

PSAP

PHARMACOTHERAPY SELF-ASSESSMENT PROGRAM

SEVENTH EDITION • BOOK 9

INFECTIOUS DISEASES



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AMERICAN COLLEGE OF CLINICAL PHARMACY

HIV INFECTION AND AIDS



By P. BRANDON BOOKSTAVER, PHARM.D., BCPS
(AQ INFECTIONOUS DISEASES), AAHIVE

Reviewed by Patrick G. Clay, Pharm.D., FCCP, CCTI; Jeffrey T. Sherer, Pharm.D., MPH, BCPS;
and Nancy S. Yunker, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Based on Centers for Disease Control and Prevention (CDC) recommendations, determine the appropriateness of patient-specific HIV screening.
2. Based on Department of Health and Human Services guidelines, devise an appropriate plan for antiretroviral therapy (ART) for the treatment-naïve patient.
3. Evaluate the appropriate timing of ART initiation after a risk-benefit assessment of potential complications.
4. Assess patients coinfecting with HIV and hepatitis and determine appropriate treatment strategies.
5. Based on CDC recommendations, devise a treatment plan for occupational and nonoccupational HIV exposure cases.
6. Based on CDC recommendations, design HIV prevention strategies including preexposure prophylaxis.
7. Determine the need for opportunistic infection (OI) prophylaxis and appropriate regimen selection.
8. Devise an optimal treatment plan for the patient with an active OI, including the patient requiring alternative treatment strategies.

INTRODUCTION

The history of acquired immunodeficiency syndrome (AIDS) in the United States began with the unusual presentation of pneumonia, identified as *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia (PCP) in five

homosexual men in the Los Angeles area in 1981. During the following 30 years, the AIDS epidemic has been responsible for the death of about 597,500 Americans. The Centers for Disease Control and Prevention (CDC) estimates almost 1.1 million Americans are living with human immunodeficiency virus (HIV), with about 56,000 new infections annually. Up to 25% of infected people may be unaware of their status and similarly responsible for up to 50% of disease transmission. Worldwide, 33.3 million people are living with HIV or AIDS.

Advances in potent antiretroviral therapy (ART) and antimicrobial prophylaxis of opportunistic infections (OIs) have stabilized rates of new HIV infection, reduced progression to AIDS, and lowered rates of AIDS-related complications and death. Rates of OI have dropped precipitously, from 89 cases per 1000 person-years in 1994–1997 to 13 cases per 1000 person-years in 2003–2007. Simultaneously, the average life expectancy now approaches that of a noninfected person; a 20-year-old with a new diagnosis of HIV is expected to live to age 70 or older with sustained viral suppression.

Although therapeutic advances and knowledge of the disease have progressed exponentially during the past 2 decades, the cumulative burden of HIV disease continues to climb. Because almost one-third of the physicians providing care for HIV-positive individuals are expected to retire within the next 10 years, almost every health care worker will be called on to play a role in medically managing HIV-positive patients.

BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. October 14, 2011:1–167. Available at aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 16, 2011.
- Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR 2009;58(RR-4):[1–204]. Available at aidsinfo.nih.gov/contentfiles/Adult_OI_041009.pdf. Accessed November 16, 2011.

ABBREVIATIONS IN THIS CHAPTER

ART	Antiretroviral therapy
CNS	Central nervous system
HBV	Hepatitis B virus
HCV	Hepatitis C virus
INSTI	Integrase strand-transfer inhibitor
IRIS	Immune reconstitution inflammatory syndrome
MAC	<i>Mycobacterium avium</i> complex
MTB	<i>Mycobacterium tuberculosis</i>
NNRTI	Nonnucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
OI	Opportunistic infection
PCP	<i>Pneumocystis jirovecii</i> pneumonia
pegIFN α	Pegylated-interferon alfa
PeP	Postexposure prophylaxis
PI	Protease inhibitor
PrEP	Preexposure prophylaxis

Transmission and Testing

Homosexual male contact continues to be the predominant method of HIV transmission in the United States, representing 54% of new HIV cases in 2008. Intravenous drug use and heterosexual contact cause about 10% and 33% of new infections, respectively. A large racial disparity exists, with about one-half of all infections occurring in African Americans. The racial disparity is even greater in the Deep South, approaching 75% of cumulative cases in some areas. African Americans represent almost two-thirds of new infections among women, the fastest growing population of HIV-positive people. Mother-to-child transmission, or vertical transmission, has declined significantly during the past decade. Virologic control (i.e., reduction in viral load to less than 1000 copies/mL) in HIV-positive mothers can reduce the risk of mother-to-child transmission to below 2%.

The annual rate of new infections has not decreased significantly during the past decade despite advances in ART and in knowledge of the disease. Undiagnosed cases, which may account for almost 25% of HIV-positive individuals, are a strong contributor to this lack of decline in new infections. Almost 75% of HIV-positive individuals have visited a health care facility in the 2 years before diagnosis, and 20% of these patients had an illness that should have prompted HIV screening. Missed opportunities to diagnose HIV in these patients also represent missed opportunities to reduce further transmission and to slow or halt the progression to AIDS.

High-risk sexual behavior continues to contribute to HIV transmission, including new opportunities

introduced through social media and online social networking. Knowledge of disease can improve behavior patterns in many patients infected with HIV. In an effort to account for these missed opportunities and to address the problem of individuals infected with HIV who are unaware of their diagnosis, the CDC in 2006 recommended an opt-out screening (no specific written consent required) policy for all patients aged 13–64 exposed to the health care system, regardless of underlying suggestion of HIV infection. State or local regulations may contain more stringent policies or requisites for consent to HIV screening that conflict with CDC recommendations. Clinicians should maintain a working knowledge of their state, local, and institutional statutes to provide appropriate screening recommendations and accurate information to patients.

Screening tests rely primarily on the detection of antibodies to HIV and carry a sensitivity approaching 100%. Aside from conventional enzyme-linked immunosorbent assay (ELISA), rapid screening tests, with results available in 20–30 minutes, are available for point-of-care testing. Rapid tests react to HIV antibodies in blood, serum, or saliva samples. A positive test result should always be confirmed by a more specific test (e.g., Western blot) for HIV diagnosis. National rates of screening increased from 40% during 2001–2005 to 45% in 2009. However, overall rates remain low, and there are continued missed opportunities for HIV testing in pharmacies, clinics, and hospitals, as well as in high-risk exposure areas such as prisons and homeless shelters. Barriers to screening (e.g., allocated time for testing, need for referrals, lack of clinician awareness of recommendations) continue to be identified. Pharmacists can play an important role in recommending HIV screening at the individual patient level and as a member of an interprofessional team identifying strategies to implement screening procedures at the department, clinic, or institution level.

Pathophysiology and Disease Course

The hallmark of HIV pathology is the destruction of CD4⁺ T lymphocytes, which leaves the host at heightened risk of OIs. Viral replication begins through binding to the host CD4⁺ cells at the glycoprotein gp120 and is believed to occur at coreceptors (i.e., chemokine receptor type 4 [CXCR4] and chemokine receptor type 5 [CCR5]). The CCR5 coreceptor is usually associated with early infection, whereas the CXCR4 coreceptor is more prevalent in advanced disease and treatment-experienced patients. The CCR5 inhibitor maraviroc blocks the coreceptor binding step in the viral replication process. The replication of HIV continues with gp41-dependent membrane fusion, allowing viral entry into the cell. The entry inhibitor enfuvirtide blocks the binding to gp41.

Inside the CD4⁺ cell, uncoating of the capsid releases single-stranded viral RNA, which is then converted to

double-stranded proviral DNA by the enzyme reverse transcriptase. Nucleoside reverse transcriptase inhibitors (NRTIs), which are nucleoside or nucleotide analogs incorporated into the proviral DNA, act as chain terminators. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) directly inhibit the enzyme and prevent further chain elongation. The enzyme integrase is responsible for transporting the proviral DNA for incorporation into the host CD4⁺ cell DNA. The integrase strand-transfer inhibitor (INSTI) raltegravir acts to block incorporation of the proviral DNA into the CD4⁺ genome. Successful integration of viral and host DNA is followed by translation into polyproteins; these are cleaved into individual proteins, forming a new virion available for budding from the CD4⁺ cell. Protease inhibitors (PIs) block this final packaging step and prohibit the assembly of new viral particles.

The viral replication process can occur billions of times daily. After initial infection, the virus rapidly disseminates throughout the body (primarily to the lymphoid tissues), accompanied by a significant rise in viral load (also termed HIV RNA) and a precipitous decline in CD4⁺ cell counts. Up to 70% of patients with new infections will experience a syndrome characterized by flu-like or mononucleosis-like symptoms (e.g., fever, adenopathy, rash, upper respiratory tract symptoms, myalgias or arthralgias, blood dyscrasias). Commonly referred to as acute HIV syndrome, this occurs most often in the first 2–4 weeks postinfection. Although it is typically self-limiting, about 10% to 20% of patients seek medical care, representing an opportunity for early diagnosis. Diagnosing HIV during this preantibody stage should include direct measurement of HIV RNA in the blood.

Rarely, an individual seems to be able to contain viral replication; the exact reason for this is undergoing intense evaluation. Most infected people have an immune response typical of viral exposure (i.e., development of antibodies against the pathogen and an increase in natural killer cells); however, despite this response, there is continued increase in viremia, steady decline in CD4⁺ cells, and emergence of OIs and AIDS-defining illness. Up to 5% of people infected with HIV remain asymptomatic, maintaining normal CD4⁺ cell counts for years without ART; these people are termed *long-term nonprogressors*. About 1% of patients infected with HIV are termed *elite controllers*, maintaining undetectable viral loads with high CD4⁺ cell counts without ART. Slow disease progression may be the result of variable genotypes of the 32-bp deletion (Δ 32) at the CCR5 coreceptor. People who are homozygous for the CCR5 Δ 32-bp deletion do not express the coreceptor on CD4⁺ cells and are subsequently resistant to HIV infection.

