans*.

TREATMENT: If negative LP, fluconazole 400 mg/day PO x 8 weeks, then 200 mg/day. If positive LP.

Dermatophytic Infections

DEFINITION: Fungal infection of skin, hair, and nails

CAUSE: *Tinea rubrum, T. mentagrophytes, M. canis, E. floccosum, T. tonsurans, T. verrucosum, T. soudanense* (*Candida* causes typical nail and skin lesions), *Malassezia furfur* causes tinea versicolor. (Note: *Candida* and *M. furfur* are not dermatophytes.)

PRESENTATION

- ***T. pedis*:** Interdigital pruritis, scaling, fissures and maceration. Concomitant nail dystrophies seen frequently. Plantar and moccasin variants seen ± interdigital involvement. Pruritic, red lesions between toes ± interdigital fissures, extension to adjacent skin and nails, scaling is always present.
- **Onychomycosis:** Starts with discoloration and thickening, usually on distal nail at one side and spreads toward the other side and toward the cuticle, leaving heaped-up keratinous debris.
- ***T. corporis*:** Circular erythematous scaling that spreads with central clearing (ringworm).
- ***T. cruris*:** Red scaly patch on inner thigh with sharply demarcated borders.

FORMS: Tinea corporis (ringworm), T. cruris (jock itch), T. pedis (athlete's foot), T. unguium or onychomycosis (nail involvement), and tinea capitis (ringworm of scalp)

DIAGNOSIS: Scrapings of skin lesion or discolored nail bed for KOH preparation.

TREATMENT

- **Onychomycosis:** Topical therapy is usually not effective.
  - Preferred treatment: Terbinafine (*Lamisil*) 250 mg/day x 8 weeks (fingernails) or 12 weeks (toenails). Terbinafine is hepatotoxic and is expensive but has better long-term results than itraconazole (*Brit J Dermatol* 1999;141[Suppl 56]:15).
  - Itraconazole (*Sporanox*) "pulse therapy," 400 mg/day for 1 week/month x 2 months (fingernails) or x 3 months (toenails). Main concerns are hepatotoxicity, drug interactions, cardiotoxicity, and cost of treating a benign infection.
- **Tinea corporis, tinea cruris, tinea pedis:** Topical agent for 2 weeks

(T. cruris) to 4 weeks (T. pedis):

- Clotrimazole (*Lotrimin*)* 1% cream or lotion bid
- Econazole (*Spectazole*) 1% cream qd or bid
- Ketoconazole (*Nizoral*) 2% cream qd
- Miconazole (*Monostat-Derm*)* 2% cream bid
- Butenafine (*Mentax*) 1% cream
- Terbinafine (*Lamisil*)* 1% cream or gel qd or bid
- Tolnaftate (*Tinactin*)* 1% cream, gel, powder, solution, or aerosol bid
- Treatment is expensive

* Available over-the-counter.

- **Refractory, chronic, or extensive disease:** Terbinafine 250 mg qd x 2 to 4 weeks; itraconazole 100-200 mg qd x 2 to 4 weeks. Griseofulvin microsized 250-500 mg bid. Griseofulvin should be last of treatment options.

Drug Eruptions

CAUSE: Most common are antibiotics, especially sulfonamides (TMP/SMX), beta-lactams, anticonvulsants, NNRTIs.

PRESENTATION: Most common – morbilliform, exanthematous, usually pruritic ± low grade fever; usually within 2 weeks of new drug and days of re-exposure. Less common and more severe forms:

- Urticaria: Intensely pruritic, edematous, and circumscribed
- Anaphylaxis: Laryngeal edema, nausea, vomiting ± shock
- Hypersensitivity syndrome: Severe reaction with rash and fever ± hepatitis, arthralgias, lymphadenopathy, and hematologic changes with eosinophilia and atypical lymphocytes, usually at 2 to 6 weeks after drug is started (*N Engl J Med* 1994;331:1272). See abacavir and nevirapine

Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous / Skin Rash / Dermatitis			
Erythema, with or without pruritis	A. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation, with or without pruritis (without the presence of any additional constitutional findings as described in Grade OR typical target lesions without blistering, vesicles, or ulcerations in the lesions. B. Urticaria	A.Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation, with or without pruritis, together with any of the following constitutional findings considered related to study drug: 1.5 x ULN AST, ALT or 2 x baseline if baseline > ULN. 2.Fever, >39o C 3.Blistering and/or vesiculation of cutaneous eruptions 4.Any site of mucosal lesions; B.Angioedema; OR C.Exfoliative dermatitis, defined as severe widespread erythema and dry scaling of the skin, with generalized superficial lymphadenopathy, and with other constitutional findings such as fever, weight loss, hypoproteinemia possibly related to study drug; OR D.Diffuse rash and serum sickness-like reactions, defined as a clinical symptom complex manifested as fever, lymphadenopathy, edema, myalgia, and/or arthralgia; OR E.Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus one of the following: 1.Cutaneous bullae, sometimes confluent with widespread sheet-like detachment of skin (<10% body surface area), (Nikolski's sign) (Stevens Johnson Syndrome, SJS). 2.Two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause.	Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus cutaneous bullae with widespread sheet-like detachment of skin (>10% of body surface area), (Nikolski's sign), (SJS/Toxic Epidermal Necrolysis (TEN) overlap syndrome; TEN)

- Toxic epidermal necrolysis: Epidermal necrosis with scalded skin appearance ± mucous membrane involvement; mortality – 50% (*N Engl J Med* 1994;331:1272)

TREATMENT: In severe and very symptomatic reactions, discontinue implicated agent

- Pruritic uncomplicated drug rashes: antihistamines, topical antipruritics, and topical corticosteroids
- Stevens-Johnson Syndrome and toxic epidermal necrolysis: Severe cases are managed as burns with supportive care; corticosteroids are not indicated (*Cutis* 1996;57:223).

Folliculitis

CAUSE: Bacterial folliculitis due to *Staphylococcus aureus* is most common. Other causes include *Pityrosporum ovale* (intrafollicular yeast), *Demodex folliculorum* (intrafollicular mite), and eosinophilic folliculitis, in which biopsy shows eosinophilic inflammation without a detectable infectious agent.

PRESENTATION: Follicular papules and pustules on face, trunk, and extremities; usually very pruritic causing excoriations; multiple exacerbations and spontaneous remissions; usually seen with CD4 counts 50-250 cells/mm^3. Folliculitis may reactivate with immune reconstitution.

DIAGNOSIS: Clinical presentation and biopsy: follicular inflammation ± follicular destruction and abscess formation. Multiple eosinophils destroying the hair follicle wall and eosinophilic abscesses are seen in eosinophilic folliculitis. Culture of pustule may grow *S. aureus*.

Scabies (*MMWR* 2002;51[RR-6]:68)

CAUSE: *Sarcoptes scabiei* (mite)

PRESENTATION: Small red papules that are intensely pruritic, especially at night. Sometimes presentation is the "burrow," a 3- to 15-mm line which represents the superficial tunnel the female mite digs at 2 mm/day to lay eggs. Usual locations are the interdigital webs of the fingers, volar aspect of the wrist, periumbilical area, axilla, thighs, buttocks, genitalia, feet, and breasts. Scabies crostosus (crusted or "Norwegian" scabies) is a severe form seen in compromised hosts, including AIDS patients. There is uncontrolled spread to involve large areas, sometimes the total skin surface with scales and crusts that show thousands of mites.

DIAGNOSIS: The mite is 0.4 x 0.3 mm, 8-legged, and shaped like a turtle. It is visible to the naked eye but burrowing precludes detection. Scrape infected area, place on a slide with a coverslip, and examine under 10x magnification to demonstrate mites or eggs.

TREATMENT: All family members and close contacts must be treated at the same time.

- Rash and pruritus may persist up to 2 weeks post-treatment – warn patients.
- Bedding and clothing must be decontaminated. Machine wash in hot water and machine dry with high heat, or dry clean.
- **Itching:** Hydroxyzine (*Atarax*) or diphenhydramine (*Benadryl*)

Seborrheic Dermatitis

CAUSE: The yeast *Pityrosporum* is recovered from lesions, but it may not play a central role in HIV-associated seborrhea (*J Am Acad Dermatol* 1992;27:37).

PRESENTATION: Erythematous plaques with greasy scales and indistinct margins on scalp, central face, post-auricular area, presternal, axillary, and occasionally pubic area

DIFFERENTIAL: Psoriasis and dermatophytic infections

DIAGNOSIS: Clinical features

TREATMENT

- **Topical steroid:** Mid-potency such as triamcinolone 0.1% or weaker (desonide 0.05%), hydrocortisone 2.5% for the face ± ketoconazole 2% cream applied twice per day for the duration of the flare only.
- **Shampoos:** Tar-based (*Z-tar, Pentrax, DHS tar, T-gel, Ionil T plus*), selenium sulfide (*Selsun, Exelderm*), or zinc pyrithione (*Head & Shoulders, Zincon, DHS zinc*) applied daily, or ketoconazole shampoo applied twice per week.

GASTROINTESTINAL COMPLICATIONS

Anorexia, Nausea, Vomiting

MAJOR CAUSES: Medications (especially antiretrovirals, antibiotics, opiates, and NSAIDs), depression, intracranial pathology, GI disease, hypogonadism, pregnancy, lactic acidosis, acute gastroenteritis

HAART: Nausea ± vomiting and/or abdominal pain are reported in 2% to 17% of patients given PIs (*J Acquir Immune Defic Syndr* 2004;37:1111). The most common agents, in rank order, are RTV, IDV, LPV/r, ATV, and SQV. The effect is dose-related. Similar symptoms are frequent with AZT.

EVALUATION: If relationship to medication unclear, consider lactic acid level, GI evaluation (endoscopy, CT scan), intracranial evaluation (head CT scan or MRI). Interruption of antiretroviral regimen or single-drug switch may be necessary.

TREATMENT: Treat underlying condition.

- **Nausea and vomiting**
  - Metoclopramide (*Reglan*) 5-10 mg PO q6-8h; ondansetron (*Zofran*) 0.2 mg/kg IV or IM.
  - Note: Phenothiazines may cause dystonia. *Zofran* efficacy is established only for cancer chemotherapy.

Aphthous Ulcers

CAUSE: Unknown

DIFFERENTIAL: HSV, CMV, drug-induced ulcers; biopsy recommended for non-healing ulcers.

CLASSIFICATION

- **Minor:** <1 cm diameter, usually self-limiting (with healing in 10 to 14 days)
- **Major:** >1 cm, deep, prolonged, heals slowly, causes pain, and may prevent oral intake (*AIDS* 1992;6:963; *Oral Surg Oral Med Oral Pathol* 1996;81:141)

TREATMENT

- **HAART:** Response of aphthous ulcers may be dramatic (Alegre M, *Int J Infect Dis* 7/18/2006;e-pub).
- **Topical treatment 2x to 4x/day**
  - Triamcinolone hexacetonide in *Orabase* – preferred (*J Am Dent*

Assoc 2003;134:200)

- **Oral and intralesional therapy (refractory cases)**
  - Prednisone 40 mg/day PO x 1 to 2 weeks then taper (*Am J Clin Dermatol* 2003;4:669)

Candidiasis, Oropharygeal (thrush)

Diarrhea, Acute

(Acute diarrhea defined as ≥3 loose or watery stools/day for 3 to 10 days)

DIAGNOSTIC EVALUATION

Medication-related

- Main antiretroviral agents: All PIs, especially nelfinavir, lopinavir/ritonavir, saquinavir, and didanosine (buffered formulation)
- Management (*Clin Infect Dis* 2000;30:908)
  - Loperamide 4 mg, then 2 mg every loose stool, up to 16/day
  - Calcium 500 mg bid; psyllium 1 tsp qd-bid or 2 bars qd-bid; oat bran 1500 mg bid

Pathogen detection (*Clin Infect Dis* 2001;32:331; *Arch Pathol Lab Med* 2001;125:1042)

- Blood culture: MAC, *Salmonella*
- Stool culture: *Salmonella, Shigella, C. jejuni, Vibrio, Yersinia, E. coli* 0157
- Stool assay for *C. difficile* toxin A and B
- O&P with Ova and Parasites

Radiology

- CT scan: most helpful with pseudomembranous colitis, CMV colitis, and lymphoma

Endoscopy: Most useful for CMV, Kaposi's sarcoma, and lymphoma

CAMPYLOBACTER JEJUNI

FREQUENCY: 4% to 8% of HIV-infected patients with acute diarrhea; rates are increased up to 39-fold in MSM (*Clin Infect Dis* 1997;24:1107; *Clin Infect Dis* 1998;26:91; *Clin Infect Dis* 2005;40:S152)

CLINICAL FEATURES: Watery diarrhea or bloody flux, fever, fecal leukocytes variable; any CD4 count

DIAGNOSIS: Stool culture

TREATMENT (*Clin Infect Dis* 2001;32:331): Erythromycin 500 mg PO qid x 5 days; fluoroquinolone resistance rates are >20%.

CLOSTRIDIUM DIFFICILE

FREQUENCY: *C. difficile* is the most common bacterial enteric pathogen and also the most common in patients with AIDS. Risk factors are antibiotic exposure, hospitalization, and advanced age. Up to 36% of HIV-infected patients with acute diarrhea (*Diag Microbiol Infect Dis* 2002;44:325). It is unclear if the high rates in AIDS patients reflect immunodeficiency plus antibiotic exposure or only antibiotic exposure (*Clin Infect Dis* 2006;42:1215).

CLINICAL FEATURES: Watery diarrhea, fecal WBCs variable; fever, hypoalbuminemia, and leukocytosis are common. Nearly all patients have recent (within 2 week of onset) exposure to antibacterial agents, especially clindamycin, ampicillin, and cephalosporins; less commonly – macrolides, TMP-SMX, and rifampin. Antiretrovirals, antivirals, antifungals, dapsone and INH are not implicated. May occur with any CD4 count; low CD4 count is not clearly associated with increased risk of this complication or with more severe disease.

DIAGNOSIS

- Stool toxin assay: Tissue culture (preferred) or EIA (may need to repeat toxin assay). Some labs use the EIA for common antigen screening and then the cytotoxin assay on positives.
- Endoscopy: pseudomembranous colitis (PMC), colitis, or normal (this procedure is not usually indicated)
- CT scan: Colitis with thickened colonic mucosa. With CD4 counts <50 cells/mm^3, the main differential is CMV colitis.

TREATMENT (*N Engl J Med* 2002;346:334)

- Vancomycin 125 mg PO qid x 10 to 14 days (preferred for serious cases or with delayed response to metronidazole)
- Metronidazole 250 mg PO qid or 500 mg PO tid x 10 to 14 days (preferred)
- Antiperistaltic agents such as loperamide (*Imodium*) or atropine/diphenoxylate (*Lomotil*) are contraindicated.

RESPONSE: Fever usually resolves within 24 hours, and diarrhea resolves in an average of 5 days. About 20% to 25% have relapses, usually 3 to 14 days after treatment has stopped. Most respond to treatment unless ileus is present; relapse post-therapy in 15% to 20% (*N Engl J Med* 2002;346:334).

ENTERIC VIRUSES

FREQUENCY: 15% to 30% of HIV infected patients with acute diarrhea

CLINICAL FEATURES: Watery diarrhea, acute, but one-third become chronic; any CD4 cell count

DIAGNOSIS: Major agents: adenovirus, astrovirus, picornavirus, calicivirus (*N Engl J Med* 1993;329:14); clinical laboratories cannot detect these viruses.

TREATMENT: Supportive treatment with fluids and antiperistaltic agents.

IDIOPATHIC

FREQUENCY: 25% to 40% of HIV infected patients with acute diarrhea

CLINICAL FEATURES: Variable noninfectious causes; rule out medications (including lactic acidosis), dietary, irritable bowel syndrome.

DIAGNOSIS: Negative studies including culture, Ova and Parasites examination, and C.Difficile toxin assay.

EMPIRIC TREATMENT, SEVERE ACUTE IDIOPATHIC DIARRHEA

- Ciprofloxacin 500 mg PO bid
- Ofloxacin 200-300 mg PO bid x 5 days ± metronidazole (*Arch Intern Med* 1990;150:541; *Ann Intern Med* 1992;117:202; *Clin Infect Dis* 2001;32:331).

Diarrhea, Chronic

(AIDS-defining criteria are chronic diarrhea with >2 loose or watery stools/day for ≥30 days.)

CRYPTOSPORIDIA

CYTOMEGALOVIRUS

ENTAMOEBA HISTOLYTICA

FREQUENCY: 1% to 3% of chronic diarrhea in AIDS patients

CLINICAL FEATURES: Colitis; bloody stools; cramps; no fecal WBCs (bloody stools); most are asymptomatic carriers; any CD4 cell count

DIAGNOSIS: Stool Ova and Parasites examination. Distinguish from non-pathogenic *E. dispar*, which is a non-pathogen and most common in positive stool exams (*J Clin Microbiol* 2003;41:5041; *Lancet* 2003;361:1025).

TREATMENT: Metronidazole 500-750 mg PO or IV tid x 5 to 10 days, then iodoquinol 650 mg PO tid x 21 days or paromomycin 500 mg PO qid x 7 days

GIARDIA LAMBLIA

FREQUENCY: 1% to 3% of chronic diarrhea in AIDS patients (not uniquely susceptible)

CLINICAL FEATURES: Enteritis; watery diarrhea ± malabsorption, bloating; flatulence; any CD4 cell count

DIAGNOSIS: Antigen detection

TREATMENT: Metronidazole 250 mg PO tid x 10 days

ISOSPORA BELLI (see Chapter 6)

MICROSPORIDIA: ENTEROCYTOZOON BIENEUSI OR ENTEROCYTOZOON (SEPTATA) INTESTINALIS (see Chapter 6)

MYCOBACTERIUM AVIUM COMPLEX (MAC) (see Chapter 6)

IDIOPATHIC (PATHOGEN-NEGATIVE)

FREQUENCY: 20% to 30% of cases of chronic diarrhea in AIDS patients who undergo a full diagnostic evaluation including endoscopy

CLINICAL FEATURES: Usually low-volume diarrhea that resolves spontaneously or is controlled with antimotility agents (*Gut* 1995;36:283). Typically not associated with significant weight loss and often resolves spontaneously.

DIAGNOSIS: Biopsy shows villus atrophy, crypt hyperplasia/no identifiable cause despite endoscopy with biopsy and EM for microsporidia (*Clin Infect Dis* 1992;15:726). These histologic changes are unlikely to explain diarrhea because they are seen in symptom-free persons with HIV (*Lancet* 1996;348:379). With pathogen-negative, persistent, large volume diarrhea, must rule out KS and lymphoma.

TREATMENT: Supportive care (frequent small feedings, bland food, avoid caffeine and lactose): atropine/diphenoxylate (*Lomotil*) or loperamide (*Imodium*), nutritional support. Consider gluten-free diet.

Esophagitis

■ TABLE 7-1: **Esophageal Disease in Patients with HIV Infection**

	Candida	Cytomegalo-virus (CMV)	Herpes Simplex Virus	Aphthous Ulcers
Frequency	50% to 70%	10% to 20%	2% to 5%	10% to 20%
Clinical features				
Dysphagia	+++	+	+	+
Odynophagia	++	+++	+++	+++
Thrush	50% to 70%	<25%	<25%	<25%
Oral ulcers	Rare	Uncommon	Often	Uncommon
Pain	Diffuse	Focal	Focal	Focal
Fever	Infrequent	Often	Infrequent	Infrequent
Diagnosis				
Endoscopy	■ Usually treated empirically ■ Pseudo-membranous plaques; may involve entire esophagus	■ Biopsy required for diagnosis ■ Erythema and erosions/ulcers, single or multiple discrete lesions, often distal.	■ Biopsy required for diagnosis ■ Erythema and erosions/ulcers, usually small, coalescing, shallow	■ Similar in appearance and location to CMV ulcers ■ Biopsy required to rule out CMV and HSV
Micro-biology	■ Brush: Yeast and pseudo-mycelium on KOH prep or PAS ■ Culture with sensitivities may be useful with suspected resistance	■ Biopsy: Intracellular inclusions and/or positive culture. ■ Highest yield with histopath of biopsy and culture. Culture not recommended false positives.	■ Brush/biopsy: Intracyto-plasmic inclusions + multinucleate giant cells, FA stain, and/or positive culture.	■ Negative studies for *Candida*, HSV, CMV, and other diagnoses.

■ TABLE 7-1: **Esophageal Disease in Patients with HIV Infection *(Continued)***

	Candida	Cytomegalo-virus (CMV)	Herpes Simplex Virus	Aphthous Ulcers
Treatment				
Acute	■ Fluconazole 200 mg/day PO, up to 800 mg/day. ■ Refractory cases: Caspofungin 70 mg/day IV x 1 then 50 mg/day *or* micofungin 150 mg qd *or* itraconazole solution 200 mg/day or voriconazole 200 mg PO *or* IV bid (many drug interactions) ■ Amphotericin 0.5-0.7 mg/kg/day IV	■ Ganciclovir 5 mg/kg IV bid x 2 to 3 weeks or valganciclovir 900 mg bid x 3 weeks, then 900 mg/day (when able to swallow). ■ Foscarnet 40-60 mg/kg q8h x 2 to 3 weeks. ■ HAART ■ Efficacy of antiviral treatment is 75%.	■ Acyclovir 200-800 mg PO 5x/day or 5 mg/kg IV q8h x 2 to 3 weeks or valacyclovir 1 gm PO tid (when able to swallow).	■ Prednisone 40 mg/day PO x 7 to 14 days, then taper 10 mg/week or more slowly. ■ Thalidomide 200 mg/day PO (*BJM* 1989;298:432; *J Infect Dis* 1999;180:61). ■ Corticosteroids by intralesional injection.
Maintenance	■ Fluconazole 100-200 mg/day PO (for recurrent or severe disease) ■ May need alternatives (above) for fluconazole-resistant cases.	■ Maintenance treatment with valgancyclovir recommended with relapsing disease	■ Maintenance treatment is arbitrary; acyclovir 200-400 mg PO 3 to 5x daily.	■ None

Notes:

1. One-third of AIDS patients in pre-HAART era developed esophageal symptoms (*Gut* 1989;30:1033). Esophageal ulcers are usually due to CMV (45%), or they are idiopathic/aphthous ulcers (40%); HSV accounts for only 5% (*Ann Intern Med* 1995;122:143).
2. With endoscopy a diagnosis is established in about 70% to 95% (*Arch Intern Med* 1991;151:1567). Response to empiric treatment often precludes need for endoscopic diagnosis of *Candida* esophagitis. Yield with barium swallow 20-30%.
3. Other diagnostic considerations: Drug-induced dysphagia (*Am J Med* 1988;88:512), including AZT (*Ann Intern Med* 1990;162:65) and ddC; infection, including *M. avium*, TB, cryptosporidia, *P. carinii*, primary HIV infection, histoplasmosis, and tumor, including KS or lymphoma (*BMJ* 1988;296:92; *Gastrointest Endosc* 1986;32:96).
4. Fluconazole is the preferred treatment for *Candida* because of established efficacy, more predictable absorption, and fewer drug interactions compared with voriconazole, ketoconazole, and itraconazole.

DIFFERENTIAL: Consider non-HIV-related causes, especially if CD4 is >200/mm^3. Most common are medication- or food-related esophagitis and GERD. With CD4 <200/mm^3: common – *Candida*; common – CMV, idiopathic; less common – HSV; rare – TB, *M. avium*, histoplasmosis, PCP, cryptosporidia, Kaposi's sarcoma, lymphoma

LIVER AND PANCREAS DISEASE

Differential diagnosis of abnormal LFTs in the patient with HIV infection (*JAMA* 2004;292:243)

HEPATITIS

- **HAV:** Acute infection (*Clin Infect Dis* 2001;32:297)
- **HBV flare** (with HBsAg):
  1. Discontinuation of TDF, 3TC, FTC (*J Hepatol* 1998;29:306; *J Infect Dis* 2002;186:23)
  2. Emergence of resistance of HBV to FTC or 3TC, less commonly to TDF
  3. Immune reconstitution
- **HCV**:

ALCOHOL TOXICITY OR OTHER SUBSTANCE ABUSE (*J Acquir Immune Defic Syndr* 2001;27:4426)

CHRONIC NONVIRAL: Alcoholic, nonalcoholic steahepatitis, autoimmune hepatitis, hemochromatosis, sarcoidosis

DRUG TOXICITY: Acetaminophen (*Clin Infect Dis* 2004;38:565), antiretroviral agents (see below), INH, statins, etc.

HYPERSENSITIVITY: Phenytoin, ABC, TMP-SMX, NVP

OPPORTUNISTIC INFECTIONS INCLUDING MAC AND CMV (*Am J Gastroenterol* 1988;83:1)

TB

HAART

- Immune reconstitution inflammatory syndrome (*J Acquir Immune Defic Syndr* 2001;27:426; *Clin Infect Dis* 2004;38:S65)
- NVP hepatitis
- PI/NNRTI transaminitis: 15-30% rate is increased 2-fold with HCV coinfection (*Clin Infect Dis* 2002;34:831; *JAMA* 2000;283:74; *Hepatology* 2002;35:182)

- Steatosis: primarily due to d4T, also AZT and ddI, usually in association with lactic acidosis;
- Dose modifications of antiretroviral drugs with severe hepatic disease: NRTIs: none except ABC – Child-Pugh class A – 200 mg bid, class B or C – contraindicated; NNRTIs: None; caution with or avoid NVP; PIs: NFV – standard; IDV/r – 200/100 mg bid; LPV/r – may need therapeutic drug monitoring; ATV – 300 mg qd for Child-Pugh class B; avoid for class C (*Clin Infect Dis* 2004;40:174).

Cholangiopathy, AIDS (*Dig Dis* 1998;16:205)

CAUSE: *Cryptosporidium* is the most common identified microbial cause. Other causes: microsporidia, CMV, and *Cyclospora*. About 20% to 40% are idiopathic.

FREQUENCY: Relatively rare and seen primarily in late stage AIDS

PRESENTATION: Right upper quadrant pain, LFTs show cholestasis. Late stage HIV with CD4 count <100 cells/mm^3.

DIAGNOSIS: Alkaline phosphatase levels are high, often ≥8x ULN. Level predicts prognosis. Usual method to establish the diagnosis is ERCP (preferred); ultrasound is 75% to 95% specific

TREATMENT: HAART is the most important treatment. Also based on cause. Treat pathogen when possible – CMV and *Cyclospora*. Usual treatment is mechanical and based on lesion.

- **Papillary stenosis:** ERCP with sphincterectomy for pain relief
- **Cholangiopathy without papillary stenosis:** Ursodeoxycholic acid (*Actigall*) 300 mg PO tid (*Am J Med* 1997;103:70). Experience limited.
- **Isolated bile duct structure:** Endoscopic stenting

RESPONSE: Average survival in HAART era is 9 months, worse with alkaline phosphatase >1000 IU/L (*Am J Gastroenterol* 2003;98:2176). HAART significantly improves this prognosis.

Viral Hepatitis

■ TABLE 7-2: **Viral Hepatitis**

Type	Seroprevalence* Transmission	Incubation Period	Diagnosis	Course
A	Fecal-oral; food; unknown source in 50% ■ Gen. population: 40% to 50% immune ■ Acute hepatitis: 50%	15 to 50 days	■ Acute: IgM ■ Prior infection or vaccination: Total HAV antibody (IgG)	■ Fulminant and fatal in 0.6%; fulminant in 15% with HCV ■ Very high ALT/AST ■ Self limited in >99% ■ No chronic form ■ Hep A vaccine is inactivated therefore safe in HIV positive. Also most individuals acquire Hep A as children- a minor illness. Each year approximately 1.5 million cases of hepatitis A occur globally.Very common in children
B	Sex, blood, and perinatal ■ Seroprevalence of HbsAb: vaccinated <10 years previously 90%; general population 3-14% ■ Seroprevalence of HbsAg (chronic HBV) ■ Between 10-18% of South African adults are hepatitis B virus carriers (HepB Ag)	45 to 160 days	■ Acute: HBsAg + anti-HBc IgM ■ Chronic: HBsAg x 6 months + anti-HBc IgG ■ Vaccinated: HBsAb	■ Fulminant and fatal in 1.4% ■ Chronic hepatitis in 6% in general population; 10% to 15% in patients with AIDS
C	Blood (>sex and perinatal) ■ General population: < 1%	15 to 50 days		■ Chronic hepatitis after acute HCV in 80% ■ Cirrhosis in 10% to 15% in 20 years but increased risk of progression with HIV coinfection or ETOH ■ HCV has little or no effect on rate of HIV infection progression

* Seroprevalence for adults in the U.S.

Hepatitis B (see Nuñez M and Soriano V, *Lancet Infect Dis* 2005;5:374)

DIAGNOSIS: Positive serology for HBsAg for ≥20 weeks indicates chronic infection.

■ TABLE 7-3: **Diagnostic Tests for Hepatitis B**

Test	Chronic HBV	Chronic HBcAg neg	Healthy Carrier	Vaccinated Immune*
HBsAg	+	+	+	—
HBsAb	—	—	—	+
HBeAg	+	—	—	—
Anti-HBcAg	—	—	—	+*
HBV DNA	$>10^5$	$>10^3$	$>10^3$	—
ALT	≠	≠	NI	NI

*Vaccinated: HBsAb
Immune post-infection: Anti-HBc and HBsAb; NI = Normal

NATURAL HISTORY: Primary HBV infection in adults is usually subclinical and self-limited. About 6%-10% patients with HBV infection became chronic carriers, as indicated by persistent HBsAg ≥6 months (*J Acquir Immune Defic Syndr* 1991;4:416; *J Infect Dis* 1991;163:1138). Of these, about 25% develop chronic active hepatitis, which progresses to cirrhosis in 15% to 30% and confers a long-term risk of hepatic carcinoma. The risk of hepatic complications is associated with HBV replication as indicated by markers of viral replication: HBeAg and HBV DNA levels. Patients with HIV have higher rates of chronic HBV infection after acute infection (10-15%). Those with HBV/HIV co-infection have higher levels of HBV DNA, and are more likely to have HBeAg and higher rates of HBV-associated liver disease (*Clin Infect Dis* 2003;37:1678; *Lancet* 2002;360:1921; *J Acquir Infect Dis Syndr* 1991;4:416). It is unclear if HBV accelerates progression of HIV, but it does increase HAART-associated hepatotoxicity (*JAMA* 283;283:74; *Clin Liver Dis* 2003;7:475).

Coinfection with HIV and HBV is complicated because 1) HIV alters the natural history of HBV by impairing the immune response; 2) the rate of grade 3-4 hepatotoxicity to HIV antiretrovirals is increased substantially (*J Infect Dis* 2002;186:23); 3) the incidence of liver-related death due to HBV is magnified 17-fold (*Lancet* 2002;360:1921); 4) HIV coinfection increases the rate of HBV resistance to lamivudine to 94% in 4 years (*AIDS* 2006;20:863); and 5) management of each disease is confounded seriously by the presence of the other due to overlapping activities of the drugs used to treat both (*J Acquir Immune Defic Syndr* 2005;41:1035; *Clin Infect Dis* 2006;43:904; *J Hepatol* 2006;44:S65).