The average time from initial infection to a diagnosis of AIDS is about 10 years without ART. The diagnosis of AIDS is made one of two ways: a serum CD4⁺

count of less than 200 cells/mm³ or the presence of an AIDS-defining illness. Included in AIDS-defining illnesses are OIs such as PCP, *Toxoplasmosis gondii*, and *Mycobacterium tuberculosis* (MTB). A complete list of AIDS-defining illnesses is included in the Department of Health and Human Services (DHHS) HIV Management Guidelines published in October 2011.

TREATMENT

On entry into care and before initiation of ART, baseline laboratory panels should be obtained to include evaluation of kidney and liver function, hematologic status, glucose-6-phosphate dehydrogenase (G6PD), and hepatitis B virus (HBV) and hepatitis C virus (HCV) status. A complete list of all recommended baseline evaluations is included in the DHHS guidelines. Because the estimated transmission rates of resistant virus range from 6% to 24%, antiretroviral resistance testing should be performed before therapy initiation. Results from resistance testing may take several weeks; therefore, certain circumstances (e.g., a captive patient who is symptomatic) may dictate initiation of ART before results are available. Resistance testing should also be used for suspected virologic failures in patients receiving ART. Therapeutic choices can be reevaluated, if necessary, at that time. Patient readiness to begin therapy must be assessed, barriers to adherence should be identified, and modifiable risk factors for nonadherence (e.g., alcohol abuse, smoking) should be addressed. Counseling for substance abuse, unstable social circumstances, and/or psychiatric disorders should be made available. Methods for increasing adherence are discussed in the following sections.

The growing availability of treatment-related data prompts frequent updates to the guidelines, as often as every 9–12 months. The therapy goals remain consistent: to reduce HIV-related morbidity and mortality, preserve immune function, minimize treatment-related adverse effects, and improve overall quality of life. Laboratory-specific goals related to immune function include complete viral suppression (HIV RNA less than 50 copies/mL) and maintenance of CD4⁺ cell counts to as high as possible, but at minimum, above the OI-risk threshold of 200 cells/mm³. With proper adherence to a potent ART regimen, successful outcomes can be expected in up to 95% of patients.

A minimum of three active agents are required in a regimen for antiretroviral-naïve patients. Two NRTIs serve as the backbone of every regimen, together with an NNRTI, PI, or INSTI as the third agent. In a PI-based regimen (i.e., two NRTIs plus one PI), therapy should also include low-dose ritonavir, a member of the PI class that possesses anti-HIV activity. Ritonavir is usually given at a low or “boosting” dose in combination with a second PI. Because of its potent cytochrome

P450 (CYP) 3A4 inhibition properties, ritonavir boosts the concentrations of the concomitant PI, allowing increased potency. Figure 1-1 shows a treatment algorithm with priority regimens as recommended by the DHHS guidelines. Given that several first-line regimens are recommended, ART selection must be patient-specific and accommodate comorbid conditions, lifestyle,

adherence barriers, and other concomitant drugs. The advantages and disadvantages associated with specific ART regimens are listed in Table 1-1.

Treatment response is evaluated on the basis of prevention of breakthrough infections and HIV-related hospitalizations; improved or sustained quality-of-life outcomes; and improved CD4⁺ cell counts and

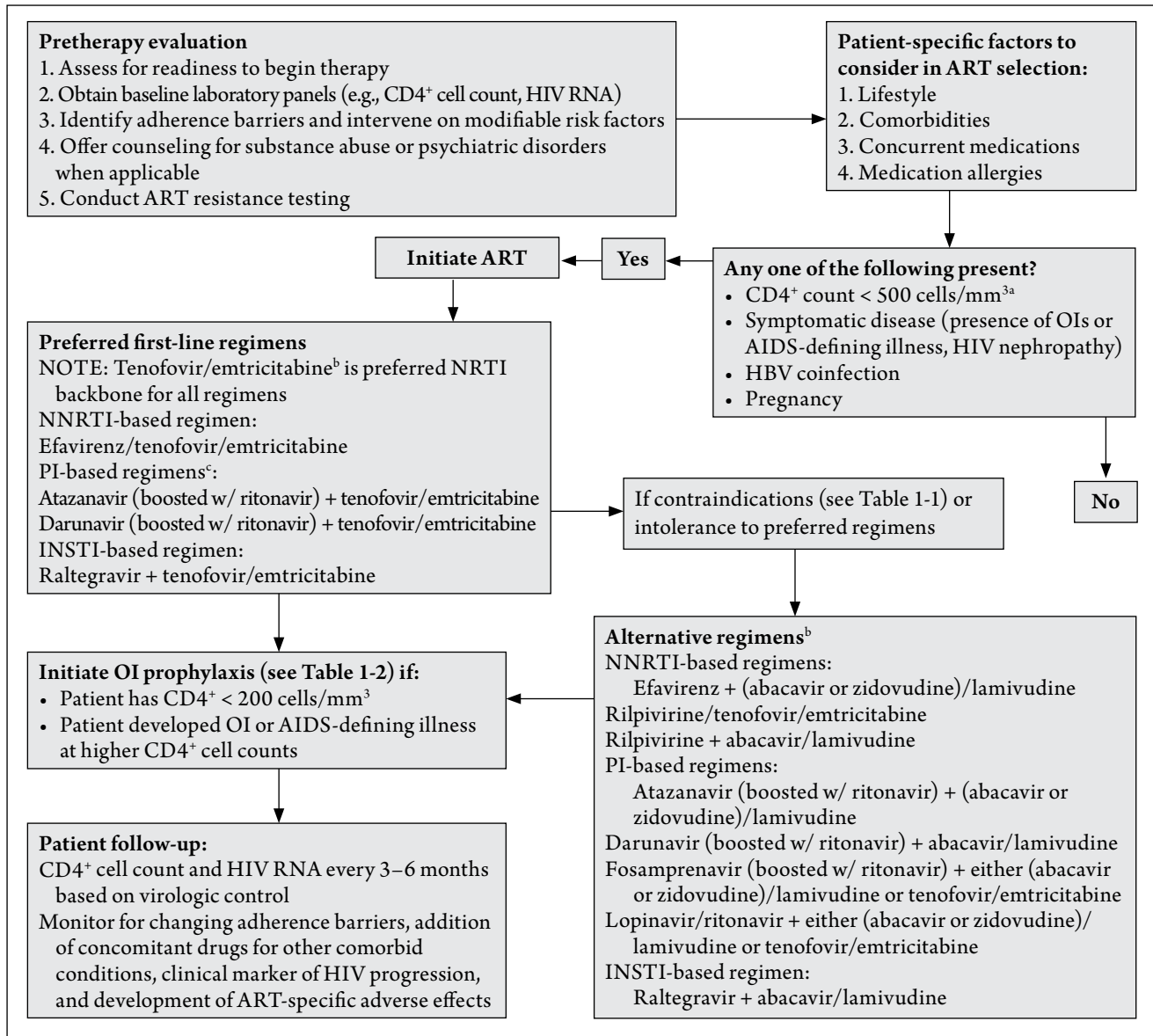


Figure 1-1. Decision tree for antiretroviral therapy (ART) initiation in treatment-naive patients.

Adapted from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. DHHS. October 14, 2011;1-167. Available at aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 18, 2011.

^aDHHS panel had a split vote on whether to make this an A or B rating.

^bLamivudine and emtricitabine can be used interchangeably in each regimen; coformulations, when available, are preferred.

^cPI-based regimens should always be boosted by ritonavir.

ART = antiretroviral therapy; DHHS = Department of Health and Human Services; HBV = hepatitis B virus; INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; PI = protease inhibitor.

Table 1-1. Properties of Commonly Used Antiretrovirals

Antiretroviral Class or Agent	Standard Dosing and Dose Adjustment	Primary Adverse Effects	Cautions/Contraindications/Monitoring
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		Class-wide: Lactic acidosis, hepatic steatosis, lipodystrophy, hyperlipidemia	
Tenofovir (TDF) <u>Coformulated:</u> TDF/FTC TDF/FTC/EFV TDF/FTC/RPV	300 mg daily <u>Renal:</u> required < 50 mL/min <u>Hepatic:</u> none	Nephrotoxicity (acute or chronic); reduced BMD	Because of anti-HBV activity, withdrawal/resistance may cause HBV flares in coinfecting patients; when discontinued, HBV therapy should be replaced Coformulations w/ emtricitabine (FTC), efavirenz (EFV)/FTC, and rilpivirine (RPV)/FTC cannot be used in patients w/ severe kidney dysfunction (CrCl <30 mL/min) because of required dose modifications <u>Monitoring:</u> kidney function; consider BMD
Emtricitabine (FTC) <u>Coformulated:</u> TDF/FTC TDF/FTC/EFV TDF/FTC/RPV	200 mg capsule daily; 240 mg solution daily <u>Renal:</u> required < 50 mL/min <u>Hepatic:</u> none	Hyperpigmentation of palms/soles (dark complexion)	Because of anti-HBV activity, withdrawal/resistance may cause HBV flares in coinfecting patients; when discontinued, HBV therapy should be replaced Do not combine with 3TC in treatment regimen Coformulations w/ TDF, TDF/EFV, or TDF/RPV cannot be used in patients w/ severe kidney dysfunction (CrCl < 30 mL/min) because of required dose modifications
Zidovudine (AZT) <u>Coformulated:</u> AZT/3TC AZT/3TC/ABC	300 mg BID; 200 mg TID (available IV or PO) <u>Renal:</u> required in end-stage kidney disease <u>Hepatic:</u> caution in moderate to severe impairment	Bone marrow suppression (macrocytic anemia, neutropenia), N/V, asthenia, myopathy, hyperpigmentation of nail beds/mucosa, lipodystrophy, lactic acidosis	Do not combine with d4T in treatment regimen <u>Monitoring:</u> CBC including MCV which may be used as an indirect marker of adherence
Abacavir (ABC) <u>Coformulated:</u> ABC/3TC AZT/3TC/ABC	300 mg BID; 600 mg daily <u>Renal:</u> none <u>Hepatic:</u> caution in moderate to severe impairment	Hypersensitivity reaction characterized by fever, rash, respiratory distress, GI effects, malaise, and SOB, possible increased risk of CV toxicity	HLA-B*5701 screening is recommended before treatment; a positive screening test precludes use because of increased risk of hypersensitivity reaction Caution in high-risk CV disease and HIV RNA > 100,000 copies/mL (because of treatment failures) <u>Monitoring:</u> hypersensitivity reaction in first several weeks after initiation
Lamivudine (3TC) <u>Coformulated:</u> ABC/3TC AZT/3TC AZT/3TC/ABC	150 mg BID; 300 mg daily <u>Renal:</u> Required < 50 mL/min <u>Hepatic:</u> None	Pancreatitis in children	Mitochondrial toxicities > FTC Do not combine with FTC in treatment regimen Because of anti-HBV activity, withdrawal/resistance may cause HBV flares in coinfecting patients; when discontinued, HBV therapy should be replaced
Didanosine (ddI)	> 60 kg: 400 mg daily < 60 kg: 250 mg daily <u>Renal:</u> required <60 mL/min <u>Hepatic:</u> None	Pancreatitis (high risk), peripheral neuropathy, nausea, optic neuritis/retinal changes	Do not combine with TDF or d4T in treatment regimen Caution in patients at high risk of CV disease
Stavudine (d4T)	> 60 kg: 40 mg BID < 60 kg: 30 mg BID <u>Renal:</u> required < 60 mL/min <u>Hepatic:</u> none	Fatal lactic acidosis, lipodystrophy, peripheral neuropathies, hyperlipidemia, diabetes mellitus, rapid neuromuscular weakness	Do not combine with ddI or AZT in treatment regimen