EVALUATION

- **Diagnosis:** Test for HBsAg, anti-HBc and anti-HBs. Interpretation of an isolated anti-HBc is unclear (*J Med Virol* 2000;62:450; *Clin Infect*

Dis 1998;26:895).

- **Evaluation:** Chronic HBV is defined by positive HBsAg >6 months. In these cases obtain HBeAg, HBsAb and HBV DNA levels. Severity of liver disease is evaluated at baseline and every 6 months with ALT, albumin, prothrombin time, platelet count, CBC and bilirubin. Some authorities recommend alfafetoprotein levels or ultrasound of the liver at 6- to 12-month intervals to monitor for hepatocellular carcinoma. It is not known whether HIV coinfection increases this risk (*Clin Infect Dis* 2005;40(suppl 3):S179). Liver biopsy is the best method to determine the grade (necroinflammatory activity) and stage (degree of fibrosis), but is usually unnecessary. The main indication is in patients with normal ALT and HBV DNA $<10^4$ c/mL.

MANAGEMENT

- **Negative screening tests:** Patients with negative HBsAg and anti-HBs should receive HBV vaccine.
- **Patients with chronic HBV co-infection** should 1) be advised to avoid or limit alcohol consumption; 2) be evaluated for HBV treatment, 3) choose antiretroviral regimens based on anti-HBV activity of nucleoside analog components (see below), and 4) be counseled on the risks of HBV transmission, including the need for contacts to be evaluated for HBV vaccine.
- **Patients with HBV/HIV co-infection may have exacerbation of hepatitis** due to: 1) discontinuation of NRTIs with anti-HBV activity (3TC, FTC, TDF); 2) emergence of HBV NRTI resistance (especially to 3TC and FTC) (*Clin Infect Dis* 1999;28:1032), 3) immune reconstitution with HAART with or without 3TC, FTC, or TDF (*Clin Infect Dis* 2004;39:1291) or 4) hepatoxicity of antiretroviral drugs .

MANAGEMENT OF HBV

HBsAg+ x 6 months

TESTS TO CLASSIFY: HBeAg, anti-HBeAg, quantitative HBV DNA, LFTs including ALT

TREATMENT INDICATIONS WITH HIV CO-INFECTION

- Evidence of HIV replication: HBeAg+ or HBV DNA $>10^5$ c/mL.
- Evidence of active liver disease: Elevated ALT, histology showing inflammation, or positive non-invasive method to assess hepatic fibrosis
- Drug selection with HIV/HBV coinfection (see below)
  - Nucleosides/nucleotides: Lamivudine reduces viral replication by mean of 4-5 $\log_{10}$ c/mL (40%-86%), but seroreversion of HBeAg is infrequent (20%-29% at 1 year), and seroreversion of HBsAg is

even less frequent (1-2%). HBV DNA replication and evidence of progressive liver disease recur when the drugs are stopped or resistance occurs (*Lancet Infect Dis* 2005;5:374). Therefore, treatment duration is ill-defined and may be indefinite. A major concern with lamivudine is the high rate of resistance mutations, especially in HIV coinfected patients.

- Nucleoside selection for coinfected patients
  - Treat HIV and HBV: HAART with TDF/FTC or TDF/3TC
  - Treat only HIV: Include ≥2 anti-HBV agent to avoid HBV flare with immune reconstitution

MONITORING

- NRTIs: Expect HBV DNA to decrease ≥1 $\log_{10}$ c/mL within 1 month; monitor HBV DNA q 3 months.

Hepatitis C (see *Ann Intern Med* 2003;138:197)

DIAGNOSIS: The standard test is anti-HCV detection by EIA with confirmation of positives by HCV RNA; the HCV RNA should be repeated if negative at 6 months because viremia may be intermittent. Unlike HIV, HCV antibody levels may also be low, especially with HIV co-infection, so HCV RNA levels are suggested when this diagnosis is suspected with negative screening serology (*Blood* 1993;82:1010; *J Infect Dis* 1994;170:433). False-negative screening serology is most common with CD4 cell counts <100/mm^3. Unlike HIV, HCV viral load does not correlate with progression.

EPIDEMIOLOGY: Less than 1% of South Africans have Hep C

Transmission rates (in absence of treatment or prophylaxis)

	HIV	HCV
Needle stick injury	0.3%	3%
Discordant couples male	13%/yr	3%/yr
Perinatal transmission	20% to 30%	2% to 5%

NATURAL HISTORY: HCV progresses to cirrhosis in 5% to 25% in 20 years; after cirrhosis, the rate of progression to liver failure is 1% to 2%/year and to hepatocellular carcinoma 1% to 7%/year (*N Engl J Med* 1995;332:1463; *N Engl J Med* 1992;327:1906; *N Engl J Med* 1999; 340:1228; *Gastroenterology* 1997;112:463).

MANAGEMENT

- All HCV/HIV co-infected patients should 1) be advised to abstain from alcohol use; 2) be informed about methods to prevent transmission of both infections (use condoms, avoid needle sharing); 3) receive vaccinations for HBV and HAV if susceptible; and 4) be

evaluated for HCV disease severity and possible treatment. For patients with cirrhosis, consider alfafetoprotein levels or ultrasound to detect hepatocellular cancer.

- HCV assessment: Baseline assessment should include evaluation of severity of liver disease including measurement of serum albumin, prothrombin time, platelet count, bilirubin, ALT, and CBC. ALT provides limited information about severity. Liver biopsy with histology provides the best information about HCV disease activity and fibrosis stage as a guide to HCV treatment decision, to estimate prognosis, and to identify other causes of liver injury (*Hepatology* 2001;33:196).
- **Goal:** The goal of HCV treatment is a sustained virologic response (SVR) defined as undetected HCV RNA 24 weeks after treatment completion, which appears to indicate HCV viral eradication.

RECOMMENDATIONS FOR EVALUATION AND TREATMENT

- **Pre-therapy: General evaluation**
  - *Lab:* CBC, ALT, AST, creatinine
  - *Assess comorbidities:* substance abuse, psychiatric disease, cardiopulmonary disease, renal disease
  - *Evaluate HIV status:* CD4 count, VL, active OIs
  - *Evaluate HCV status:* HCV genotype, HCV viral load, ALT

    Consider liver biopsy; if contraindicated, unavailable, or refused, may elect to give therapy without biopsy. (Liver biopsy is most important when SVR is less likely, as with genotype 1.)
  - *Counsel patient on benefits and risks*
  - Consider modification of HAART. Avoid ddI contraindicated with ribavirin and AZT (exacerbates treatment-related anemia).

THERAPY: PegIFN alfa 2a 180 mcg SC q week + ribavirin x48 weeks. The dose of ribavarin should be 800 mg PO qd for genotype 2/3; for genotype 1 a dose of 1000-2000 mg/day is preferred, although the trials were generally done with 800 mg/day. The 48-week duration applies to all genotypes.

MONITORING

- Reinforce: birth control now and for 6 months after completion of treatment
- Lab: CBC, ALT at weeks 2 and 4, then at 4- to 8-week intervals

  ANC <750/mm^3 – use G-CSF or reduce interferon

  <500/mm^3 – discontinue interferon; consider G-CSF

  Hgb <10 g/dL – consider EPO or reduce ribavirin 200 mg/d

<8 g/dL – discontinue ribavirin; consider EPO

HIV: VL + CD4 count at 12-week intervals

Thyroid: TSH at 3- to 6-month intervals

- Neuropsychiatry – evaluate monthly
- HCV: quantitative HCV RNA at 12 weeks. If positive or HCV decrease of ≤2 log with genotype 1, discontinue therapy (since the probability of SVR <1%) or consider maintenance interferon. With genotype 2/3, continue to 24 wks or discontinue.
- End of therapy: HCV RNA PCR

- Post-therapy: HCV RNA PCR at 6 months

Pancreatitis (*Am J Med* 1999;107:78)

MAJOR CAUSES

- **Drugs**, especially ddI or ddI + d4T ± hydroxyurea. May be complication of lactic acidosis (NRTI-associated mitochondrial toxicity) or secondary to PI-associated hypertriglyceridemia with elevated triglyceride levels – usually >1000 mg/dL. Less common drugs: d4T, RTV, INH, rifampin, LPV/r, TMP-SMX, pentamidine, corticosteroids, sulfonamides, erythromycin, paromomycin.
- **Opportunistic infections:** CMV. Less common: MAC, TB, cryptosporidium, toxoplasmosis, cryptococcus
- **Conditions that cause pancreatitis in general population**, especially alcoholism. Less common: Gallstones, hypertriglyceridemia (avg level is 4500 mg/dL), post ERCP (3% to 5% of procedures), trauma.

DIAGNOSIS

- **Amylase** >3x ULN Other causes of hyperamylasemia: other intra-abdominal conditions, diseases of salivary gland, tumors (lung and ovary), renal failure macroamylasemia; sensitivity: 85% to 100% (*Am J Gastroenterol* 1990;85:356).
- **Other tests**
  - Lipase: As sensitive as amylase but more specific. Need for amylase plus lipase is arbitrary.
  - CT Scan: Best method to image (*Radiology* 1994;193:297). Used to 1) exclude other serious intra-abdominal conditions, 2) stage pancreatitis, and 3) detect complications.

TREATMENT: Supportive – IV fluids, pain control, and NPO

PROGNOSIS: Best predictor of outcome is APACHE II score (*Am J Gastroenterol* 2003;98:1278)

HEMATOLOGIC COMPLICATIONS

Anemia

■ TABLE 7-4: **Definition of Anemia**

		Men	Women
Average	Hematocrit %	46.0 ± 4.0	40.0 ± 4.0
	Hemoglobin (g/dL)	15.7 ± 1.7	13.8 ± 1.5
	Reticulocytes	1.6 ± 0.5	1.4 ± 0.5
	Mean corpuscular vol	88.0 ± 8.0	88.0 ± 8.0
Anemia	Hematocrit	<41%	<36%
	Hemoglobin (g/dL)	13.5	12.0

SYMPTOMS: Oxygen delivery becomes impaired with activity when the hemoglobin levels <8-9 g/dL and becomes impaired at rest with hemoglobin levels <5 g/dL (*JAMA* 1998;279:217). Symptoms of chronic anemia include exertional dyspnea, fatigue, and a hyperdynamic state (bounding pulses, palpitations, roaring in ears). Late complications include confusion, CHF, angina. There is a consistently observed relationship between anemia and survival with HIV infection (*J Acquir Immune Defic Syndr* 1998;19:29; *Clin Infect Dis* 2002;34:260; *J Acquir Immune Defic Syndr* 2004;37:1245). Symptoms due to acute bleeding are those of hypovolemia with postural dizziness, lethargy, postural hypotension, and shock.

CAUSES

- **HIV:** HIV infection of marrow progenitor cells (*Clin Infect Dis* 2000;30:504). Incidence correlates with immune state: 12% with CD4 count <200 /mm^3, 37% with AIDS-defining OI (*Blood* 1998;91:301). Anemia predicts death independent of CD4 count and viral load (*Semin Hematol Suppl* 4;6:18; *AIDS* 1999;13:943; *AIDS Rev* 2002;4:13; *J Acquir Immune Defic Syndr* 2004;37:1245).
  - Findings: Normocytic, normochromic, low reticulocyte count, low erythropoeitin (EPO) level
  - Factors that correlate with anemia are: CD4 <200/mm^3, high VL, female sex, use of AZT, reduced BMI and black race (*Clin Infect Dis* 2004;38:1454; *J Acquir Immune Defic Syndr* 2004;37:1245).
  - Treatment: HAART. With immune reconstitution, prior reports show increases in Hgb of 1.0-2.0 gm/dL at 6 months (*J Acquir Immune Defic Syndr* 2001;28:221; *AIDS* 1999;13:943), but results are inconsistent (*Clin Infect Dis* 2000;30:504). Consider EPO (starting at 40,000 units/week) with symptomatic and refractory cases (see Figure 7-1).

- **Marrow-infiltrating infection or tumor** (lymphoma, especially non-cleaved cell type, or Kaposi's sarcoma, rare) or infection (MAC, tuberculosis, CMV, histoplasmosis)
  - Findings: Normocytic, normochromic, low platelet count, evidence of etiologic mechanism
  - Treat underlying cause
- **Parvovirus B19:** Infects erythroid precursors; symptoms reflect marginal reserve (sickle cell disease, etc.) and inability to eradicate infection due to immune deficiency.
  - Findings: Normocytic, normochromic anemia, without reticulocytes, positive IgG and IgM serology for parvovirus, positive serum dot blot hybridization or PCR for parvovirus B19. The diagnosis is most likely with severe anemia, i.e., hematocrit <24%, no reticulocytes and CD4 count <100 cells/mm^3 (*J Infect Dis* 1997;176:269).
  - Treatment: May eradicate pathogen with HAART (*Clin Infect Dis* 2001;32:E122). Standard treatment with persistent parvovirus B19 and immunosuppression is IVIG 400 mg/kg/day x 5 days (*Ann Intern Med* 1990;113:926)
- **Nutritional deficiency:** Common in late stage HIV, including B12 deficiency in 20% of AIDS patients (*Eur J Haematol* 1987;38:141) and folate deficiency due to folic acid malabsorption (*J Intern Med* 1991;230:227).
  - Findings: Megaloblastic anemia (MCV >100 not ascribed to AZT or d4T) ± hypersegmented polymorphonuclear cells, low reticulocyte count with serum B12 (cobalamin) level <125-200 pg/mL (*Semin Hematol* 1999;36:75) or a serum folate level <2-4 ng/mL (<2 ng/mL is more definitive). Note: A single hospital meal may improve the RBC folate level.
  - Treatment: Folate deficiency – folic acid 1-5 mg/day x 1 to 4 months. B12 deficiency – cobalamin 1 g IM qd x 7 days, then every week x 4, then every month or 1-2 g PO qd (*Blood* 1998;92:1191).
- **Iron deficiency:** Usually indicates blood loss, especially from GI tract.
  - Findings: Most studies to detect iron deficiency show the likely cause is anemia of chronic disease with decreased Fe (<60 ug/dL), low transferrin (<300 ug/dL), and normal or increased ferritin. Ferritin level <40 ng/mL suggests iron deficiency and a level <15 ng/mL is 99% sensitive for this diagnosis but only 50% specific (*J Gen Intern Med* 1992;7:145).
  - Treatment: Detect and treat source of loss + ferrous sulfate 325 mg tid.
- **Drug-induced marrow suppression ± red cell aplasia:** Most common with AZT; less common with ganciclovir, amphotericin, ribavirin, pyrimethamine, interferon, TMP-SMX, phenytoin (also seen

with HIV *per se*, parvovirus B19, and non-Hodgkin's lymphoma).

- Findings: Normocytic, normochromic anemia (macrocytic with AZT or d4T), low or normal reticulocyte count.
- Treatment: Discontinue implicated agent ± EPO (see algorithm, .

- **Drug-induced hemolytic anemia:** Most common with dapsone, primaquine, and ribavirin. Hemolytic anemia is also seen with TTP.. The risk with dapsone and primaquine is dose-related and most common with G6PD deficiency.
  - Findings: Reticulocytosis, increased LDH, increased indirect bilirubin, methemoglobinemia, and reduced haptoglobin. The combination of a haptoglobin <25 mg/dL + elevated LDH is 90% specific and 92% sensitive for hemolytic anemia (*JAMA* 1980;243:1909). The peripheral smear may show spherocytes and fragmented RBCs. Note: Coombs test is commonly positive.
  - Treatment: Consists of oxygen, transfusion, and discontinuation of implicated drug. Severe cases in absence of G6-PD deficiency are treated with IV methylene blue (l mg/kg) (*J Acquir Immune Defic Syndr* 1996;12:477). Activated charcoal may be given to reduce dapsone levels .

Idiopathic Thrombocytopenia Purpura (ITP)

DEFINITION: Unexplained platelet count <100,000/mL

CAUSES

- **Most cases** are ascribed to HIV infection of multi-lineage hematopoietic progenitor cells in the marrow (*Clin Infect Dis* 2000;30:504; *N Engl J Med* 1992;327:1779).
- **Drug induced:** Review of 561 reports showed the best supporting data for a causal role for drugs in patients without HIV infection were for heparin, quinidine, and TMP-SMX (*Ann Intern Med* 1998;129:886). Others with "level 1 evidence" that are used in HIV-infected patients: rifampin, amphotericin, vancomycin, ethambutol, sulfisoxazole, and lithium.

TREATMENT (*Clin Infect Dis* 1995;21:415; *N Engl J Med* 1999;341:1239)

- **HAART:** Two reports showed that with viral suppression and CD4 count rebound, median platelet count increase was 18,000/mL and 45,000/mL at 3 months (*Clin Infect Dis* 2000;30:504; *N Engl J Med* 1999;341:1239).
- **Drug-induced:** Median time to recovery with discontinuation of the implicated agent is 7 days (*Ann Intern Med* 1998;129:886).
- **Standard treatments of ITP** (prednisone, IVIG, splenectomy, etc.): Response rates are 40% to 90%; the main problem is durability (*Clin Infect Dis* 1995;21:415).

■ TABLE 7-5: **Treatment of ITP by Clinical Presentation**

Clinical Status	Treatment
Asymptomatic	■ HAART ■ Discontinue implicated drug and monitor response.
Persistent symptomatic or required for procedure	■ Above ■ Prednisone 30-60 mg/day with rapid taper to 5-10 mg/day. Risk of OI. Only 10% to 20% have sustained response. ■ IVIG 400 mg/kg days 1, 2 and 14, then every 2 to 4 weeks. Raises platelet count within 4 days; median peak response time is 3 weeks. Very expensive. ■ Rho(D) immune globulin (*WinRho*) 25-50 µg/kg over 3 to 5 minutes in Rh(+) patients, repeat day 3 to 4 prn, then at 3 to 4 week intervals as needed. Similar to IVIG but rapid infusion and less expensive (10% cost of IVIG). Hemolysis may occur peaking at day 6; response at 1-3 days, peaks at day 8. ■ Splenectomy – experience is variable: some good (*Arch Surg* 1989;124:625), some bad (*Lancet* 1987;2:342).
Hemorrhage	Packed red cells/platelet transfusions plus prednisone 60-100 mg/day or IVIG 1 g/kg days I, 2, and 14.

Neutropenia

DEFINITION: Absolute neutrophil count <750/mm^3

CAUSE: Usually due to HIV *per se* or to drugs.

SYMPTOMS: Reported risk of bacterial infections is variable, but the largest review shows an increase in hospitalization with an ANC <500/mm^3 (*Arch Intern Med* 1997;157:1825). Other reviews show that few HIV infected patients have excessive neutropenia-associated infections (*Clin Infect Dis* 2001;32:469).

TREATMENT

- **HIV-associated:** HAART – ANC increase with immune reconstitution is variable (*Clin Infect Dis* 2000;30:504; *J Acquir Immune Defic Syndr* 2001;28:221).
- **Drug-associated:** Most common causes are AZT, ganciclovir, or valganciclovir; other causes include amphotericin, sulfonamides, pentamidine, antineoplastic drugs, and interferon. Treatment is to discontinue the implicated drug and/or give G-CSF or GM-CSF.

Thrombotic Thrombocytopenia Purpura (TTP)

DEFINITION: Thrombotic microangiopathy, hemolytic uremic syndrome (HUS), and TTP represent syndromes characterized by hemolytic anemia, thrombocytopenia, and renal failure, often with fever and neurologic changes (*Clin Infect Dis* 2006;42:1488).

CAUSE: Platelet thrombi in selected organs

FREQUENCY: Unclear, may be early or late in course (*Ann Intern Med* 1988;109:194)

LAB DIAGNOSIS: 1) Anemia; 2) Thrombocytopenia (platelet count 5,000-120,000/mL); 3) Peripheral smear shows fragmented RBCs (schistocytes, helmet cells) ± nucleated cells; 4) Increased creatinine; 5) Evidence of hemolysis: increased reticulocytes, indirect bilirubin, and LDH and low haptoglobin; and 6) Normal coagulation parameters

TREATMENT: The usual course is progressive with irreversible renal failure and death. Standard treatment is plasma exchange until platelet count is normal and LDH is normal (*N Engl J Med* 1991;325:393). An average of 7 to 16 exchanges are required to induce remission. With poor response, add prednisone 60 mg/day; other interventions include IVIG, antiplatelet drugs, vincristine, and splenectomy.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

DEFINITION: Atypical inflammatory disorders associated with immune recovery.

PATHOGENESIS: Qualitative and quantitative recovery of pathogen-specific cellular and humoral responses have been noted to multiple opportunistic pathogens including MTB, MAC, CMV, EBV, HBV, HCV and *C. albicans* (*Science* 1997;277:112; *Clin Infect Dis* 2000;30:882; *AIDS* 2002;616:2129; *J Infect Dis* 2002;185:1813).

CLINICAL FEATURES: The interval from ART to IRIS is 1 week to several months; most occur in the first 8 weeks. The baseline CD4 is usually <50/mm^3 at initiation of HAART and increases 2- to 4-fold in year one. There are two patterns: 1) HAART given at the time of OI treatment with IRIS complicating the response to treatment, and 2) HAART given to a clinically stable patient with new expression of a dormant and previously unrecognized condition.

TREATMENT PRINCIPLES: In most cases HAART and OI therapy are continued. Symptomatic treatment is commonly successful with NSAIDs. Some patients require steroids; discontinuation of HAART is rarely required except in life-threatening cases.

■ TABLE 7-6: **IRIS: Infectious Diseases**

Pathogen	Clincal expression
Chlamydia trachomatis	Reiter syndrome
Cryptococcosis	Initial prevention or exacerbation of meningitis; necrotizing pneumonia with nodules and mediastinitis; skin abscess; spinal cord infection
CMV retinitis	Uveitis, vitritis, retinitis, cataracts, macular edema, epiretinal membrane
Herpes simplex	Erosive lesions
Hepatitis B	Hepatitis flare
Hepatitis C	Hepatitis flare; cryoglobulinemia
HHV-8	Worsening of Kaposi sarcoma; Castleman disease
Human papillomavirus	Warts
JC virus	Inflammatory PML with enhancement or MRI
Molluscum contagiosum	Increased skin lesions
M. avium complex	Lymphadenitis (cervical, thoracic, abdominal); pneumonitis, endobronchial lesions; osteomyelitis; septic arthritis; perispinal abscess; Addison disease; skin lesions; peritonitis, ileitis, colitis; hepatosplenomegaly; hypercalcemia
M. tuberculosis	Fever, lymphadenopathy (abdominal, mediastinal, cervical), pneumonitis, pleural effusions, lung abscesses, expanding CNS lesions
P. jiroveci	Progressive pneumonia; ARDS; granulomatous pneumonia
Parvovirus B19	Encephalitis
Toxoplasmosis	Encephalitis

■ TABLE 7-7: **IRIS: Non-infectious Diseases**

Condition	Clinical expression
Autoimmune disorder	Hyperthyroidism; SLE, rheumatoid arthritis, pyomyositis, alopecia
Malignancy	Kaposi sarcoma with skin and mucosal lesions, pneumonitis, adenopathy Non-Hodgkins lymphoma – relapse
Folliculitis	Flare

MALIGNANCIES

RISK: A review of AIDS and cancer registries for 1981-96 involving 8,828 AIDS patients >60 years of age found the following relative risks compared to controls without AIDS: Kaposi's sarcoma, 545; NHL, 24.6; Hodgkin's lymphoma, 13.1; anal cancer, 8.2; leukemia, 2.4; and lung cancer, 1.9. There were no cases of cervical cancer (*J Acquir Immune Defic Syndr* 2004;36:861).

■ TABLE 7-8: **Major HIV-associated Tumors with Risk Based on CD4 Count**

Cancer	Relative risk vs general population			
	n	Total	CD4 >200	CD4 <50
Kaposi's sarcoma	1937	258	140	309
Non-Hodgkin's lymphoma	1158	78	44	111
Lymphoblastic lymphoma	201	134	40	109
CNS lymphoma	320	175	27	330
Cervical cancer	26	9	10	8

Analysis is from cancer registries and AIDS registries in 11 U.S. regions, 1990-96 (*J Acquir Immune Defic Syndr* 2003;32:527)

ANAL CANCER: This tumor is associated with human papillomavirus (HPV), primarily types 16 and 18.

DIAGNOSIS: Risks – for MSM, history of anogenital condylomas; for women, abnormal cervical cytology or cervical carcinoma.

TREATMENT: The options are surgery with abdominal perineal resection or combination radiation + chemotherapy.

Kaposi's Sarcoma

CAUSE: HHV-8. Mechanism of infection is thought to be by HHV-8 in saliva (*J Acquir Immune Defic Syndr* 2006;42:420; *Sex Transm Infect* 2006;82:229).

FREQUENCY: Rate is up to 20,000-fold higher with HIV compared with general population and 300-fold higher than other immunosuppressed patients (*Lancet* 1990;335:123; *J Natl Cancer Inst* 2002;94:1204). The incidence increased >200-fold in women as well (*J Acquir Immune Defic Syndr* 2004;36:978). The postulated mechanism is upregulation of cytokines that regulate angiogenesis and lymphangiogenesis by HIV (*Lancet* 2004;364:740). The rate has decreased in the HAART era (*JAMA* 2002;287:221) by up to 100-fold in one report; PI and NNRTI-based HAART appear equally effective (*AIDS* 2003;17:F17).

PRESENTATION: Firm purple to brown-black macules, patches, nodules, papules that are usually asymptomatic – neither pruritic, nor painful, and usually on legs, face, oral cavity, and genitalia. Complications include lymphedema (especially legs, face, and genitalia) and visceral involvement (especially mouth, GI tract, and lungs). HAART reduces the frequency of KS (*J Acquir Immune Defic Syndr* 2003;33:614), and when it develops during antiretroviral therapy the course is less aggressive (*Cancer* 2003;98:2440).

DIFFERENTIAL: Bacillary angiomatosis (biopsy with silver stain to show organisms); hematoma, nevus, hemangioma, B-cell lymphoma, and pyogenic granuloma. Biopsy should be performed on at least one lesion to confirm the diagnosis; this is especially important with rapidly growing lesions.

■ TABLE 7-9: **Frequency, Presentation, and Diagnosis of Kaposi's Sarcoma**

Site	Frequency*	Presentation	Diagnosis
Skin	>95%	Purple or black-brown nodular skin or oral lesions ± edema	Appearance and biopsy
Oral	30%	Usually palate or gums	Appearance and biopsy (skin biopsy preferred)
GI	40%	Pain, bleeding, or obstruction ■ Most are asymptomatic ■ Most have skin lesions ■ May occur at any level	Endoscopy to see hemorrhagic nodule; biopsy is often negative (*Gastrolenterology* 1988;89:102). Assume diagnosis if skin biopsy is positive
Lung	20%-50%	Dyspnea, cough, wheezing, and/or hemoptysis. may cause parenchymal or endobronchial lesions or pleural effusion. Pleural effusion: serosanguinous cytology negative. X-ray: infiltrates diffuse or nodular.	CT scan and bronchoscopy. Endobronchial TB – red raised lesions – biopsy often negative.

PROGNOSIS: CD4 count plus tumor burden staging (ACTG – *J Clin Oncol* 1989;7:201). TIS: Extent of Tumor (T), Immune status (I), Severity of systemic illness (S). TIS predicts survival (*J Clin Oncol* 1997;15:385). Good prognosis – lesions confined to skin, CD4 count >150/mm^3, no "B" symptoms.

TREATMENT

- **HAART:** Associated with lesion regression, decreased incidence, and prolonged survival (*J Clin Oncol* 2001;19:3848; *J Med Virol*

1999;57:140; *AIDS* 1997;11:261; *Mayo Clin Proc* 1998;73:439; *AIDS* 2000;14:987).

- **Treatment:** Some patients with stable, asymptomatic KS may be observed, though KS is almost always an indication for HAART.
- **Systemic vs local therapy:** Indications for liposomal anthracyclines or paclitaxel (Table 7-12) include visceral KS (pulmonary, gastrointestinal, etc.); extensive KS-associated lymphedema; or extensive and rapidly progressive cutaneous KS. Some have advocated systemic treatment with extensive tumor burden (>25 skin lesions, visceral involvement with symptoms, extensive edema, "B" symptoms, or failure to respond to local treatment) (*Lancet* 1995;346:26).
- Treatment of Kaposi's Sarcoma should be undertaken by an expert in the field

RESPONSE: Kaposi's sarcoma cannot be cured; goals of therapy are to reduce symptoms and prevent progression. HAART is associated with reduced tumor burden. Antiviral drugs directed against HHV-8 have no established benefit (*J Acquir Immune Defic Syndr* 1999;20:34).

- **Local therapy:** Local injections of vinblastine cause reduced lesion size but not elimination in most patients (*Cancer* 1993;71:1722).
- **Systemic therapy:** Liposomal anthracyclines usually show good results with few side effects. Paclitaxel is as effective but more toxic due to neutropenia and thrombocytopenia; side effects are dose related; lower doses appear as effective with less marrow suppression.
- **Immune reconstitution KS:** In a review of 150 treatment-naïve patients with KS who started HAART, 10 (6.6%) developed progressive KS (*J Clin Oncol* 2005;23:5224). Clinical presentation consists of worsening KS with adenopathy, more skin lesions, skin lesions that are more violaceous and associated with more edema (*Clin Infect Dis* 2004;39:1852).

HIV-associated lymphomas

Most are B cell lymphomas. Histologic types include B cell diffuse large cell lymphoma, primary effusion lymphoma, primary B cell CNS lymphoma, Burkitt's lymphoma, and Hodgkin's disease. In an analysis of 6,788 NHL cases, 96 (1.4%) were T-cell lymphomas; the relative risk in AIDS patients vs the general population was 15.

Non-Hodgkin's Lymphoma (NHL)

CAUSE: Immunosuppression (CD4 count <100 cells/mm^3) and EBV (50% to 80%)

FREQUENCY AND TYPE: NHL is 200 to 600 times more common among HIV-infected patients compared with the general population (*Int J Cancer* 1997;73:645; *J Acquir Immune Defic Syndr* 2004;36:978).

PRESENTATION: Compared with NHL in the general population, HIV infected patients have high rates of stage IV disease with "B" symptoms and sparse node involvement. Common sites of infection and forms of clinical presentation are fever of unknown origin, hepatic dysfunction, marrow involvement, lung disease (effusions, multinodular infiltrates, consolidation, mass lesions, or local or diffuse interstitial infiltrates, hilar adenopathy), GI involvement (any level – pain and weight loss), and CNS (aseptic meningitis, cranial nerve palsies, CNS mass lesions).

DIAGNOSIS: Lymph nodes that are >2 cm or progressively enlarging should be biopsied. Patients without adenopathy or with nondiagnostic biopsies should undergo biopsy of liver, marrow, or other site of pathology. Biopsies of nodes are generally preferred to fine-needle aspiration. With GI tract and hepatic involvement, a CT scan is usually more useful than endoscopy. Exudative pleural effusions are frequently seen with lung involvement – bronchoscopy is usually negative unless accompanied by lung biopsy, which has a diagnostic yield of about 60% (*Chest* 1996;110:729).

TREATMENT

- **Standard:** CHOP (cyclophosphamide, doxorubicin, adriamycin, vincristine, and prednisone). Intrathecal methotrexate or cytosine arabinoside may be given for CNS prophylaxis and should be given with meningeal involvement (*J Clin Oncol* 2001;19:2171).