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Table 1-1. Properties of Commonly Used Antiretrovirals (Continued)

Antiretroviral Class or Agent	Standard Dosing and Dose Adjustment	Primary Adverse Effects	Cautions/Contraindications/Monitoring
Non-nucleoside Reverse Transcriptase Inhibitors		Class-wide: rash	Class-wide: long terminal half-life; drug-drug interactions (CYP 450)
Efavirenz (EFV)	600 mg daily at bedtime <u>Renal:</u> none	Rash, CNS toxicity may present as dizziness, HA, insomnia, vivid dreams/nightmares, inability to concentrate, hyperlipidemia	Contraindicated in first trimester of pregnancy; avoid in women of child-bearing potential Take at bedtime and on an empty stomach to decrease risk of CNS effects Coformulation w/ TDF/FTC cannot be used in patients w/ severe kidney dysfunction (CrCl < 30 mL/min) because of required dose modifications of NRTIs <u>Monitoring:</u> lipid panel
Coformulated TDF/FTC/EFV	<u>Hepatic:</u> none; caution in severe impairment		
Nevirapine (NVP)	200 mg daily x 14 days; then 200 mg BID (dose titration reduces risk of rash/intolerance) <u>Renal:</u> none <u>Hepatic:</u> none; caution in severe impairment	Rash including SJS, hepatotoxicity, transaminitis, fever	Do not use in women with CD4 ⁺ > 250 cells/mm ³ or men with CD4 ⁺ > 400 cells/mm ³ because of increased risk of hepatotoxicity Avoid in post-exposure prophylaxis regimens <u>Monitoring:</u> LFT, rash during initial therapy
Etravirine (ETV)	200 mg twice daily (tablet may be dissolved in water for patients unable to swallow) <u>Renal:</u> none <u>Hepatic:</u> none; caution in severe impairment	Rash including, SJS, N/V, HA, peripheral neuropathy	Etravirine is 3A4 substrate, and drug-drug interactions are possible. Do not coadminister with boosted protease inhibitors or strong 3A4 inducers <u>Monitoring:</u> rash, especially development of SJS. Take with food to optimize absorption.
Rilpivirine (RPV)	25 mg once daily Coformulated: TDF/FTC/RPV	Depressive disorders, HA, insomnia, fat redistribution	Rilpivirine is 3A4 substrate, and drug-drug interactions are likely. Do not coadminister with boosted protease inhibitors or strong 3A4 inducers Avoid concomitant PPIs because of inhibition of pH-dependent absorption. Take with food to optimize absorption.
Protease Inhibitors		Class-wide: hyperlipidemia; elevated blood glucose	Class-wide: drug-drug interactions with 3A4 inducers/inhibitors/substrates
Atazanavir (ATV)	ATV 300 mg + RTV 100 mg daily (recommended) or 400 mg daily (alternative) <u>Renal:</u> none <u>Hepatic:</u> caution in moderate to severe impairment	Indirect hyperbilirubinemia, rash, prolonged PR/QT interval, fat maldistribution, nephrolithiasis	Coadministration with PPI (omeprazole equivalent of > 20 mg daily) is contraindicated because of pH-dependent absorption. <u>Monitoring:</u> bilirubin (can be used as indirect marker of adherence); lipid panel
Darunavir (DRV)	DRV 800 mg + RVT 100 mg daily or DRV 600 mg + RTV 100 mg BID <u>Renal:</u> none <u>Hepatic:</u> caution in moderate to severe impairment	Rash, including SJS, new onset diabetes mellitus, diarrhea, nausea, transaminitis	Caution in sulfa-allergic patients (contains sulfonamide moiety) <u>Monitoring:</u> rash, especially upon treatment initiation

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Table 1-1. Properties of Commonly Used Antiretrovirals (Continued)

Antiretroviral Class or Agent	Standard Dosing and Dose Adjustment	Primary Adverse Effects	Cautions/Contraindications/Monitoring
Lopinavir (LPV)/Ritonavir (RTV) (coformulated)	LPV 400 mg/RTV 100 mg BID or LPV/RTV 800/200 mg in treatment naïve patients <u>Renal</u> : none <u>Hepatic</u> : caution in moderate to severe	N/V, severe diarrhea, asthenia, hyperlipidemia (triglyceride predominant), transaminitis	Once-daily dosing associated with higher rate of GI adverse effects Once-daily dosing should not be used in pregnancy. Dosing should be increased during third trimester. <u>Monitoring</u> : tolerability of GI effects, especially in once-daily dosing; lipid panel
Fosamprenavir (FPV)	FPV 1400 mg + RTV 200 mg daily or FPV 700 mg + RTV 100 mg BID <u>Renal</u> : none <u>Hepatic</u> : caution in moderate to severe	Rash, oral paresthesias, hyperlipidemia, hypertriglyceridemia, fat maldistribution	Caution in sulfa-allergic patients (contains sulfonamide moiety) <u>Monitoring</u> : rash, especially upon treatment initiation; lipid panel
Tipranavir (TPV)	TPV 500 mg + RTV 200 mg BID <u>Renal</u> : none <u>Hepatic</u> : caution in moderate to severe	Rash, hepatitis, transaminitis, diarrhea	Caution in sulfa-allergic patients (contains sulfonamide moiety) Rash occurs at higher rate in women on oral contraceptives <u>Monitoring</u> : rash, especially upon treatment initiation; lipid panel; LFTs
Nelfinavir (NFV)	1250 mg BID 750 mg TID <u>Renal</u> : none <u>Hepatic</u> : caution in moderate to severe	Diarrhea, flatulence, nausea, rash, transaminitis, phenylketonuria	Use caution as 1 gram powder contains 11.2 mg of phenylalanine <u>Monitoring</u> : lipid panel
Saquinavir (SQV)	SQV 1000 mg + RTV 100 mg BID <u>Renal</u> : none <u>Hepatic</u> : caution in moderate to severe	PR and QT prolongation, hepatotoxicity, transaminitis, GI intolerance	Least effect on lipids of all PIs Caution in patients at high risk of QT prolongation <u>Monitoring</u> : baseline ECG and repeat as necessary; lipid panel
Ritonavir (RTV)	100–200 mg per dose as boosting agent for other PIs <u>Renal</u> : none <u>Hepatic</u> : caution in moderate to severe hepatic impairment	N/V, diarrhea, pancreatitis, hyperlipidemia (including triglyceridemia), new onset diabetes mellitus, taste perversion, hepatitis	Full dose (600 mg BID) no longer recommended. <u>Monitoring</u> : lipid panel
Integrase Strand Transfer Inhibitor			
Raltegravir (RAL)	400 mg BID <u>Renal</u> : none <u>Hepatic</u> : none	GI disturbances, transaminitis, myalgias and CPK elevations	800 mg once daily dose not recommended. GI effects may be increased with concomitant tenofovir and PPI (because of enhanced absorption)
Chemokine Receptor Type 5 Inhibitor			
Maraviroc (MVC)	300 mg BID 150 mg BID – in combo w/ 3A4 inhibitors 600 mg BID – in combo w/ 3A4 inducer (If inducer and inhibitor, dose as with inhibitor only) <u>Renal</u> : none <u>Hepatic</u> : none	Hepatotoxicity, coughing, GI disturbances, dizziness, musculoskeletal effects	Tropism testing must be done before initiation; use in CCR5-tropic virus only Caution with concomitant inducers/inhibitors of 3A4; dose adjustment required

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Table 1-1. Properties of Commonly Used Antiretrovirals (Continued)

Antiretroviral Class or Agent	Standard Dosing and Dose Adjustment	Primary Adverse Effects	Cautions/Contraindications/Monitoring
Fusion Inhibitor			
Enfuvirtide (T-20)	90 mg subcutaneous injection BID <u>Renal</u> : none <u>Hepatic</u> : none	Injection site reaction, increased risk of bacterial pneumonia, hypersensitivity reaction	Injection site reactions expected to occur in every patient; site rotation of injections is recommended.