RESPONSE: Initial response rates are 50% to 60%, but relapse rates are high and the long-term prognosis is poor with median survival <1 year. The usual cause of death is progressive lymphoma or progressive HIV with OIs (*Semin Oncol* 1998;25:492). The prognosis is significantly better with HAART; one report showed an 84% 1 year survival with HAART + chemotherapy (*AIDS* 2001;15:1483). The prognosis with lymphoma plus HIV infection in the HAART era is significantly worse than for lymphoma alone, but one report shows that patients who achieve complete remission with chemotherapy had a 3-year survival (74%) that was comparable to that of HIV-negative patients with NHL (*Clin Infect Dis* 2004;38:142). Another report shows HAART is associated with reduced chemotherapy-related toxicity as well as improved survival (*J Clin Oncol* 2004;22:1491).

Primary CNS Lymphoma (PCNSL) (see Chapter 6)

Primary Effusion Lymphoma

CAUSE: HHV-8 and EBV (*N Engl J Med* 1995;332:1186; *Clin Microbiol Rev* 2002;15:439)

FREQUENCY: Rare: tumor registries crossed with AIDS registries show a frequency of 0.004% or 0.14% of non-Hodgkin's lymphoma in patients with AIDS (*J Acquir Immune Defic Syndr* 2002;29:418)

PRESENTATION: Serous effusions (pleural, peritoneal, pericardial, joint spaces) with no masses (*Hum Pathol* 1997;28:801)

DIAGNOSIS: Effusions are serous, contain high-grade malignant lymphocytes and HHV-8.

TREATMENT

- **HAART plus CHOP** (*J Clin Oncol* 2003;21:3948)

RESPONSE: This tumor usually does not extend beyond serosal surfaces, but prognosis is poor, with median survival of 2 to 6 months (*J Acquir Immune Defic Syndr* 1996;13:215; *J Clin Oncol* 2003;21:3948). Most patients show response to therapy with decrease in effusion size. Failure to respond to two cycles of CHOP indicates additional cycles will fail, indicating a role for liposomal doxorubicin or liposomal daunorubicin. HHV-8 levels increase with relapse and do not respond to antiviral therapy (*J Med Virol* 2003;71:399). The CD4 count is the most important predictor of progression (*Clin Infect Dis* 2005;40:1022).

NEUROLOGIC COMPLICATIONS: Peripheral nervous system

HIV-Associated Neuromuscular Weakness Syndrome (HANWS)

CAUSE: Postulated to be caused by mitochondrial toxicity attributed to deoxy NRTIs, primarily d4T (*N Engl J Med* 2002;346:811; *Clin Infect Dis* 2003; 15:131; *AIDS* 2004;18:1403).

CLINICAL FEATURES: Clinical features include ascending paresis, areflexia and cranial neuropathies. CPK levels are often elevated.

DIAGNOSIS (ACTG, 2002)

- New onset limb weakness ± sensory involvement that is acute (1 to 2 weeks) or subacute (>2 weeks) involving legs or legs and arms

- Absence of alternative confounding illnesses: Guillain-Barré syndrome, myasthenia gravis, myelopathy, hypokalemia, stroke

TREATMENT: Discontinue d4T and/or other causative NRTIs. Supportive care. Follow-up in the cases summarized above showed improvement in only 16/44 (36%).

Cytomegalovirus radiculitis (see Chapter 6)

Inflammatory Demyelinating Polyneuropathy

CAUSE: Unclear; immunopathogenic mechanism with inflammation and breakdown of peripheral nerve myelin is suspected.

FREQUENCY: Uncommon

DIAGNOSIS: There are two forms: acute demyelinating neuropathy (AIDP, Guillain-Barré Syndrome), which occurs early in the course of HIV, and a more chronic relapsing motor weakness, CIDP, which usually occurs in late-stage HIV. Both present with a progressive ascending paralysis with mild sensory involvement. CSF shows increased protein and mononuclear pleocytosis; EMG and nerve conduction studies are critical for diagnosis. Nerve biopsy may be needed; should show mononuclear, macrophage infiltrate, and internodal demyelination (*Ann Neurol* 1987;21:3240).

TREATMENT

- **AIDP**
  - Plasmapheresis: Five exchanges with maintenance as needed.
  - Alternative is IVIG 0.4 g/kg/day x 5 days (monitor renal function).
- **CIDP:** Oral prednisone (1 mg/kg/day) or intermittent plasmapheresis or IVIG; each continued until there is a therapeutic response.

RESPONSE: Treatment usually halts progression; CIDP may require prolonged courses (*Ann Neurol* 1987;21:3240).

■ TABLE 7-10: **Differential Diagnosis of Lower Extremity Symptoms in Patients with HIV Infection**

Syndrome	Symptoms	Clinical Features	Ancillary Studies/ Treatment
Distal sensory neuropathy (DSN)	■ Pain and numbness in toes and feet; ankles, calves, and fingers involved in more advanced cases ■ CD4 cell count <200/mm^3, but can occur at higher CD4 level	■ Reduced pinprick/vibratory sensation ■ Reduced or absent ankle jerks ■ Contact allodynia (hypersensitivity) present most cases	■ Skin biopsy shows epidermal denervation ■ Electromyography/ nerve conduction velocities (EMG/NCV) show a predominantly axonal neuropathy ■ Quantitative sensory testing or thermal thresholds may be helpful
Antiretroviral toxic neuropathy (ATN)	■ Same as DSN (above), but symptoms occur after initiation of ddI, ddC, d4T. ■ Any CD4 cell count. ■ More common in older patients and patients with diabetes	■ Same as DSN (above)	■ EMG/NCVs show a predominantly axonal neuropathy ■ Discontinuation of presumed neuro-toxic medication if severe ■ Symptoms may worsen for a few weeks (coasting) before improving
HIV-associated neuromuscular weakness syndrome	■ Ascending paresis with areflexia ± cranial nerve or sensory involvement ■ Usually associated with prolonged d4T use	■ Lactate and CPK levels usually ? ■ EMG/nerve conduction studies – axonal neuropathy and myopathy	■ Discontinue NRTIs, especially d4T ■ Prognosis for survival is poor
HIV-associated myopathy/AZT myopathy	■ Pain and aching in muscles, usually in thighs and shoulders. ■ Weakness with difficulty when rising from a chair or reaching above shoulders ■ Any CD4 cell count	■ Mild/moderate muscle tenderness ■ Weakness, predominantly in proximal muscles (i.e., deltoids, hip flexors) ■ Normal sensory exam/normal reflexes	■ CPK ↑ ■ EMG shows irritable myopathy ■ Discontinue AZT and follow CPK every 2 weeks. Symptoms/signs/ CPK should improve within 1 month

continued on next page

■ TABLE 7-10: **Differential Diagnosis of Lower Extremity Symptoms in Patients with HIV Infection *(Continued)***

Syndrome	Symptoms	Clinical Features	Ancillary Studies/ Treatment
Polyradiculitis	■ Rapidly evolving weakness and numbness in legs (both proximally and distally), with bowel/bladder incontinence ■ CD4 count >500/mm^3 or <50/mm^3	■ Diffuse weakness in legs ■ Diffuse sensory abnormalities in legs and buttocks ■ Reduced/absent reflexes at knees and ankles	■ EMG/NCV show multilevel nerve root involvement ■ Spinal fluid helpful in determining CMV or HSV as cause ■ Treat CMV polyradiculopathy with ganciclovir or foscarnet
Vacuolar myelopathy	■ Stiffness and weakness in legs with leg numbness. ■ Bowel/bladder incontinence in advanced cases ■ CD4 cell count <200/mm^3	■ Weakness and spasticity, mainly in hip, knee, and ankle flexors ■ Brisk knee jerks, upgoing toes ■ If sensory neuropathy coexists, then distal sensory loss and reduced/ absent jerks	■ Spinal fluid may show elevated protein 0-10 cells/mm^3 ■ Exclude B-12 deficiency and HTLV-1 co-infection ■ Thoracic spinal imaging normal ■ No established therapy, but physical therapy or methionine (3 g bid) and HAART may be helpful (*Neurology* 1998;51:266)
Inflammatory demyelinating polyneuropathies	■ Predominantly weakness in arms and legs, with minor sensory symptoms. ■ CD4 count: may occur at any level	■ Diffuse weakness including facial musculature, asymmetric in early cases, with diffuse absent reflexes ■ Minor sensory signs	■ EMG/NCVs show a demyelinating polyneuropathy ■ Spinal fluid shows a very high protein with mild to moderate lymphocytic pleocytosis, but all cultures are negative ■ Treatment: Plasmapheresis. IVIG and/or HAART
Mononeuritis or mononeuritis multiplex	■ Mix of motor and sensory defects ■ Asymmetric ■ Evolves over weeks ■ CD4 count is variable	■ EMG and nerve conduction – asymmetric and multifocal defects ■ R/O CMV (CSF or sural nerve biopsy) and HCV	■ CD4 count >200 cells/mm^3 – possible steroids ■ CD4 counts <50 cells/mm^3 and severe – treat for CMV

Sensory Neuropathies (see algorithm)

Distal sensory neuropathy (DSN) and antiretroviral toxic neuropathy (ATN) (see *AIDS* 2002;16:2105)

CAUSE: HIV infection *per se*, usually with CD4 count <200 cells/mm^3 and/or dideoxy NRTIs (d-drugs): ddI, d4T, and ddC); most common with ddI + d4T (*AIDS* 2000;14:273). DSN and ATN are indistinguishable by clinical features or biopsy.

FREQUENCY: 20% with advanced HIV over 1 year and 52% over 2 years (*Neurology* 2002;58:1764)

DIFFERENTIAL: Toxic neuropathies due to drugs (metronidazole, B6 overdose, dapsone, INH, vincristine), diabetes, entrapment neuropathies, B12 deficiency, alcoholism, uremia, inflammatory demyelinating polyneuropathy, and acute neuromuscular syndrome

DIAGNOSIS: Dysesthesia and contact hypersensitivity of feet with decreased or absent ankle reflexes. Invasive neurodiagnostic tests may be useful but are usually unnecessary. Skin biopsy shows epidermal denervation. Electromyography/nerve conduction studies show predominantly axonal neuropathy. Quantitative sensory tests or thermal tests show elevated thresholds.

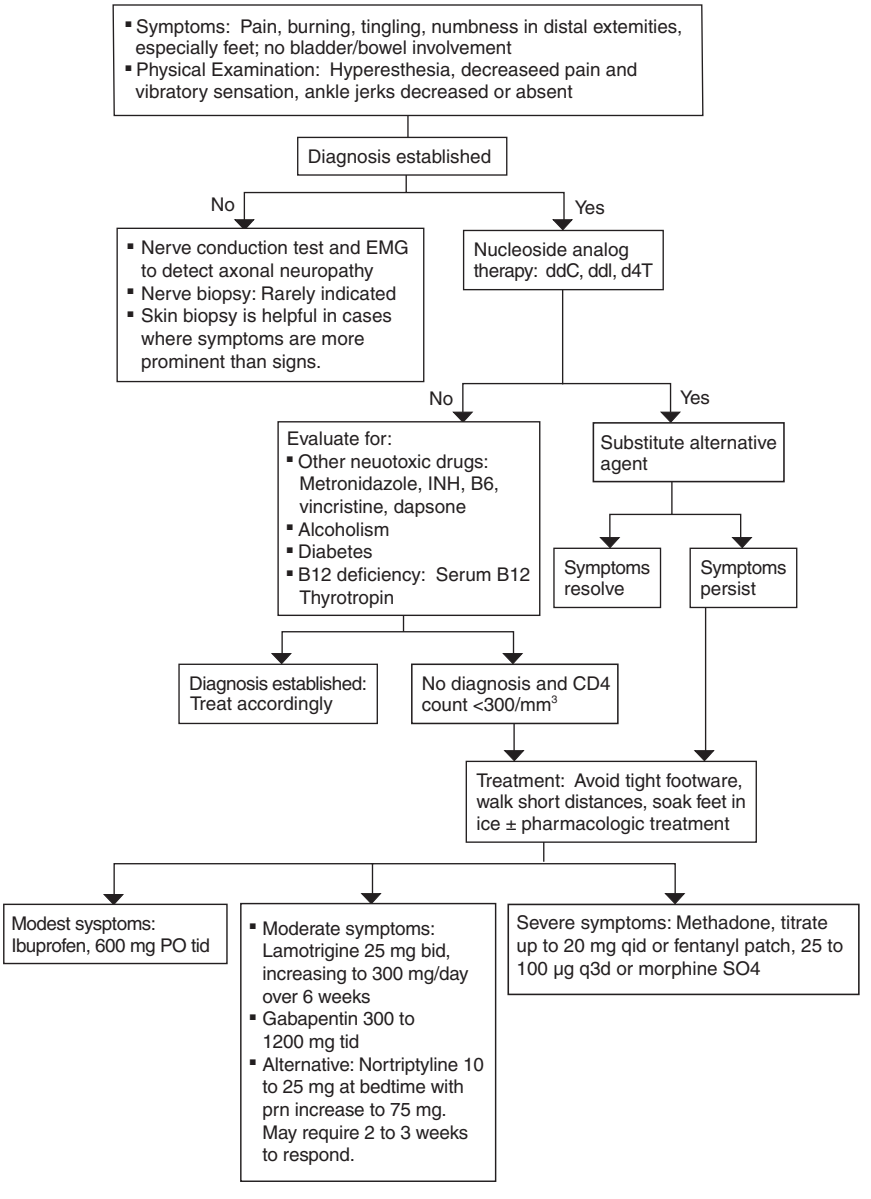
TREATMENT

- **ATN:** Avoid d4T, ddI, and ddC; acceptable alternative agents in this class are AZT, 3TC, FTC, ABC, and TDF.
- **DSN**: Possible response reported with HAART (*Lancet* 1998;352: 1906).
- **Symptomatic treatment**
  - Gabapentin (*Neurontin*) 300-1200 mg PO tid (*J Neurol* 2004; 251:1260).
  - Lamotrigine (*Lamictal*) 25 mg bid increasing to 300 mg/day over 6 weeks; one of the few treatments with confirmed benefit in clinical trials (*Neurology* 2000;54:2115). Longer trial confirmed efficacy but only in patients who were receiving neurotoxic ARTs (*Neurology* 2003;60:1508-14). Generally not a first line agent due to high incidence of rash.
  - Tricyclic antidepressants nortriptyline 10 mg hs increased by 10 mg q5d to maximum 75 mg hs or 10-20 mg PO tid; other tricyclics (amitriptyline, desipramine, or imipramine) are considered comparable. One trial failed to show response to tricyclics (*JAMA* 1998;280:1590).
  - Ibuprofen 600-800 mg tid

- Phenytoin 200-400 mg/day
- Severe pain: Methadone – up to 20 mg qid; fentanyl patch 25-100 mcg/hour q72h or morphine (note: drug interactions between fentanyl and protease inhibitors).
- Avoid tight footwear, limit walking, bridge at foot of the bed, use foot soaks.

RESPONSE: Sensory neuropathy due to NRTIs is usually reversible if the implicated agent is discontinued early, e.g., within 2 weeks of the onset of symptoms. If continued, the pain becomes irreversible and may be incapacitating. Response may require up to 12 weeks after discontinuing nucleosides (*Neurology* 1996;46:999).