BID = twice daily; BMD = bone mineral density; CPK = creatine phosphokinase; CrCl = creatinine clearance; CV = cardiovascular; CBC = complete blood count; ECG = electrocardiography; GI = gastrointestinal; HA = headache; HBV = hepatitis B virus; LFT = liver function tests; MCV = mean corpuscular volume; NNRTI = ; nonnucleoside reverse transcriptase inhibitors; NRTI = Nucleoside reverse transcriptase inhibitors; N/V = nausea/vomiting; PPI = proton pump inhibitor; SJS = Stevens-Johnson syndrome; SOB = shortness of breath.

Information from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 14, 2011; 1–167. Available at aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 18, 2011.

suppressed or undetectable viral load (i.e., HIV RNA less than 50 copies/mL), which should be monitored every 3–6 months.

For virologic failure secondary to developed resistance or cases of transmitted resistance, several antiretrovirals may have activity; these include raltegravir, maraviroc (if R5-tropic virus), the second-generation NNRTIs (i.e., etravirine and rilpivirine), and enfuvirtide. Certain PIs (e.g., darunavir, tipranavir) may also be options in drug-resistant strains. The results of resistance testing and knowledge of strain-specific mutations should guide patient-specific therapy. Regimen selection should be made in consultation with clinicians with advanced HIV knowledge. More information on regimen selection is available in the DHHS guidelines.

Initiating Treatment

The decision of when to initiate therapy is constantly debated, but data continue to suggest that early initiation offers long-term benefits. The primary determinant of treatment for asymptomatic individuals is CD4⁺ count. Guidelines suggest therapy initiation at CD4⁺ cell counts of 500 cells/mm³ or less, irrespective of symptoms (see Table 1-1). Non-AIDS-related and AIDS-related adverse effects, progression to AIDS, and mortality were all reduced in patients who initiated ART early (i.e., at CD4⁺ greater than 350 cells/mm³) compared with those in whom therapy was deferred. Most recently, risk of transmission in serodiscordant couples (i.e., 1 positive, 1 negative) was also reduced in this same cohort of patients. In patients with CD4⁺ cell counts greater than 500 cells/mm³, therapy should be on a case-by-case basis because conflicting data exist on the benefits of initiating ART.

Hospitalized Patients

Patients often present with an acute AIDS-defining illness at initial diagnosis; these patients are termed *late-testers*. Guidelines recommend initiation of ART as soon as possible for symptomatic patients. When HIV infection is diagnosed during hospitalization, the decision to initiate therapy is complex, and traditional methods of verifying readiness are limited. Optimally, an interdisciplinary team of physicians, nurses, social workers, and pharmacists with expertise in HIV care should direct the treatment initiation and management of the HIV-positive patient. Considerations in initiating therapy in the hospitalized patient include fluctuating kidney function; lack of consistent oral access; and a heightened risk of immune reconstitution inflammatory syndrome (IRIS), a pronounced immune response to ART that produces significant morbidity and mortality in patients currently with concurrent AIDS-defining illness or OI. In addition, medication errors are prominent in hospitalized patients receiving ART, stressing the importance of specialist assessment of these regimens. The risks of initiating therapy are balanced against the advantages of early therapy in symptomatic patients. Thus, initiation of ART in the hospitalized patient may be justified when hemodynamic and ADME ([drug] absorption, distribution, metabolism, and excretion) parameters are stabilized, patient willingness to start therapy has been secured, and appropriate outpatient follow-up has been established.

Active OI

In most patients with acute OI, the potential benefits of early initiation of ART outweigh the risks. Early initiation of ART may improve recovery time and, combined with prophylactic antibiotics, will reduce the risk of subsequent OIs. The immune restoration provided by

ART is ultimately the best preventive measure for further infections. Increased life expectancy and improved quality of life are seen in early versus delayed ART initiation. Cryptococcal meningitis and *Mycobacterium avium* complex (MAC) infection carry a substantial risk of IRIS, and ART may be deferred in these patients for several days or weeks. Targeted antimicrobial therapy for these infections should be initiated as early as possible. In patients with active MTB infection, initiating ART within 2–8 weeks of antituberculosis therapy produces a better-sustained response and increased survival.

Acute HIV Syndrome

Acute HIV syndrome offers a special opportunity for early initiation of ART. Although improved clinical outcomes have not been fully established, many theoretical benefits exist for initiating ART during acute HIV syndrome. Because of the high degree of viremia (more than 100,000 copies/mL), rapid destruction of host immunity occurs. Patients newly infected with HIV are also 8–10 times more likely to transmit the virus to others because of their potentially unknown HIV status and high degree of viremia and viral shedding in the genital tract. Early ART during acute HIV infection may reduce the number of circulating virions, thereby leading to preserved immune function and reduced likelihood of viral transmission. The risks of initiating ART in these patients are similar to those in other patients (i.e., short- and long-term ART adverse effects, risk of nonadherence, development of resistance, and burden of lifelong commitment to drugs).

ROLES OF THE NEWEST ANTIRETROVIRALS

Integrase Strand–Transfer Inhibitors

Raltegravir, the lone member of the INSTI class of ART, has a favorable adverse effect profile and is commonly dosed twice daily without need for dosage adjustment for kidney or liver dysfunction. Drug interactions are less likely because raltegravir lacks effect on the CYP system. However, potentially significant interactions have been noted with proton pump inhibitors (i.e., increased absorption in basic environment); with etravirine, a second-generation NNRTI; and, most recently, with chelation secondary to divalent cation-containing products.

Raltegravir maintains activity against triple-class resistant strains (i.e., those with NRTI, NNRTI, and PI resistance mutations). The exact incidence of triple-class resistance in the HIV-positive population is unknown, but estimates of 4% to 13% have been proposed. A series of clinical trials in patients with triple-class-resistant virus found raltegravir superior to placebo in patients receiving an optimized background therapy, as measured by undetectable viral load in highly treatment-experienced patients at 48 and 96 weeks. Additional

studies have shown equal or enhanced viral suppression in highly treatment-experienced patients switched to raltegravir from enfuvirtide, a fusion inhibitor available as injectable only. These data support raltegravir's use in highly treatment-experienced patients with multiclass resistance, as well as in simplifying treatment regimens that include enfuvirtide injections.

In antiretroviral-naïve patients, raltegravir has shown efficacy comparable with traditional efavirenz-based regimens. Clinical trial data have consistently shown a significantly lower incidence of adverse events in the raltegravir arm versus comparators. Adverse effects are primarily limited to gastrointestinal effects, mild musculoskeletal toxicity, and elevated liver enzymes.

The DHHS guidelines recognize raltegravir's role in ART-experienced patients and as a preferred regimen in ART-naïve patients (Figure 1-1). Several studies have investigated the impact of therapeutic switches from PI-based therapy to raltegravir. The results were conflicting, with only one study showing noninferiority of raltegravir to the comparator. A higher rate of treatment failures in the raltegravir arm may be caused by highly treatment-experienced patients who, despite having undetectable viral loads (less than 50 copies/mL), have underlying NRTI resistance, a possible risk factor for raltegravir resistance.

These data suggest that raltegravir is an option for patients who are intolerant of current regimens or who are developing long-term complications and require a change in therapy. In addition, replacing a ritonavir-boosted PI regimen may reduce the pill burden and should be a consideration in therapy changes. Despite the potent antiviral activity and pharmacokinetic profile, once-daily dosing (800 mg) cannot be recommended because of the higher rate of treatment failures compared with the twice-daily regimen. Phase III studies of a second INSTI, elvitegravir, have shown promising results in both treatment-experienced patients and as part of a four-agent combination tablet for once-daily therapy in ART-naïve patients.

CCR5 Inhibitors

Maraviroc

Maraviroc, a CCR5 coreceptor antagonist, blocks viral attachment to the CD4⁺ lymphocyte at the CCR5 coreceptor. This approach was developed on the basis of the evolving understanding of how HIV is prevented from entering cells in people who show innate resistance to AIDS progression. Because the activity of maraviroc is limited to CCR5-tropic virus, confirmation of viral tropism is required before initiating therapy. Viral tropism refers to the preferential selective coreceptor binding of a particular viral strain, classified as CCR5-, CXCR4-, or dual/mixed-tropic (i.e., viral strains that can use both R5 and X4 coreceptors). Although viral tropism can shift over time for several

reasons, 80% to 90% of initial infecting strains use the CCR5 coreceptor. In clinical practice, tropism testing in the United States is primarily limited to the second-generation assay, which requires an HIV RNA viral load of at least 1000 copies/mL. Maraviroc becomes a viable option only if the tropism testing confirms an R5-tropic virus. Results may require several weeks to be available, precluding the drug's use in acute instances in which administration is a priority (e.g., currently hospitalized patients, symptomatic disease, women presenting late in the course of pregnancy).

Twice-daily maraviroc is currently FDA approved for both treatment-experienced and treatment-naive patients, although the DHHS guidelines do not recommend this as a preferred option in treatment-naive patients. In clinical studies, the overall tolerability of maraviroc was comparable with other agents, although secondary safety analyses have identified the potential for hepatotoxicity and negative cardiovascular effects, including myocardial ischemia or infarction. Drug-drug interactions secondary to 3A4 induction or inhibition are common with maraviroc, requiring preemptive dose adjustment as outlined in Table 1-1.

Given its activity against ART-resistant strains, maraviroc offers an option in highly treatment-experienced patients, assuming R5 tropism. However, it is common for a shift to occur in viral tropism to X4 or dual/mixed tropism with time. A shift from CCR5 viral tropism will result in a loss of maraviroc effectiveness and a more rapid decline in CD4⁺ cell counts. If a rise in viral load or decline in CD4⁺ cell count indicates potential virologic failure, follow-up tropism and resistance testing should be performed.

Nonnucleoside Reverse Transcriptase Inhibitors

Etravirine

A second-generation NNRTI, etravirine offers greater potency and maintains activity against most NNRTI-resistant strains. Etravirine was approved by the U.S. Food and Drug Administration (FDA) in 2008 for treatment-experienced patients on the basis of a pooled analysis of two large randomized controlled trials in highly treatment-experienced patients. Etravirine has not been extensively studied in treatment-naive patients and therefore is unlikely to be recommended as a first-line option in this population.

Etravirine is dosed twice daily and should be given after a meal to optimize absorption. Significant drug-drug interactions are present because of its extensive metabolism by CYP 3A4 and its mixed induction and inhibition effects on 3A4, 2C9, and 2C19. A detailed list of all known interactions and suggested modifications is available in the DHHS guidelines. Given its activity against drug-resistant strains, etravirine is a therapeutic option for treatment-experienced patients. The clinician should consider the significant drug-drug

interactions and administration requirements in optimizing etravirine pharmacokinetics.

Rilpivirine

Approved in 2011, rilpivirine represents a new second-generation NNRTI. Similar to etravirine, rilpivirine offers greater potency compared with first-generation agents, including activity against some first-generation NNRTI-resistant strains. In two large randomized controlled trials conducted in treatment-naive patients, rilpivirine combined with tenofovir/emtricitabine showed noninferiority at 48 weeks to a guideline-preferred regimen of efavirenz/tenofovir/emtricitabine. However, patients with a higher baseline HIV RNA (i.e., more than 100,000 copies/mL) had a lower virologic response compared with those on the efavirenz regimen. Approval was granted on the basis of these findings, and the combination of rilpivirine/tenofovir/emtricitabine is recognized in the DHHS guidelines as an alternative regimen for the treatment-naive patient. Rilpivirine is available as a once-daily 25-mg tablet and coformulated into a single-tablet regimen with tenofovir/emtricitabine.

To enhance absorption, it is important to administer rilpivirine with food, preferably with a high-fat meal. Given the pH-dependent absorption, coadministration with gastric modifiers such as antacids, H₂-antagonists, and proton-pump inhibitors should be avoided. Drug-drug interactions are of particular concern because rilpivirine is extensively metabolized by CYP 3A4 and possesses mixed induction and inhibition effects on additional CYP enzymes. The most common adverse effects seen with this agent are rash, delusions, and depression. There is also potential for a dose-dependent QTc-prolongation effect. Rilpivirine in combination with tenofovir/emtricitabine offers another alternative, once-daily NNRTI-based regimen for the treatment-naive patient.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

An unintended consequence of potent ART, IRIS occurs in 15% to 30% of patients with a previously diagnosed OI or AIDS-defining illness. In a somewhat paradoxical effect, rapid immune restoration creates an inflammatory response that may cause clinical deterioration of a previously diagnosed infection or that may unmask a previously undiagnosed occult infection.

Mechanism and Presentation

Several mechanisms have been proposed for IRIS. One hypothesis suggests that as viral load decreases and CD4⁺ cells increase, a shift in memory T cells to the periphery occurs. The number of available CD4⁺ cells

in the periphery rises, accompanied by a high antigen load and subsequent interleukin-2 release, resulting in hyperactivation of the immune system.

Symptoms of IRIS are consistent with an inflammatory process similar to those of the OI being uncovered; symptoms typically occur within 4–8 weeks of ART initiation. Symptoms would occur in the presence of a decreased HIV RNA and increased CD4⁺ cell count, representing viral suppression and improved immune function. The presentation would not mimic the normal clinical course of a previously diagnosed or newly diagnosed OI; rather, it would be more inflammatory. In addition, IRIS would not follow the temporal pattern of an acute drug toxicity, which should be present soon after ART initiation, often waning in severity during the first 2–3 weeks of therapy.

Treatment

Except for central nervous system (CNS) disease (e.g., cryptococcal meningitis), mortality from IRIS is low; however, patients often require hospitalization. Treatment should target the unmasked OI, and ART should be continued whenever possible. Nonsteroidal anti-inflammatory drugs or corticosteroids may be used to manage symptoms of IRIS. When a corticosteroid is used, prednisone at a dosage of 1–1.5 mg/kg/day tapered over several weeks is appropriate. Limited prospective trial evidence suggests that in IRIS occurring during active MTB, prednisone tapered over 4 weeks (1.5 mg/kg/day for 2 weeks; then 0.75 mg/kg/day for 2 weeks) improves symptoms, reduces the need for hospitalization, and improves quality of life. Symptoms of IRIS may mimic treatment failures of MTB and other infections, necessitating an accurate diagnosis to distinguish between the two.

Risk Factors

Risk factors for IRIS include a low CD4⁺ count (i.e., less than 50 cells/mm³) or low CD4⁺ percentage (i.e., less than 10%); high baseline HIV RNA; rapid decline in HIV RNA during first 3 months; and initiation of ART soon after diagnosis of OI or AIDS-defining illness. A patient's risk of IRIS increases as immune status worsens and in the presence of active infections. Sex, race, and antiretroviral class have not been consistently associated with risk of IRIS.

The syndrome has been documented in almost every bacterial, viral, fungal, and parasitic OI; however, higher morbidity and mortality may occur when associated with cytomegalovirus retinitis, cryptococcal meningitis, and mycobacterial disease. About 20% of patients with cryptococcal meningitis will develop IRIS. Of those, about one in five patients with cryptococcal-associated IRIS will die. Initiation of ART in disseminated MAC may produce IRIS in up to 33% of patients. Despite this risk, initiation of ART within 2 weeks of

starting treatment for a newly diagnosed OI is associated with enhanced clinical outcomes and increased survival benefit and is recommended in all patients, excluding active MTB. Delaying ART by several days to weeks after initiating targeted antimicrobial therapy in cryptococcal and disseminated MAC infections may be warranted to reduce the risk of significant morbidity from IRIS. Failure to initiate ART may represent a missed opportunity. Almost 20% of patients with MTB will experience IRIS, potentially leading to significant mortality and morbidity. Antiretroviral therapy should be initiated within 2–8 weeks for patients with active MTB; however, a response to targeted MTB therapy should be noted before starting antiretrovirals.

HEPATITIS COINFECTION

HIV-HBV Coinfection

Although HBV is not endemic to the United States, an estimated 43,000 individuals were newly infected in 2007; however, only 1/10th of these new cases were reported to the CDC. Globally, almost 350 million people live with chronic HBV infection. About 10% of HIV-positive individuals in the United States are coinfecting with HBV. Coinfection leads to higher concentrations of HBV DNA, lower rates of spontaneous hepatitis B e antigen seroconversion, higher rates of cirrhosis, and increased liver-related mortality. Risk of progression to chronic HBV is 21% in unvaccinated HIV-positive individuals, although the risk is expected to be higher if it is the result of vertical transmission.

Treatment goals remain consistent with HBV- or HCV-positive cases not coinfecting with HIV. Guidelines recommend that any patient coinfecting with chronic HBV receive ART. Regimen selection depends on whether HBV, HIV, or both are treated. Pegylated-interferon alfa (pegIFN α) or adefovir should be considered a first-line treatment option in patients in whom ART initiation is not planned. Response rates to pegIFN α are significantly higher in patients with CD4⁺ cell counts greater than 500 cells/mm³. Individuals receiving only HBV-targeted therapy should avoid agents with mild suppressive HIV activity (e.g., entecavir, telbivudine). Entecavir has mild HIV activity and may select for M184V, a viral mutation associated with NRTI resistance; therefore, it should not be used without a fully suppressive antiretroviral regimen. Telbivudine should be avoided in all coinfecting patients because of its potential to select for resistant strains.

The NRTIs with anti-HBV activity (i.e., tenofovir, lamivudine, and emtricitabine) should not be used to treat HBV except when part of an antiretroviral regimen. Patients being treated for both HBV and HIV infection should receive tenofovir plus either emtricitabine or lamivudine as the NRTI component of the antiretroviral regimen, plus an appropriate third

active agent from another antiretroviral class. If the antiretroviral regimen does not contain tenofovir, or if tenofovir is contraindicated, entecavir (or alternatively, pegIFN α or adefovir) should be used. If it becomes necessary to discontinue or change ART, HBV treatment should be maintained with substitution of other anti-HBV agents to prevent HBV flares and disease progression. Use of the HBV vaccine for individuals infected with HIV but not immune to HBV should be reserved for patients with CD4⁺ cells greater than 200 cells/mm³ because of the relatively low vaccine success rates in patients with lower CD4⁺ cell counts.

HIV-HCV Coinfection

An estimated 3.2 million Americans are infected with HCV, with an estimated 17,000 new infections in 2007. Up to 30% of HIV-positive individuals are coinfecting with HCV, with intravenous drug use being the biggest shared risk factor. Coinfection with HIV and HCV accelerates the progression to cirrhosis, and patients with low CD4⁺ cell counts (i.e., less than 200 cells/mm³) may have poorer overall response to HCV-targeted therapy, especially in HCV genotype 1, the most common subtype in North America. Management of individuals with HCV-HIV coinfection should be conducted in a guideline-supported fashion similar to monoinfected individuals with few exceptions.

Patients who will receive ribavirin therapy for HCV should avoid concomitant didanosine, stavudine, or zidovudine because of drug-drug interactions and additive toxicity. Optimally, patients with low CD4⁺ cell counts should attempt some immune restoration with ART to increase counts to greater than 200 cells/mm³ (or greater than 350 cells/mm³, if possible) to increase the likelihood of HCV treatment success.

Drug-induced liver toxicity is also a particular concern in these coinfecting patients. Data regarding significant toxicity are primarily with agents that are now rarely used as first-line antiretrovirals (e.g., didanosine, stavudine, nevirapine, full-dose ritonavir, tipranavir). Careful monitoring is needed for patients taking antiretrovirals known to increase the risk of hepatotoxicity, and dose modification based on the Child-Pugh score should be performed when appropriate. Although potentially unavoidable, interruption of ART may lead to rapid progression of liver fibrosis.

The future of HCV therapy will likely include triple therapy with the addition of an HCV-targeted PI. The FDA recently label approved telaprevir and boceprevir for treatment of HCV in combination with pegIFN α plus ribavirin. The addition of PI therapy to standard treatment resulted in a sustained virologic response in 70% to 75% of patients, compared with 40% in the standard therapy group. Successful results have also occurred in patients whose previous standard treatment has failed, in those with HCV genotype 1, and in

patients with HCV-HIV coinfection. A higher rate of adverse events including hematologic effects (anemia, thrombocytopenia, and leucopenia) and rash occurred in the PI treatment groups. Telaprevir and boceprevir may produce significant drug interactions requiring dose modification because of their inhibitory effects on the CYP 3A4 isoenzyme.