■ FIGURE 7-1: **Sensory Neuropathies in Patients with AIDS**



■ TABLE 7-11: **Central Nervous System Conditions in Patients with HIV Infection**

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT Scan/MRI	Cerebrospinal Fluid (CSF)	Other Diagnostic Tests
Toxoplasmosis (2% to 4%)	■ Fever, reduced alertness, headache,focal neurological deficits (80%), seizures (30%) ■ Evolution: <2 weeks ■ CD4 count <100/mm^3	■ Location: Basal ganglia, gray-white junction ■ Sites: Usually multiple ■ Enhancement: prominent; Usually ring lesions (1 to 2 cm) ■ Edema/mass effect: Usually not as great as lymphoma	■ Normal: 20% to 30% ■ Protein: 10 to 150/mg/dL ■ WBC: 0 to 40 (monos) ■ Experimental: Toxo ag (ELISA) or PCR	■ Toxoplasmosis serology (IgG) false-negative in <5% ■ Response to empiric therapy: >85%; most respond by day 7 (*N Engl J Med* 1993;329:995) ■ MRI: Repeat at 2 weeks ■ Definitive diagnosis: Brain biopsy
Primary CNS Lymphoma (2%)	■ Afebrile, headache, focal neurological findings; mental status change (60%), personality or behavioral; seizures (15%) ■ Evolution: 2 to 8 weeks ■ CD4 count <100/mm^3	■ Location: Periventricular, anywhere, 2 to 6 cm ■ Sites: One or many ■ Enhancement: Prominent; usually solid, irregular ■ Edema/mass effect: Prominent	■ Normal: 30% to 50% ■ Protein: 10 to 150/mg/dL ■ WBC: 0 to 100 (monos) ■ EBV PCR in 50%	■ Suspect with negative toxoplasma. IgG, single lesion, or failure to respond to empiric toxoplasmosis treatment (MRI and clinical evaluation at 2 weeks) ■ Thallium 201 SPECT scan (90% sensitive and specific)
Cryptococcal meningitis (8% to 10%)	■ Fever, headache, alert (75%); less common are visual changes, stiff neck, cranial nerve deficits, seizures (10%); no focal neurologic deficits ■ Evolution: <2 weeks ■ CD4 count <100/mm^3	■ Usually normal or shows increased intracranial pressure ■ Enhancement: Negative or meningeal enhancement ■ Edema mass effect: Ventricular enlargement/ obstructive hydrocephalus	■ Protein: 30 to 150/mg/dL ■ WBC: 0 to 100 (monos) ■ Culture positive: 95% to 100% ■ India ink pos: 60% to 80% ■ Crypt Ag: >95% sensitive and specific	■ Cryptococcal antigen in serum – sensitivity 95% ■ Definitive diagnosis: CSF antigen sensitivity and specificity >99% and/or positive culture

continued on next page

■ TABLE 7-11: **Central Nervous System Conditions in Patients with HIV Infection *(Continued)***

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT Scan/MRI	Cerebrospinal Fluid (CSF)	Other Diagnostic Tests
CMV (>0.5%)	■ Fever ±, delirium, lethargy, disorientation; headache; stiff neck, photophobia, cranial nerve deficits; no focal neurologic deficits ■ Evolution: <2 weeks ■ CD4 count <100/mm^3	■ Location: Periventricular, brainstem ■ Site: Confluent ■ Enhancement: Variable, prominent to none.	■ CSF may be normal ■ Protein: 100 to 1000/mg/dL ■ WBC: 10 to 1000 (polys)/mL ■ Glucose usually decreased ■ CMV PCR positive ■ CSF cultures usually negative for CMV	■ Definitive diagnosis: Brain biopsy with histopathology and/or positive culture ■ Hyponatremia (reflects CMV adrenalitis) ■ Retinal exam for CMV retinitis
HIV Dementia (7%)	■ Afebrile; triad of cognitive, motor, and behavioral dysfunction. ■ Early: Decreased memory, concentration, attention, coordination; ataxia ■ Late: Global dementia, paraplegia, mutism ■ Evolution: Weeks to months ■ CD4 count <200/mm^3	■ Location: Diffuse, deep white matter hyperintensities ■ Site: Diffuse, ill-defined ■ Enhancement: Negative ■ Atrophy: Prominent ■ No mass effect	■ Normal: 30% to 50% ■ Protein: Increased in 60% ■ WBC: Increased in 5% to 10% (monos) ■ Beta-2 microglobulin elevated (>3 mg/L)	■ Neuropsychological tests show subcortical dementia ■ HIV dementia scale for screening
Neurosyphilis (0.5%)	■ Asymptomatic meningeal: headache, fever, photophobia, meningismus ± seizures, focal findings, cranial nerve palsies ■ Tabes dorsalis: Sharp pains, paresthesias, decreased DTRs, loss of pupil response	■ Aseptic meningitis: May show meningeal enhancement ■ General paresis: Cortical atrophy, sometimes with infarcts ■ Meningovascular syphilis: strokes	■ Protein: 45 to 200/mg/dL ■ WBC: 5 to 100 (monos) ■ VDRL positive: Sensitivity = 65%, specificity = 100% positive ■ Experimental: PCR for *T. pallidum*	■ Serum VDRL and FTA-ABS are clue in >90%; false-negative serum VDRL in 5% to 10% with tabes dorsalis or general paresis

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■ TABLE 7-11: Central Nervous System Conditions in Patients with HIV Infection *(Continued)*

Agent/Condition Frequency (All AIDS Patients)	Clinical Features	CT Scan/MRI	Cerebrospinal Fluid (CSF)	Other Diagnostic Tests
Neurosyphilis (0.5%) – *continued*	■ General paresis: Memory loss, dementia, personality changes, loss of pupil response ■ Meningovascular: Strokes, myelitis ■ Ocular: Iritis, uveitis, optic neuritis ■ Any CD4 cell count			■ Definitive diagnosis: Positive CSF VDRL (found in 60% to 70%) ■ Note: Most common forms in HIV-infected persons are ocular, meningeal, and meningovascular.
PML (1% to 2%)	■ No fever; no headache; impaired speech, vision, motor function, cranial nerves ■ Late: ¬ cognition ■ Evolution: Weeks to months ■ CD4 count <100/mm^3; some >200/mm^3	■ Location: White matter, subcortical, multifocal ■ Sites: Variable ■ Enhancement: Negative ■ No mass effect	■ Normal CSF ■ PCR for JC virus: 80%	■ Brain biopsy: Positive DFA stain for JC virus
Tuberculosis (0.5% to 1%)	■ Fever, reduced alertness, headache, meningismus, focal deficits (20%) ■ CD4 count <350/mm^3	■ Intracerebral lesions in 50% to 70% (*N Engl J Med* 1992;326:668; *Am J Med* 1992;93:524)	■ Normal: 5% to 10% ■ Protein: Normal (40%) - 500/mL ■ WBC: 5 to 2000 (average is 60% to 70% monos) ■ Glucose: 4 to 0/mL ■ AFB smear positive: 20%	■ Chest x-ray: active TB in 50%; PPD positive: 20% to 30% ■ Definitive diagnosis: Positive culture CSF

Normal values: Protein: 15 to 45 mg/dL; traumatic tap: 1 mg/1000 RBCs; glucose: 40-80 mg/dL % or CSF/blood glucose ratio >0.6; leukocyte counts: <5 mononuclear cells/mL, 5 to 10 is suspect, 1 PMN is suspect; bloody tap: 1 WBC/700 RBC; opening pressure: 80 to 200 mm H_2O.

CSF analysis in asymptomatic HIV-infected persons shows 40% to 50% have elevated protein and/or pleocytosis (>5 mononuclear cells/mL); the frequency of pleocytosis decreases with progressive disease.

Cytomegalovirus Encephalitis

CAUSE: CMV + CD4 count <50/mm^3

FREQUENCY: <0.5% of AIDS patients

PRESENTATION: Rapidly progressive delirium, cranial nerve deficits, nystagmus, ataxia, headache with fever ± CMV retinitis

DIAGNOSIS: MRI shows periventricular confluent lesions with enhancement. CMV PCR in CSF is >80% sensitive and 90% specific; and cultures of CSF for CMV are usually negative.

TREATMENT: Ganciclovir

Dementia (HIV-Associated Dementia or HAD)

CAUSE: Chronic encephalitis with progressive or static encephalopathy due to CNS HIV infection with prominent immune activation

INCIDENCE: 7% after AIDS in pre-HAART era; 2% to 3% more recently (*Neurology* 2001;56:257). Despite a decrease in incidence, the prevalence is increasing with longer survival (*AIDS* 2003;17:1539).

PRESENTATION: Late stage HIV with CD4 count <200 cells/mm^3 and subcortical dementia. See Table 7-12 and 7-13. Early symptoms: apathy, memory loss, cognitive slowing, depression, and withdrawal. Motor defects include gait instability and reduced hand coordination. Late stages show global loss of cognition, severe psychomotor retardation, and mutism. There may be seizures, which are usually easily controlled. The rate of progression is highly variable, but the average from first symptoms to death in the pre-HAART era was 6 months (*Medicine* 1987;66:407). Physical examination in early disease shows defective rapid eye movement, rapid limb movement, and generalized hyperreflexia. In late stages, there is tremor, clonus, and frontal release signs.

TESTING

■ TABLE 7-12: **HIV Dementia Scale (*AIDS Reader* 2002;12:29)**

Maximum Score	Test*
See below	Memory registration: 4 words given (hat, dog, green, peach) and have the patient repeat them.
6	Psychomotor speed: Record the time, in seconds, that it takes the patient to write the alphabet. Score: <21 sec = 6, 21.1-24 sec = 5, 24.1-27 sec = 4, 27.1-30 sec = 3, 30.1-33 sec = 2; 33.1-36 sec = 1, >36 = 0
4	Memory recall: Ask for the four words from above. For words not remembered give semantic clue, e.g. "animal" (dog), "color" (green), etc. 1 point for each correct answer.
2	Construction: Copy a cube and record time. Score: <25 sec = 2, 25-35 sec = 1, >35 = 0

* ≤7/12 is threshold for dementia but is non-specific requiring additional neurologic evaluation.

■ TABLE 7-13: **AIDS Dementia Complex Staging**

Stage 0	Normal
Stage 0.5	Subclinical: Minimal – equivocal symptoms; no work impairment.
Stage 1.0	Mild – minimal intellectual or motor impairment; able to do all but more demanding work or ADL.
Stage 2.0	Moderate – cannot work or perform demanding ADL; capable of self care.
Stage 3.0	Severe – major intellectual disability; unable to walk unassisted.
Stage 4.0	End stage – near vegetative stage; paraplegia or quadriplegia.

DIAGNOSIS: History, physical examination, and screening with HIV Dementia Scale as noted above.

TREATMENT: The HIV Dementia Scale (see Table 7-12) can be used to follow response to HAART. HAART has reduced the frequency of HAD, but there are sparse data to show efficacy of HAART for reversing established HAD (*J Neurovirol* 2002;8:136; *J Neurol* 2004;10:350). It is also unclear whether CNS penetration is important in the selection of agents. Antiretroviral agents with the best CNS penetration based on CSF levels are AZT, d4T, ABC, NVP, and IDV; levels are somewhat lower for EFV, ddI, 3TC, and FPV (*J Acquir Immune Defic Syndr* 1998;235:238; *AIDS* 1998;12:537). Adjunctive therapies to block immune activation are being tested in trials of NMbA receptor antagonists and antioxidants such as selegiline.

RESPONSE: HAART is associated with significant increases in survival (*AIDS* 2003;17:1539) and reduced incidence of HAD, but its role in treatment of HAD specifically is unclear (*Brain Pathol* 2003;13:104).

Primary CNS Lymphoma (PCNSL)

CAUSE: Virtually all are EBV-associated (*Lancet* 1991;337:805).

FREQUENCY: 2% to 6% in pre-HAART era – 1000 times higher than in the general population (*Lancet* 1991;338:969). The incidence has declined in the HAART but not as that of much as other HIV complications (*J Acquir Immune Defic Syndr* 2000;25:451).

PRESENTATION: Focal or non-focal signs. Symptoms include confusion, headache, memory loss, aphasia, hemiparesis, and/or seizures without fever for <3 months. CD4 count is usually <50/mm^3.

DIAGNOSIS: The CD4 count is usually <50 cells/mm^3. MRI with contrast usually shows a single enhancing lesion, but there may be multiple lesions and MRI sometimes shows ring forms (*Am J Neuroradiol* 1997;18:563). These lesions usually involve the corpus callosum, periventricular area, or periependymal area; they are often >4 cm in diameter and usually show a mass effect (*Neurology* 1997;48:687). The diagnosis is established with brain biopsy, positive CSF cytology and possibly by EBV DNA in CSF. Major differential diagnosis is toxoplasmosis.

Factors favoring CNS lymphoma are: 1) typical neuro imaging results (above), 2) negative anti-*Toxoplasma* IgG serology, 3) failure to respond to empiric treatment of toxoplasmosis within 1 to 2 weeks, 4) lack of fever, and 5) thallium SPECT scan with early thallium uptake. CSF EBV PCR is >94% specific and 50-80% sensitive (*Clin Infect Dis* 2002;34:103; *J Natl Cancer Inst* 1998;90:364; *Lancet* 1992;342:398). Stereotactic brain biopsy is definitive and usually reserved for patients who fail to respond to toxoplasmosis treatment (*AIDS* 1995;9:1243; *Clin Infect Dis* 2002;34:103). A review of five reports with 486 AIDS patients undergoing stereotactic brain biopsy showed a 4% morbidity rate (*Clin Infect Dis* 2002;34:103).

THERAPY

- **Standard:** Radiation plus corticosteroids (*J Neuro Sci* 1999;163:32) or methotrexate (*J Clin Oncol* 2003;21:1044)
- **Chemotherapy:** May be combined with radiation plus corticosteroids. Usually reserved for patients with elevated CD4 counts.

RESPONSE: Response rates to radiation therapy plus corticosteroids is 20% to 50%, but these results are temporary, and the average duration of life following the onset of symptoms was only about 4 months in the pre-HAART era (*Crit Rev Oncol* 1998;9:199; *Semin Oncol* 1998;25:492). A trial with methotrexate showed a 74% radiographic response rate with modest toxicity (*J Clin Oncol* 2002;31:171).

Progressive Multifocal Leukoencephalopathy (PML)

CAUSE: Activation of JC virus (which is ubiquitous) in patients who are immunodeficient.

FREQUENCY: 1% to 2% of AIDS patients (*J Infect Dis* 1999;180:261)

PRESENTATION: Cognitive impairment, visual field deficits, hemiparesis speech defects, incoordination with *no* fever. CD4 count is usually 35-100/mm^3, but a subset of 7% to 25% have CD4 counts >200/mm^3 (*Clin Infect Dis* 2002;34:103).

DIAGNOSIS

- MRI shows hypodense lesions of white matter without edema or enhancement.
- PCR for JCV in CSF with sensitivity of 80% and specificity of 95% (*Clin Infect Dis* 2005;40:738).

TREATMENT: None with established merit. HAART may be associated with improvement stabilization or progression. One report shows PML response to HAART with enhancing lesions on MRI suggesting immune reconstitution inflammatory syndrome (*AIDS* 1999;13:1426).

PROGNOSIS: Median duration of survival is 1 to 6 months. Response to HAART is possible, but some patients have developed PML while receiving HAART (*Clin Infect Dis* 2002;34:103). The most important predictor of survival is baseline CD4 cell count.

Toxoplasmosis (see Chapter 6)

OPHTHALMIC COMPLICATIONS

CMV RETINITIS

MICROANGIOPATHY: HIV microangiopathy may present with cotton wool spots, intraretinal hemorrhages, and/or microaneurysms. These are more common with low CD4 counts; they are inconsequential and require no treatment. Microaneurysms associated with anemia often respond to increased hematocrit. Other findings may respond to HAART.

PNEUMOCYSTIS JIROVECI CHOROIDOPATHY: Diagnosis – yellow or orange lesions at posterior pole of retina; treatment – standard PCP regimens.