PREEXPOSURE PROPHYLAXIS

Prevention of HIV has long been part of controlling the HIV epidemic. Proven strategies to decrease transmission risk include male circumcision, condom use, and treatment of active sexually transmitted infections. However, implementation limitations and inconsistent use may prohibit realization of their maximal benefit, and transmission continues at an unacceptable rate in many communities. The ultimate prevention tool, vaccination, remains a focus of investigation. Classically, most vaccines induce neutralizing antibodies that prevent viral replication, but the complexity of the HIV envelope has made such vaccine development challenging. A paucity of data in human trials of vaccines suggests some minimal protection that tends to wane, often in a relatively short time (i.e., 24 weeks). Future studies will need to target prevention of acquisition as opposed to neutralization of viral replication once infected.

The use of preexposure prophylaxis (PrEP) in the form of oral or topical ART may represent a viable and effective option for high-risk patients. The Preexposure Prophylaxis Initiative study compared the use of once-daily tenofovir plus emtricitabine with placebo in high-risk homosexual men. Tenofovir plus emtricitabine showed a 44% relative reduction in HIV transmission compared with placebo, but this was only seen in individuals who were greater than 90% adherent to the regimen. Oral PrEP has not been fully investigated in women and thus cannot be recommended. Standard prevention methods should always be continued, even if oral PrEP is being considered. The CDC has proposed interim guidelines for use of oral PrEP.

Topical options for HIV prevention are also under investigation. In several randomized trials, topical gel microbicides failed to show efficacy in reducing HIV transmission, with several studies showing increased risk of HIV infection. Recent investigations have turned to topical tenofovir 1% gels, specifically in women; these gels may be a viable alternative to oral PrEP, delivering higher local concentrations and reducing concerns about toxicity and long-term resistance.

POSTEXPOSURE PROPHYLAXIS

Occupational

The risk of HIV transmission is relatively small in cases of either occupational or nonoccupational exposures. It

is extremely rare for health care workers to contract HIV secondary to occupational exposure, with risks of about 0.3% for percutaneous sticks and 0.09% for mucous membrane or nonintact skin exposures from a known HIV-positive source patient. Transmission risks are increased with deep injury, visible blood on the device, injury from a device placed in the source patient's artery or vein, and high HIV RNA in the source patient (i.e., greater than 1500 copies/mL). Larger volumes of infected materials exposed to mucous membranes may also increase the likelihood of transmission.

The decision to initiate prophylaxis is based primarily on the degree of exposure and on the HIV status, or known HIV risk factors, of the source patient. Figure 1-2 summarizes the approach on postexposure prophylaxis (PeP) treatment recommendations. If initiated, treatment should be given for 28 days, and HIV antibody testing should be done at the time of contact and at 6 weeks, 3 months, and 6 months postexposure. Overtreatment is likely commonplace, and perhaps justified, given the risk of ART for 4 weeks compared with the level of fear and anxiety in the exposed health care worker.

The most appropriate PeP is unknown; however, tenofovir-based regimens are better tolerated than zidovudine-based regimens. Potential adverse effects, drug-drug interactions, and other relative contraindications to specific ART should be considered when individualizing the PeP regimen. If exposure to a known patient with HIV infection occurs, information on viral load, resistance, and history of antiretroviral exposure should be used in the drug-selection decision. Current practices have resulted in zero documented occupational transmissions in the past 5 years in the United States.

Nonoccupational

The use of PeP for nonoccupational exposures should be available for select, isolated exposures. Patients who commonly engage in high-risk behavior will not benefit from the 4-week prophylactic courses. According to studies, the availability of PeP has not increased risky behavior, although the availability of potent ART leading to enhanced control of HIV may instill a false sense of security and lead to reduced condom use.

Patients who present with a nonoccupational sexual, percutaneous, or other exposure within 72 hours should be assessed for PeP. If the source person is known to be HIV positive, and a substantiated exposure to the presenting patient is ascertained, the patient should be offered PeP. When the HIV status of the source person is unknown, yet the source person is known to be at high risk of HIV infection and a substantial exposure has occurred, PeP should be considered (see Figure 1-2). Drug selection is similar to that in occupational exposure and should be individualized using available data from the source person and exposed individual. Evidence is lacking to support three- over two-drug

regimens, although both are supported in guidelines given the theory of enhanced viral suppression with potent ART. Therapy should be continued for 28 days or until confirmation that the source person is HIV negative. Antibody testing for HIV infection should occur before treatment and at 4–6 weeks, 3 months, and 6 months posttreatment.

OPPORTUNISTIC INFECTIONS

Epidemiology

The incidence of OIs or AIDS-defining illnesses has significantly declined with the introduction of potent ART and use of antimicrobial prophylaxis. The annual rate of decline in the United States seems to have plateaued since 2003. Primary risk factors for OIs include depressed CD4⁺ cell counts (less than 200 cells/mm³, with further risk at less than 50 cells/mm³) and high viral loads (greater than 100,000 copies/mL).

The most common OIs in the developed world include candidiasis, PCP, cytomegalovirus, mycobacterial infections, and cryptococcus. *M. tuberculosis* infections occur at a higher rate in patients with HIV infection, especially in endemic areas, but appear to be less dependent on CD4⁺ counts. Advanced and uncontrolled disease is a significant risk factor for opportunistic malignancies, including Hodgkin and non-Hodgkin lymphomas, cervical and anal cancer, and Kaposi sarcoma. Potent ART has reduced the burden of malignancies such as Kaposi sarcoma; however, despite greater control of HIV disease, a trend exists for malignancies appearing at higher CD4⁺ counts (greater than 200 cells/mm³) compared with the pre-ART era. Recent analysis has also shown similar trends in OIs, with almost 30% of OIs occurring at CD4⁺ cell counts above 200 cells/mm³.

Prophylaxis

The treatment of choice to reduce the likelihood of OI is control of HIV disease and support of higher immune function through ART. However, antimicrobial prophylaxis is important for patients who fall below high-risk CD4⁺ thresholds (see Table 1-2). Primary prophylaxis is currently recommended only in prevention of PCP (CD4⁺ cell count less than 200 cells/mm³), toxoplasmosis (CD4⁺ cell count less than 100 cells/mm³), and MAC (CD4⁺ cell count less than 50 cells/mm³). Prophylaxis is generally continued until patients on potent ART remain above CD4⁺ thresholds for at least 3–6 months. Continued prophylaxis should be used in patients initiating ART at risk of IRIS and in those who develop OIs at higher than the standard thresholds.

Before initiating prophylaxis, patients should be carefully evaluated for drug allergies, specifically to sulfonamides, given the high allergy rates reported among patients with HIV infection. In addition, laboratory

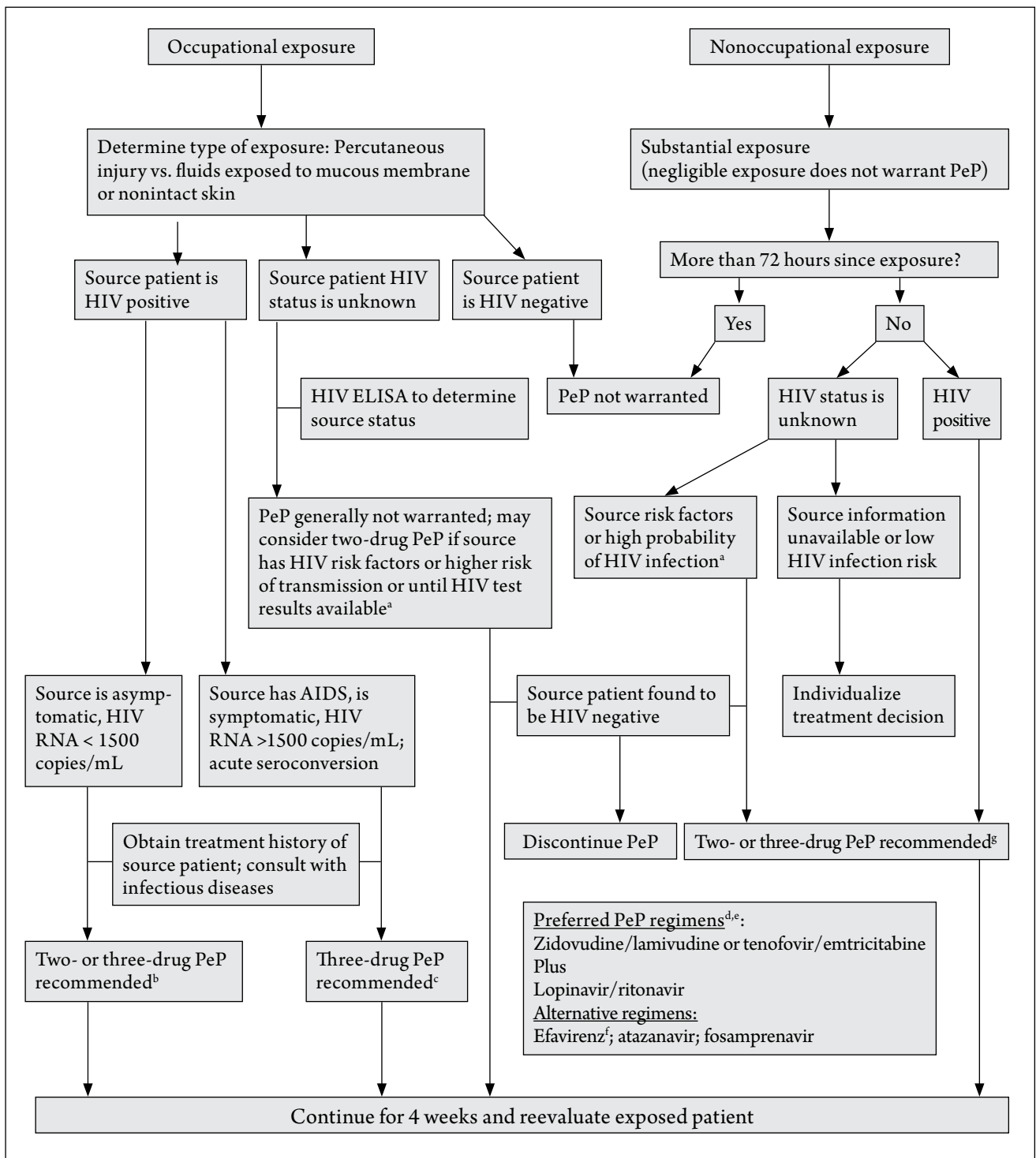


Figure 1-2. Postexposure prophylaxis (PeP) evaluation and treatment algorithm.