TOXOPLASMOSIS RETINITIS: Diagnosis is based on multiple white or cream-colored retinal lesions without hemorrhages (as commonly seen with CMV) and without pigmented lesions (as seen in with toxoplasmosis retinitis in immunocompetent hosts. Treatment is similar to regimens for CNS toxoplasmosis.

SYPHILIS: Ocular forms include uveitis, optic neuritis, and chorioretinitis. Standard treatment is aqueous penicillin G 18-24 million units/day IV x 10-14 days.

ZOSTER OPHTHALMICUS: Diagnosis is presumptive based on typical dermatomal rash in the distribution of the first branch of the trigeminal nerve. Treatment should be in conjunction with an ophthalmologist and usually consists of IV acyclovir 30 mg/kg/day x 10-14 days, followed by oral ganciclovir 1 gm PO tid.

ORAL COMPLICATIONS

Gingivitis

CAUSE: Anaerobic bacteria

PHASES: Linear gingival erythema ∅ necrotizing gingivitis ∅ necrotizing periodontitis ∅ necrotizing stomatitis

■ TABLE 7-14: **Phases of Gingivitis**

Lesion	Location	Clinical Features
Linear gingival erythema	Gingiva	Painless, bright red at gingival margin
Necrotizing gingivitis	Gingiva	Painful, red gingiva and ulceration
Necrotizing periodontitis	Gingiva and bone	Painful, red gingiva and loose teeth
Necrotizing stomatitis	Gingiva, bone, and soft tissue	Painful, red gingiva and removable teeth

TREATMENT

- **Routine dental care:** Brush and floss ± topical antiseptics: *Listerine* swish x 30-60 seconds bid, *Peridex*, etc.
- **Dental consultation:** Curettage and debridement
- **Antibiotics** (necrotizing stomatitis): Metronidazole; alternatives – clindamycin and amoxicillin-clavulanate

Oral Hairy Leukoplakia (OHL) (*Clin Infect Dis* 1997;25:1392)

CAUSE: Intense replication of EBV

PRESENTATION: Unilateral or bilateral adherent white/gray patches on lingual lateral margins ± dorsal or ventral surface of tongue. Patches

are irregular folds and projections.

DIFFERENTIAL: Candidiasis: OHL does not respond to azoles and cannot be scraped off, unlike *Candida*; Others: squamous cell carcinoma or traumatic leukoplakia.

DIAGNOSIS: Diagnosis is usually clinica.

IMPLICATIONS: Found almost exclusively with HIV, indicates low CD4 count, predicts AIDS, and responds to HAART.

TREATMENT (*Clin Infect Dis* 1997;25:1392): Rarely symptomatic and rarely treated, but occasional patients have pain or have concern about appearance. The options include:

- **HAART** (preferred)
- **Other:** topical podophylline

Salivary Gland Enlargement

CAUSE: The most common cause is diffuse infiltrative lymphocytosis syndrome (DILS), a condition associated with HIV and with Sjögren's syndrome (*Arthritis Rheum* 2006;55:466; *Ann Intern Med* 1996;125:494)

PRESENTATION: Parotid enlargement, cystic, unilateral or bilateral, non-tender, usually asymptomatic; may be painful, cosmetically disfiguring, or cause xerostomia (*Ear Nose Throat J* 1990;69:475; *Arthritis Rheum* 2006;55:466).

DIFFERENTIAL: Must differentiate cystic from solid lesion with CT scan (*Laryngoscope* 1998;98:772) and/or fine needle aspiration (FNA). FNA useful for microbiology and cytology and decompression. May require biopsy to exclude tumor, especially lymphoma. Biopsy usually shows histology resembling Sjögren's Syndrome; characteristic features are severe salivary duct atypia and foci of lymphocytes, predominantly CD8+ lymphocytes (*Arch Pathol Lab Med* 2000;124:1773; *J Oral Pathol Med* 2003;32:544); alternatively, there may be "non-specific chronic sialadenitis" (*Oral Dis* 2003;9:55). The most common pathogens when there is infection are mycobacteria and CMV. The frequency of this complication has decreased substantially during the HAART era (*Arthritis Rheum* 2006;55:466).

TREATMENT

- FNA for decompression of fluid-filled parotid cysts; may require large-bore needle for aspiration.
- **Xerostomia:** Sugarless chewing gum, artificial saliva, pilocarpine

PULMONARY COMPLICATIONS

Pneumonia

PRESENTATION: Cough, dyspnea, and fever ± sputum production

CAUSE: The single major prospective study of pulmonary complications of HIV was discontinued in the pre-HAART era – 1995 (*Am J Respir Crit Care Med* 1997;155:72). A more recent similar study concerned 885 HIV-infected women from the HIV Epidemiologic Research (HER) cohort followed in 1993-2000. An analysis of bacterial pneumonia in these women found a rate of 8.5 cases per 100 patient-years, 10-fold higher than the rate in age-matched controls (*Clin Infect Dis* 2006;43:90). Among those with a CD4 count <200 cells/mm^3, the rate was 17.9/100 patient-years. Incidence of pneumonia was significantly lower in those with high CD4 counts, TMP-SMX prophylaxis, and lack of HAART. For 195 cases the fatality rate was 8%, and the dominant pathogens were *S. pneumoniae* (43 cases) and *S. aureus* (22). Critical factors in evaluating the HIV infected patient with suspected pneumonia are

- **HIV stage** based on CD4 count (see Table 7-16, p. 316)
- **Time course:** Pyogenic infections and influenza evolve rapidly. PCP develops slowly in HIV-infected patients, with an average duration of 3 weeks prior to presentation.
- **Radiographic findings:** A negative chest x-ray generally excludes pneumonia, though 10% to 20% with PCP have a false negative x-ray (*J Acquir Immune Defic Syndr* 1994;7:39); infiltrates can be shown in these cases with thin-section CT scan (*Am J Radiol* 1997;169:967). Rare false-negative x-rays can be seen with tuberculosis, MOTT, and cryptococcosis (see Table 7-15). Intrathoracic lymphadenopathy on chest x-ray or CT scan suggests TB, lymphoma, KS, or atypical mycobacterial infection (*J Acquir Immune Defic Syndr* 2002;31:318).
- **Prophylaxis:** TMP-SMX (see Figure 7-3, p. 283) effectively reduces incidence of PCP, and bacterial pneumonia including *S. pneumoniae, Legionella, H. influenzae*, and *S. aureus*. Influenza vaccine appears to decrease the risk of influenza (*Arch Intern Med* 2001;161:441). *Pneumovax* shows variable results (*Br Med J* 2002;325:292). INH substantially reduces the risk of TB.
- **Bacteria:** The most common bacterial causes of pneumonia are, in rank order: *S. pneumoniae, H. influenzae, P. aeruginosa,* and *S. aureus* (*Clin Infect Dis* 2006;43:90; *Clin Infect Dis* 1996;23:107; *Am J Respir Crit Care Med* 1995;152:1309; *N Engl J Med* 1995;333:845; *J Infect Dis* 2001;184:268; *AIDS* 2002;16:2361; *J Acquir Immune Defic Syndr* 1994;7:823; *AIDS* 2003;17:2109). The risk of pneumococcal bacteremia is increased 150- to 300-fold with

HIV infection. *H. influenzae* pneumonia usually involves non-typeable strains (*JAMA* 1992;268:3350). *P. aeruginosa* is a cause of pneumonia in late stage HIV infection and often causes bacteremia and relapses (*J Acquir Immune Defic Syndr* 1994;7:823).

- **Atypical:** Pneumonia due to *M. pneumoniae, C. pneumoniae*, and *Legionella* appears to be relatively uncommon in patients with HIV infection (*Eur J Clin Microbiol Infect Dis* 1997;16:720; *N Engl J Med* 1997;337:682; *N Engl J Med* 1995;333:845; *Am J Resp Crit Care Med* 1995;152:1309; *Clin Infect Dis* 1996;23:107; *Am J Resp Crit Care Med* 2000;162:2063; *Clin Infect Dis* 2004;40[suppl 3]:S150).

DIAGNOSTIC SPECIMENS

- **Expectorated sputum:** Controversial, due in part to poor technique in collecting, transporting, and processing specimens.
- **Expectorated sputum for *M. tuberculosis*:** The yield with three specimens is 50% to 60% for AFB stain; and somewhat higher with PCR at 75% to 85% (*Am J Respir Crit Care Med* 2001;164:2020).
- **Induced sputum:** Recommended as an alternative to expectorated sputum for detection of AFB in patients who cannot produce an expectorated sample and as an alternative to bronchoscopy for detection of PCP. Sensitivity for detection of TB by AFB smear is about the same as it is for expectorated sputum; for PCP sensitivity is 56% (*Eur Resp J* 2002;20:982).
- **Bronchoscopy:** The yield for PCP is 95% or comparable to open-lung biopsy (*JAMA* 2001;286:2450). For *M. tuberculosis*, sensitivity is similar to that for expectorated sputum. For other bacteria, bronchoscopy is no better than expectorated sputum unless it is accompanied by quantitative culture.
- **Miscellaneous:** Tests to consider in atypical or nonresponsive pulmonary infections include *Legionella* urinary antigen, *H. capsulatum* serum and urinary antigen, serum cryptococcal antigen, CT scan and bronchoscopy with biopsy.

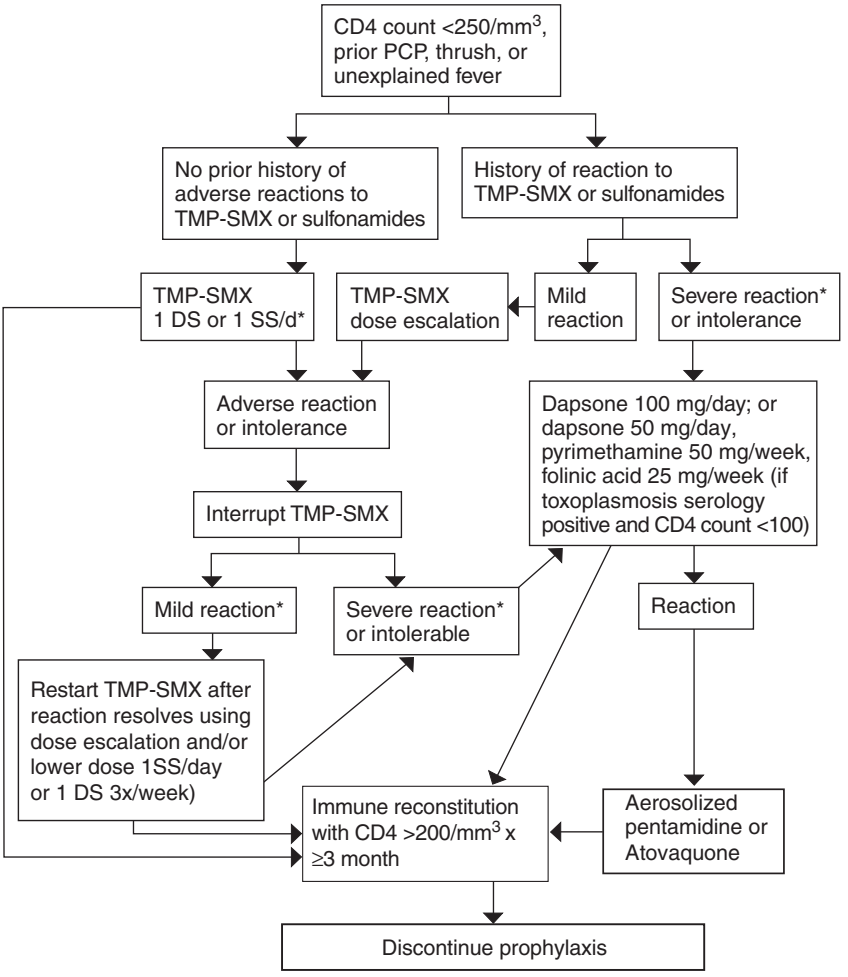
■ TABLE 7-15: Correlation of Chest X-ray Changes and Etiology of Pneumonia

Change	Common	Uncommon
Consolidation	Pyogenic bacteria, Kaposi's sarcoma, cryptococcosis	*Nocardia, M. tuberculosis, M. kansasii, Legionella, B. bronchiseptica*
Reticulonodular infiltrates	*P. jiroveci, M. tuberculosis*, histoplasmosis, coccidioidomycosis	Kaposi's sarcoma, toxoplasmosis, CMV, leishmania, lymphoid interstital pneumonitis
Nodules	*M. tuberculosis*, cryptococcosis	Kaposi's sarcoma, *Nocardia*
Cavity	*M. tuberculosis, S. aureus* (IDU), *Nocardia, P. aeruginosa*, cryptococcosis, coccidioidomycosis, histoplasmosis, aspergillosis, anaerobes	*M. kansasii*, MAC, *Legionella, P. carinii*, lymphoma, *Klebsiella, Rhodococcus equi*
Hilar nodes	*M. tuberculosis*, histoplasmosis, coccidioidomycosis, lymphoma, Kaposi's sarcoma	*M. kansasii*, MAC
Pleural effusion	Pyogenic bacteria, Kaposi's sarcoma, *M. tuberculosis* (congestive heart failure, hypoalbuminemia	Cryptococcosis, MAC, histoplasmosis, coccidioidomycosis, aspergillosis, anaerobes, *Nocardia*, lymphoma, toxoplasmosis, primary effusion lymphoma

■ TABLE 7-16: Etiology Correlated with CD4 Count

CD4 >200 cells/mm^3	*S. pneumoniae, M. tuberculosis, S. aureus* (IDU), influenza Non-Hodgkin lymphoma
CD4 50-200 cells/mm^3	Above + *P. jiroveci*, cryptococcosis, histoplasmosis, coccidioidomycosis, *Nocardia, M. kansasii*, Kaposi's sarcoma
CD4 <50 cells/mm^3	Above + *P. aeruginosa, Aspergillus*, MAC, CMV

■ FIGURE 7-2: **PCP Prophylaxis**



* **Severe:** Urticaria, angioedema, Stevens-Johnson reaction, or fever. **Intolerance:** GI symptoms, rash/pruritis. **Mild:** Tolerable with aggressive supportive care and/or dose reduction.

RENAL COMPLICATIONS (see *Ann Intern Med* 2003;139:214; IDSA/CDC Guidelines, *Clin Infect Dis* 2005;40:1559; *Clin Infect Dis* 2006;42:1488)

DIAGNOSES IN HIV-INFECTED PERSONS: HIVAN, membranous nephropathy, membranoproliferative glomerulo-nephritis, diabetic nephropathy, hypertensive nephropathy, and IgA nephropathy.

OVERVIEW

- Recommendations for routine testing (*Clin Infect Dis* 2005;40:1559)
  - Baseline urinalysis and calculated estimate of renal function
  - Annual screening if high risk (African American, CD4 <200/mm^3, or HIV RNA >4000 c/mL) or high-risk disease (diabetes, hypertension, HCV)

- Proteinuria >1+ (dipstick) or calculated GFR <60 mL/min/1.73 m^2 (MDRD equation) – refer to nephrologist
- Chronic kidney disease – defined as renal disease >3 months.

■ TABLE 7-17: **National Kidney Foundation Stages for Chronic Kidney Disease**

Stage	Description	GFR
1	Normal GFR	>90
2	Mild ¬ GFR	60-89
3	Moderate ¬ GFR	30-59
4	Severe ¬ GFR	15-29
5	Renal failure	<15

- Cockroft-Gault equations for calculating creatine clearance:

  Male

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

  Female

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

- Chronic kidney disease: ultrasound to detect stones and assess renal size

  small: <9 cm – often severe kidney disease

  large: HIVAN (but nonspecific)

- Other studies: HBV, HCV, complement, ANA, cryoglobulin, quantitative immunoglobulin, blood glucose, protein electrophoresis

■ **Dialysis:** The prognosis with hemodialysis or peritoneal dialysis plus HAART is similar to that without HIV infection (*J Am Soc Nephrol* 2002;13:1889; *Am J Kidney Dis* 2000;36:574).

■ **Acute renal failure (ARF):** Incidence is reported at 6 cases per 100 patient-years (*Kidney Int* 2005;67:1526). Most common HIV-associated causes are HIVAN, TTP, HCV cryoglobulinemia, and drug-related (*Clin Infect Dis* 2006;42:1488). Predictors include concurrent diabetes, chronic renal or liver disease, and hepatitis (*AIDS* 2006;20:561). Drugs most likely to cause ARF in this population are aminoglycosides, amphotericin, cidofovir, foscarnet, pentamidine, TMP-SMX, and high-dose acyclovir. Antiretroviral drugs implicated are IDV with indinavir crystalluria (*J Acquir Immune Defic Syndr* 2003;32:135) and TDF with acute tubular necrosis (*Clin Infect Dis* 2006;42:283). See Chapter 5 for drug information.

■ **Nephrotoxic drugs:**

Hepatitis C Coinfection (see *J Am Soc Nephrol* 1999;10:1566)

CAUSE: Mixed cryoglobulinemia

SYMPTOMS: Palpable purpura, decreased complement, and renal disease with hematuria and proteinuria; may present with acute renal failure and/or nephrotic syndrome.

DIAGNOSIS: 1) evidence of hepatitis C (positive EIA and HCV RNA); 2) renal disease (hematuria and proteinuria) that may be in the nephrotic range; 3) low complement; 4) renal biopsy evidence of HCV-immune complexes; and 5) circulating cryoglobulins ± skin biopsy of purpuric lesion.

HIV-Associated Immune-Mediated Glomerulonephritides

DEFINITION: Immune complex-mediated glomerulonephritis includes postinfectious glomerulonephritis, membranous nephritis, IgA nephritis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and membranoproliferative glomerulonephritis (*Ann Intern Med* 2003;139:214; *Kidney Int* 2005;67:1381; *Nephrol Dial Transplant* 1993;8:11; *Clin Infect Dis* 2006;42:1488).

FREQUENCY: Estimated at 15%-80% in HIV-infected patients (*Clin Infect Dis* 2006;42:1488). Unlike HIVAN, there is no predisposition in persons of African descent.

TREATMENT: HAART, ACE inhibitors, and/or corticosteroids (*Clin Nephrol* 2003;60:187; *Nephrol Dial Transplant* 1997;12:2796).

Nephrotoxic Drugs

- Common nephrotoxins include aminoglycosides, amphotericin B, cidofovir, foscarnet, pentamidine, TMP-SMX, high-dose IV acyclovir, and NSAIDS.
- Indinavir can cause both nephrolithiasis and indinavir nephropathy (renal insufficiency due to crystalluria) (*J Acquir Immune Defic Syndr* 2003;32:135). Urinalysis demonstrates sterile pyuria.
- Tenofovir has not caused renal toxicity in clinical trials involving treatment-naïve patients, but case reports and cohort studies have shown modest declines in renal function, especially in patients with impaired baseline renal function and/or advanced HIV disease (*Clin Infect Dis* 2005;40:1194). Renal function decline does not appear to be progressive. There have also been reports of proximal renal tubular dysfunction (Fanconi's syndrome), which may be idiosyncratic. Renal function should be monitored using Cockcroft-Goult or MDRD equations.

Abbreviations

Drug Abbreviations

3TC	Lamivudine
5-FC	Flucytosine
ABC	Abacavir
APV	Amprenavir
ATV	Atazanavir
AZT, ZDV	Zidovudine
d4T	Stavudine
ddI	Didanosine
DLV	Delavirdine
DRV	Darunavir
EFV	Efavirenz
EMB	Ethambutol
ENF, T20	Enfuvirtide
EPO	Erythropoietin
FPV	Fosamprenavir
FTC	Emtricitabine
G-CSF	Filgrastim
HU	Hydroxyurea
IDV	Indinavir
INH	Isoniazid
LPV/r	Lopinavir/Ritonavir
NFV	Nelfinavir
NVP	Nevirapine
PZA	Pyrazinamide
RIF	Rifampin
RTV	Ritonavir
SM	Streptomycin
SMX	Sulfamethoxazole
SQV	Saquinavir
TDF	Tenofovir disoproxil fumarate
TMP	Trimethoprim
TMP-SMX	Trimethoprim-sulfamethoxazole
TPV	Tipranavir

Drug Administration Abbreviations

bid	Twice a day
caps	Capsules
cc	Cubic centimeter
cm	Centimeter
cm^2	Centimeters squared
d/c	Discontinue
dL	Deciliter
DS	Double strength
dx	Diagnosis
g	Gram
H_2O	Water
Hg	Mercury
h	Hour
hs	Hours of sleep
IM	Intramuscular
IU	International unit
IV	Intravenous
kg	Kilogram
L	Liter
m	Meter
m^2	Meters squared
max	Maximum
mcg	Microgram
mEq	Milliequivalent
mg	Milligram
mil	Million
min	Minimum
mL	Milliliter
mm	Millimeter
mM	Millimole
mo	Month
MU	Million units
N	Normal (solution) or total sample size
ng	Nanogram
OTC	Over-the-counter
PO	By mouth
PSI	Pounds per square inch
pt-yrs	Patient-years
q	Every

Drug Administration Abbreviations *(Continued)*

qd	Every day
qhs	At bedtime
qid	Four times a day
qod	Every other day
SQ	Subcutaneously
sol'n	Solution
SS	Single strength
tabs	Tablets
tid	Three times per day
tiw	Three times per week
U	Unit
vol	Volume
wk	Week
wgt	Weight
x	Times
XL	Extended release
yr	Year
µg	Microgram
µL	Microliter
µM	Micrometer
µmol	Micromole

Other Abbreviations

ACTG	AIDS Clinical Trial Group (U.S.)
ADL	Activities of daily living
ADR	Adverse drug reaction
AETC	AIDS Education Training Center (U.S.)
AFB	Acid-fast bacillus
Al	Aluminum
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-HAV	Hepatitis A antibody
anti-HBc	Hepatitis B core antibody
anti-HBs	Hepatitis B surface antibody
anti-HCV	Hepatitis C antibody
ART	Antiretroviral therapy
ASCUS	Atypical sqamous cells of undetermined significance
AST	Aspartate aminotransferase
AWP	Average wholesale price
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention (U.S.)
CF	Complement fixation
CMV	Cytomegalovirus
CNS	Central nervous system
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CROI	Conference on Retroviruses and Opportunistic Infections
C-section	Cesarean section
CSF	Cerebrospinal fluid
CT	Computerized tomography
CTL	Cytotoxic T lymphocyte
DEXA	Dual energy x-ray absorptiometry
DFA	Direct fluorescent antibody
DHHS	Department of Health and Human Services (U.S.)
DOT	Directly observed therapy
EBV	Epstein-Barr virus
EDTA	Ethylenediamine tetraacetic acid
EIA	Enzyme immunosorbent assay
EM	Electron microscopy
ERCP	Endoscopic retrograde cholangio-pancreatography
ETOH	Alcohol
FOB	Fiberoptic bronchoscopy
FDA	Food and Drug Administration (U.S.)
G6-PD	Glucose-6-phosphate dehydrogenase
GFR	Glomerular filtration rate
GI	Gastrointestinal
HAART	Highly active antiretroviral therapy
HAD	HIV-associated dementia
HAV	Hepatitis A virus
$HBeAg^-$	Hepatitis B early antigen
HBIG	Hepatitis B immune globulin
HBV	Hepatitis B virus
HCFA	Health Care Financing Administration (U.S.)

General Abbreviations *(Continued)*

HCV	Hepatitis C virus
HCW	Health care worker
HDL	High density lipoprotein
Hgb	Hemoglobin
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus 1
HSV-2	Herpes simplex virus 2
HTLV-1	Human T-cell leukemia virus 1
HTLV-2	Human T-cell leukemia virus 2
IAS	International AIDS Society
IAS-USA	International AIDS Society-U.S.A.
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy
ICL	Idiopathic CD4 lymphocytopenia
IDSA	Infectious Diseases Society of America
IFA	Immunofluorescent assay
IFN	Interferon
IG	Immune globulin
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-2	Interleukin 2
IM	Intramuscular
IOM	Institute of Medicine (U.S.)
IRIS	Immune reconstitution inflammatory syndrome
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat (analysis)
IVIG	Intravenous immune globulin
JCV	JC virus
KOH	Potassium hydroxide
KS	Kaposi's sarcoma
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFT	Liver function test
LP	Lumbar puncture
LSIL	Low-grade squamous intraepithelial lesion
LVEF	Left ventricular ejection fraction
MAC	*Mycobacterium avium* complex
MACS	Multicenter AIDS Cohort Study
MAO	Monoamine oxidase
MCV	Mean corpuscular volume
MDRTB	Multidrug-resistant tuberculosis
Mg	Magnesium
MSM	Men who have sex with men
MSSA	Methicillin-sensitive *Staph aureus*
NASBA	Nucleic acid sequence-based amplification
NCEP	National Cholesterol Education Program (U.S.)
NCI	National Cancer Institute (U.S.)
NIAID	National Institute of Allergy and Infectious Diseases (U.S.)
NIH	National Institutes of Health (U.S.)
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
N.S.	Not significant
NSAID	Nonsteroidal anti-inflammatory drug
OHL	Oral hairy leukoplakia
OI	Opportunistic infection
OP	Opening pressure
Pap smear	Papanicolaou smear
PBMC	Peripheral blood mononuclear cells
PCP	*Pneumocystis jiroveci* pneumonia
PCR	Polymerase chain reaction
PEP	Postexposure prophylaxis
PGL	Persistent generalized lymphadenopathy
PHS	Public Health Service (U.S.)
PID	Pelvic inflammatory disease
PI	Protease inhibitor
PML	Progressive multifocal leukoencephalopathy
PMN	Polymorphonuclear leukocyte
PPD	Purified protein derivative (of tuberculin)
PUVA	Psoralen ultraviolet A-range

General Abbreviations *(Continued)*

RBC	Red blood cells
rHU EPO	Recombinant human erythropoietin
RIBA	Recombinant Immunoblot assay
RPR	Rapid plasma regain
RT	Reverse transcriptase
RT-PCR	Reverse transcriptase polymerase chain reaction
SIL	Squamous intraepithelial lesion
SSRI	Selective serotonin reuptake inhibitor
STD	Sexually transmitted disease
STEPS	Systems for Thalidomide Education and Prescribing Safety
STI	Structured treatment interruption
SVR	Sustained viral response
TAM	Thymidine analog mutation
TB	Tuberculosis
TEN	Toxic epidermal necrolysis
THC	Tetrahydrocannabinol
TLC	Total lymphocyte count
TNF-alpha	Tumor necrosis factor-alpha
TSH	Thyroid-stimulating hormone
TST	Tuberculin skin test
ULN	Upper limit of normal
USPHS	Public Health Service (U.S.)
UTI	Urinary tract infection
UVB	Ultraviolet B
VL	Viral load
VRDL	Venereal disease research laboratory
vs	Versus
VZIG	Varicella zoster immune globulin
VZV	Varicella zoster virus
WBC	White blood count
WB	Western blot
WHO	World Health Organization
XDRTB	Extensively drug-resistant tuberculosis

Table Index

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Page numbers followed by "f" indicate figures; those followed by "t" indicate tables.

■ TABLE 4-10 A: **Antiretroviral Drugs Approved by the FDA for Treatment of HIV Infection**

Generic Name (Abbreviation)	Brand Name	Manufacturer	FDA Approval Date
Zidovudine (AZT, ZDV)	*Retrovir*	GlaxoSmithKline	March 1987
Didanosine (ddI)	*Videx*	Bristol-Myers Squibb	October 1991
Zalcitabine (ddC)*	*Hivid*	Hoffmann-La Roche	June 1992
Stavudine (d4T)	*Zerit*	Bristol-Myers Squibb	June 1994
Lamivudine (3TC)	*Epivir*	GlaxoSmithKline	November 1995
Saquinavir (SQVhgc)	*Invirase*	Hoffmann-La Roche	December 1995
Ritonavir (RTV)	*Norvir*	Abbott Laboratories	March 1996
Indinavir (IDV)	*Crixivan*	Merck & Co., Inc.	March 1996
Nevirapine (NVP)	*Viramune*	Boehringer Ingelheim	June 1996
Nelfinavir (NFV)	*Viracept*	Pfizer	March 1997
Delavirdine (DLV)	*Rescriptor*	Pfizer	April 1997
Zidovudine/Lamivudine (AZT/3TC)	*Combivir*	GlaxoSmithKline	September 1997
Saquinavir (SQVsgc)*	*Fortovase*	Hoffmann-La Roche	November 1997
Efavirenz (EFV)	*Sustiva*	DuPont Pharmaceuticals	September 1998
Abacavir (ABC)	*Ziagen*	GlaxoSmithKline	February 1999
Amprenavir (APV)*	*Agenerase*	GlaxoSmithKline	April 1999
Lopinavir/Ritonavir (LPV/r)	*Kaletra*	Abbott Laboratories	September 2000
Zidovudine/lamivudine/ abacavir (AZT/3TC/ABC)	*Trizivir*	GlaxoSmithKline	November 2000
Tenofovir DF (TDF)	*Viread*	Gilead Sciences	October 2001
Enfuvirtide (ENF)	*Fuzeon*	Roche	March 2003
Atazanavir (ATV)	*Reyataz*	Bristol-Myers Squibb	June 2003
Emtricitabine (FTC)	*Emtriva*	Gilead Sciences	July 2003
Fosamprenavir (FPV)	*Lexiva*	GlaxoSmithKline	November 2003
Lamivudine/abacavir (3TC/ABC)	*Epzicom*	GlaxoSmithKline	August 2004
Tenofovir/emtricitibine (TDF/FTC)	*Truvada*	Gilead Sciences	August 2004
Tipranavir (TPV)	*Aptivus*	Boehringer Ingelheim	June 2005
Darunavir (DRV)	*Prezista*	Tibotec	June 2006
Efavirenz/tenofovir/ emtricitabine (EFV/TDF/FTC)	*Atripla*	Gilead Sciences Bristol-Myers Squibb	July 2006

*Withdrawn from the market.

INFORMATION ON FPD

In the ten years since FPD was established in 1997 by the South African Medical Association it has become the largest health sector training institution in Southern Africa and has become the first self funding health sector training institution to receive full registration as a private institution of higher education (private university status) (Registration Certificate number 2002/HE07/013).

FPD's regional focuses is on Education, Research and Health Sector Capacity Development. Over the past 10 years the organization has provided high quality education to 63,757 healthcare professionals and managers in 10 countries on one or more of FPD's 85 existing courses.

FPD also has a significant commitment to improving health sector operational capacity through projects aimed at improving service delivery. These include:

- Positive Life Project – a public-private partnership that supports 36,000 patients on AIDS treatment.

- That's it Project – a public-private initiative aimed at strengthening TB services and the linkage between HIV/AIDS and TB services

- The Compass Project – a project that identifies AIDS service needs, develops directories of service providers and develops the capacity of grass roots organisations to address service gaps.

- African Medical Placements – a project that addresses shortages of professional staff by matching foreign qualified health care professions to vacancies in the public sector.

- PEPFAR Fellowship Programme – a project that seconds newly qualified Masters degree students to spend 6 months with an AIDS service organisation.

FPD is also dedicated to the dissemination and development of scientific knowledge. Research is a dedicated focus area of FPD and is actively pursued by units such as our Infectious Diseases unit. FPD's Conference division is also regularly organising large national and international conferences including the South African National AIDS Conference and the South African National TB Conference.

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