^aMen who have sex with men; intravenous drug users; multiple sexual partners.

^bConsider expanded three-drug regimen in large-bore or deep puncture sticks; with known ART treatment history of source patient in consultation with infectious diseases; consider using lower threshold of < 50 copies/mL for three-drug regimen.

^cConsider two-drug regimen in small-volume infected fluid exposures.

^dInformation on ARV exposure, treatment history, HIV RNA, CD4⁺, and resistance patterns should guide ARV selection for PeP in consultation with infectious diseases.

^eTwo-drug PeP is a dual NRTI regimen (i.e., zidovudine/lamivudine).

^fEfavirenz first line in nonoccupational PeP guidelines; should be avoided in pregnancy or in women of childbearing age.

^gTwo-drug regimens should be considered in patients with adherence and/or toxicity concerns.

evaluation for G6PD deficiency should be performed. Patients with a known G6PD deficiency should avoid dapsone and primaquine, agents commonly used in the management of PCP, because of the risk of hemolytic anemia.

Although adherence to ART and antimicrobial prophylaxis significantly reduces the likelihood of infection, significant morbidity and mortality is still associated with the development of OIs. The clinical presentation of PCP and MAC is discussed in the following sections. Prophylactic and treatment recommendations for these and other common OIs are outlined in Table 1-2.

Clinical Presentation and Treatment

P. jiroveci Pneumonia

Early suggestion and identification of PCP is essential to appropriate therapeutic management, although treatment should not be withheld while the diagnosis is confirmed. Patients with PCP often present with symptoms of cough, dyspnea, and shortness of breath of insidious onset for days or weeks. Fever is common, as is hypoxia (mild to severe) and an elevated blood lactate dehydrogenase concentration. Chest radiography may be non-specific or include a “ground-glass” appearance.

Recommended first-line therapy is trimethoprim/sulfamethoxazole. Second-line alternatives include clindamycin plus primaquine, or atovaquone. The addition of a prednisone taper is recommended in patients with severe disease, as evidenced by a partial pressure of oxygen in arterial blood of less than 70 mm Hg. Differentiation from community-acquired pneumonia (CAP) may be difficult at first, and empiric therapy should include treatment for CAP in hospitalized patients.

Nontuberculosis Mycobacterium Infections

Nontuberculosis *Mycobacterium* infections may occur in patients with HIV infection; the most common of these infections is MAC, which is ubiquitous in the environment, seen at very depressed CD4⁺ cell counts (less than 50 cells/mm³). Patients with end-stage HIV infection not receiving ART often present with disseminated MAC with a clinical syndrome of fatigue, fever, lymphadenopathy, night sweats, abdominal pain, and diarrhea. Bone marrow infiltration manifesting as severe anemia is common. Localized disease may manifest as pneumonitis, pericarditis, or CNS disease; less commonly, skin and soft tissue infection may be seen in patients who receive ART. Recommended treatment of MAC includes clarithromycin or azithromycin combined with ethambutol. Adding rifabutin as a third agent is optional for cases of severe disease or documented resistance. Drug resistance or contraindications to previously mentioned agents may require the addition of another agent such as fluoroquinolone or amikacin.

Additional OIs and their typical clinical presentations include the following: toxoplasmosis (CNS disease); cryptococcal (CNS disease); candidiasis (oropharyngeal

[thrush] or esophagitis); cytomegalovirus (retinitis); cryptosporidiosis; microsporidiosis; and isosporiasis (chronic diarrheal disease). Table 1-2 summarizes treatment recommendations for each of these OIs. Alternative treatment options are included; these are increasingly important in resource-limited areas and given the current state of drug shortages in the United States.

ROLE OF THE PHARMACIST

Early studies of unboosted PI therapy showed that adherence rates of at least 95% were required for optimal viral suppression. Recent studies of more potent ART suggest that adherence rates of 80% to 85%, or perhaps lower, are sufficient to achieve viral suppression. Most patients with HIV infection have adherence rates at or below 70%. Individuals with HIV infection constitute a challenging population that often has many risk factors for nonadherence such as lower socioeconomic status, intravenous drug use, smoking and alcohol abuse, underlying psychiatric disorder, younger age, lack of inner-circle support, African American or Hispanic race, and homelessness. Risk assessment for nonadherence should be conducted at initial clinic visits before ART initiation. Any modifiable risk factors should be addressed; however, ART should not be withheld in a symptomatic patient or in an individual with a very low CD4⁺ count because of known risk factors for nonadherence.

Several strategies clinicians may use include setting several early clinic appointments to ensure readiness or providing a practice prescription (e.g., vitamins) to test adherence by mimicking the pill burden and frequency of the ART regimen. These strategies are not feasible for therapy initiation for a patient given a new diagnosis in the hospital or acute initiation in symptomatic patients, stressing the need for open clinician-patient dialog about the critical importance of adherence and established follow-up.

The advent of several once-daily first-line treatment options, including single-tablet regimens, offers an inherent advantage of less-frequent administration and decreased pill burden, which are known predictors of adherence. Some clinicians suggest the SIMPLE principles can enhance ART adherence (Box 1-1). Medication therapy management strategies applied to HIV-positive patients in a community setting increase adherence and reduce the number of drug changes necessitated by nonadherence and failing regimens; these strategies increase the overall cost of care by an average of only 3%. Consequences of nonadherence in HIV may be unparalleled in any other disease, leading to antiretroviral resistance, regimen failures, and subsequent progression of disease, development of OIs, and potential increased risk of transmission. Transmission of drug-resistant HIV is as high as 20% in some communities, caused in part by the nonadherence of treatment-experienced patients.

Table 1-2. Prophylactic and Treatment Options for Common Opportunistic Infections

Opportunistic Infection	CD4⁺ Threshold for Prophylaxis	Prophylaxis Options	Treatment Options
<i>Pneumocystis jiroveci</i> pneumonia	< 200 cells/mm ³ Primary Prophylaxis Indicated: YES	<u>Preferred:</u> Trimethoprim/sulfamethoxazole (TMP/SMX) 1 DS daily <i>or</i> TMP/SMX 1 SS daily <u>Alternatives:</u> 1. Dapsone ^a 100 mg/day 2. Pentamidine 300 mg daily (aerosolized) 3. Atovaquone 1500 mg PO daily 4. Dapsone ^a 50 mg PO daily + Pyrimethamine 75 mg PO weekly + leucovorin 25 mg PO weekly	<u>Preferred:</u> TMP/SMX 15–20 mg/kg divided every 6–8 hours (PO or IV) × 21 days <i>plus</i> Prednisone (40 mg BID × 5 days; 40 mg/day × 5 days; 20 mg/day × 11 days) <i>*If PaO₂ < 70 mm Hg</i> <u>Alternatives:</u> 1. Clindamycin 600–900 mg IV every 6–8 hours + primaquine ^a 15–30 mg/day 2. Atovaquone 750 mg PO BID 3. Pentamidine 4 mg/kg IV daily 4. TMP 320 mg PO Q8 + dapsone ^a 100 mg PO daily
<i>Toxoplasmosis gondii</i>	< 100 cells/mm ³ + IgG antibody to toxoplasma Primary Prophylaxis Indicated: YES	<u>Preferred:</u> TMP/SMX 1 DS PO daily <u>Alternatives:</u> 1. TMP/SMX 1 SS PO daily 2. Atovaquone 1500 mg PO daily 3. Dapsone ^a 50 mg PO daily + pyrimethamine 75 mg PO daily + leucovorin 25 mg PO daily <u>Secondary or chronic maintenance therapy:</u> 1. Sulfadiazine 500-1000 mg PO every 6 hours + pyrimethamine 25-50 mg daily + leucovorin 10–25 mg/day 2. Clindamycin 300–450 mg every 6 hours + pyrimethamine 25–50 mg/day + leucovorin 10–25 mg/day	<u>Preferred:</u> Pyrimethamine 200 mg x1 PO; then 50–75 mg/day + sulfadiazine 1000–1500 mg PO every 6 hours + leucovorin 10–20 mg/day × minimum of 6 weeks <u>Alternatives:</u> 1. Pyrimethamine 200 mg x1 PO; then 50–75 mg/day + clindamycin 600–900 mg IV every 8 hours or 300–450 mg PO every 6 hours 2. Pyrimethamine 200 mg x1 PO; then 50–75 mg/day + TMP/SMX 15–20 mg/kg IV daily (divided every 6–8 hours)
<i>Cryptococcus neoformans</i>	< 100 cells/mm ³ Primary Prophylaxis Indicated: NO	<u>Secondary prophylaxis:</u> Fluconazole 200–400 mg/day (indefinite to lifelong treatment)	<u>Preferred:</u> Induction therapy: Amphotericin B 0.7–1 mg/kg/day IV × 2 weeks ± flucytosine 100 mg/kg/day divided every 6 hours (therapeutic drug monitoring may be indicated) <u>Maintenance therapy:</u> Fluconazole 400–800 mg/day to complete 8- to 10-week course Alternative induction therapy: Fluconazole 800 mg + flucytosine 100 mg/kg/day divided every 6 hours
Cytomegalovirus	< 50 cells/mm ³ + CMV antibody positive Primary Prophylaxis Indicated: NO	<u>Secondary prophylaxis preferred:</u> 1. Valganciclovir 900 mg PO daily <i>or</i> 2. Foscarnet 60–90 mg/kg/day IV	<u>Preferred:</u> 1. Ganciclovir 5 mg/kg BID IV × 14–21 days 2. Foscarnet 90 mg/kg BID IV × 14–21 days <u>Alternatives:</u> Ganciclovir intraocular device (for CMV retinitis only)

(Continued on next page)

Table 1-2. Prophylactic and Treatment Options for Common Opportunistic Infections (*Continued*)

Opportunistic Infection	CD4 ⁺ Threshold for Prophylaxis	Prophylaxis Options	Treatment Options
Candidiasis (esophageal or oropharyngeal)	Consider: recurrent or severe episodes Primary Prophylaxis Indicated: NO	<u>Secondary prophylaxis preferred:</u> Fluconazole 100–200 mg/day	<u>Preferred:</u> 1. Fluconazole 100–200 mg IV or PO daily × 14–21 days 2. Nystatin 500,000 units every 6 hours (oral thrush only) <u>Alternative:</u> 1. Caspofungin 70 mg × 1, 50 mg/day, or micafungin 150 mg/day × 14 days 2. Amphotericin B 0.7 mg/kg/day
<i>Mycobacterium avium complex</i> (MAC)	< 50 cells/mm ³ Primary Prophylaxis Indicated: YES	<u>Preferred:</u> Azithromycin 1200 mg once weekly or 250 mg/day (daily dose seldom used in clinical practice; efficacy not established in clinical trials; increased risk of reversible ototoxicity with daily dose) <u>Alternatives:</u> 1. Clarithromycin 500 mg PO BID 2. Rifabutin 300 mg/day	<u>Preferred:</u> Clarithromycin 500 mg PO BID or Azithromycin 600 mg/day <i>plus</i> Ethambutol 15–25 mg/kg PO daily <i>plus/minus</i> Rifabutin 300–450 mg/day <u>Alternatives/additional agents:</u> 1. Amikacin 7.5 mg/kg/day 2. Fluoroquinolone (moxifloxacin 400 mg/day or levofloxacin 500 mg/day) 3. Streptomycin
<i>Mycobacterium tuberculosis</i>	Not applicable	<u>Treatment – latent infection preferred:</u> Isoniazid (INH) 300 mg/day + pyridoxine 50 mg PO daily <u>Alternatives:</u> INH 900 mg twice weekly + pyridoxine 100 mg twice weekly	<u>Treatment – active infection preferred:</u> Rifampin 600 mg/day + INH 300 mg/day + pyrazinamide 20–25 mg/kg/day + ethambutol 15–25 mg/kg/day <i>Consider substituting rifabutin for rifampin to avoid DDI (if applicable)</i> <i>*Rifapentine therapy should not be used in HIV-positive patients</i>

^aShould not be used in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency

BID = twice daily; CMV = cytomegalovirus; DDI = drug-drug interaction; DS = double-strength (TMP/SMX, 160 mg/800 mg); IgG = immunoglobulin G; IV = intravenously; PaO₂ = partial pressure of oxygen in arterial blood; PO = by mouth; SS = single-strength (TMP/SMX, 80 mg/400 mg).

Nonadherence is not solely the responsibility of the patient. Unintended or iatrogenic nonadherence may result from significant drug-drug interactions, treatment interruptions because of hospitalization, or even the current AIDS Drug Assistance Program crisis. Introduction of drugs without careful evaluation and dose adjustment in the face of drug-drug interactions may result in significant alteration of metabolism and reduction in absorption, greatly affecting serum drug concentrations. Protease inhibitors, NNRTIs, and maraviroc are substrates of the CYP enzyme system and, in combination with potent inducers without proper dose adjustments, may result in subinhibitory concentrations, leaving the patient exposed to a partial regimen. Impaired absorption may result with acid-suppressive therapy (e.g., proton pump inhibitors in combination with

atazanavir and/or rilpivirine). Hospitalized patients with HIV infection may have antiretroviral regimen error rates of almost 80%, resulting in therapy delays or exposure to incorrect or partial regimens. Unfamiliarity with antiretroviral regimens, perceived toxicity of ART, lack of perceived benefit of continuing therapy while hospitalized, and restricted formularies may all contribute to increased error rates. Errors in ART regimens (e.g., incomplete regimen, inappropriate dosing) can lead to increased risk of adverse effects, virologic failure, and/or development of resistance.

CONCLUSION

The disease trajectory of HIV has changed dramatically during the previous 2 decades, and HIV now

Box 1-1. SIMPLE Acronym for ART Adherence

Simplifying regimen characteristics
Imparting knowledge
Modifying patient beliefs
Patient communication
Leaving the bias
Evaluating adherence

ART = antiretroviral therapy.

represents a treatable, long-term illness. Advances in treatments and new drug targets, coupled with emerging data on optimal treatment initiation, will continue to foster frequent updates to treatment guidelines. Pharmacists have the responsibility to maintain a current working knowledge of HIV management to optimize antiretroviral adherence, minimize adverse effects, and reduce medication errors. New opportunities for pharmacists in HIV management will continue to emerge in PrEP and as vehicles for enhanced screening to help reduce the burden of HIV disease.

ANNOTATED BIBLIOGRAPHY

1. Centers for Disease Control and Prevention. HIV Surveillance Report, 2009; vol. 21. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed November 21, 2011.

The CDC HIV Surveillance Report provides an overview on the current epidemiology of HIV disease in the United States and dependent areas. This report includes HIV diagnoses made as of December 31, 2009, and subsequently reported to the CDC by June 30, 2010. Data from 40 states and five dependent areas with confidential name-based HIV reporting are represented. The mean infection rate was 17.4 per 100,000 people—representing about 75% of HIV diagnoses in the United States. Rates were highest among African Americans at 66 per 100,000. The mean rate of AIDS diagnoses was 11.2 per 100,000. Survival at 36 months continued to increase (from 89% in 2001 to 91% in 2005) among patients receiving a diagnosis between 2001 and 2005, although the annual rates of increase were small.

2. Campsmith ML, Rhodes PH, Hall HI, Green TA. Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006. *J Acquir Immune Defic Syndr* 2010;53:619–24.

People unaware of their HIV diagnosis represent a large cohort of patients in the United States and a potential source for continued transmission. These investigators created an extended back-calculation model using cumulative HIV and AIDS diagnosis data as of 2006, combined with time to first diagnosis and disease severity statistics. The model estimated that 21% of patients with HIV infection in the United States

were undiagnosed in 2006. Men who contracted disease through either heterosexual or homosexual sex were among the highest groups of unknown disease at 26.7% and 25.3%, respectively. The population of intravenous drug users had among the lowest rates of people without diagnoses. These data highlight the need for global opt-out screening as recommended by the CDC.

3. Centers for Disease Control and Prevention. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. *MMWR* 2006;55(RR-14):1–17. Available at www.cdc.gov/mmwr/pdf/rr/rr5514.pdf. Accessed November 21, 2011.

The 2006 CDC guidelines for HIV testing represent a significant update to practice recommendations from the 2001 guideline. These recommendations are intended to apply to all health care settings including emergency departments, inpatient and outpatient facilities, and physician clinics. Main recommendations include the following: HIV testing is recommended in all people aged 13–64 years after notification that testing will be performed; written consent is not required because general medical consent should be considered enough; and high-risk patients should be screened at least annually. To strengthen the original recommendations for HIV testing during pregnancy issued by the Public Health Service in 1995 and updated in 2001, these guidelines recommend that HIV testing be part of the initial panel of laboratory tests and repeated during the third trimester. Some state laws may be more restrictive and conflict with the CDC recommendations. A compendium of state-specific requirements has been compiled by the National HIV/AIDS Clinician's Consultation Center and is available at www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws. Accessed November 21, 2011.

4. Centers for Disease Control and Prevention. Vital Signs: HIV Testing and Diagnosis Among Adults – United States, 2001–2009. *MMWR* 2010;59:1550–5. Available at [ftp://ftp.cdc.gov/pub/Publications/mmwr/wk/mm59e1130.pdf](http://ftp.cdc.gov/pub/Publications/mmwr/wk/mm59e1130.pdf). Accessed November 21, 2011.

Using data published from 2001 to 2009 on patients who reported at least one HIV screening test, these investigators assessed the impact of the 2006 recommendations for increased screening among patients seen in health care facilities. The summary of 2001–2006 data suggest that testing occurred in 40% of patients, increasing to about 45% in 2009; this was an absolute increase of 11.4 million people tested from 2006 to 2009. A similar trend was reported among those given a diagnosis late in disease. Transmission is 3–4 times more likely in patients unaware of their diagnosis. Early identification may help avert additional HIV infections and generate an estimated lifetime health care cost savings of \$367,000 per patient. Although the trends are positive and encouraging, there is a continued need for heightened awareness of more testing.

5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral

Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. October 14, 2011; 1–166. Available at www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 21, 2011.

These DHHS guidelines for the HIV care of adults and adolescents were released in October 2011 and represent a minor revision of the previous guidelines released in January 2011. The main changes were related to recommendations for treatment-naïve patients. The January 2011 guidelines are a significant update to the December 2009 guidelines. They offer a comprehensive view of treatment decisions, monitoring, antiretroviral adverse effects, and drug-specific dosing tables. Key updates in January 2011 include the following. (1) Patients with CD4⁺ cell counts less than 500 cells/mm³ should be offered the opportunity for therapy. (2) Patients with stable disease may be monitored less frequently (6 or even 12 months as opposed to every 3–4 months). (3) Raltegravir and maraviroc were added to the treatment algorithm, including raltegravir as a preferred regimen for treatment-naïve patients. The preferred PI-based regimens now include boosted atazanavir and boosted darunavir. Tables included in the guideline offer excellent reference tools for HIV management for pharmacists and physicians. Additional guidelines are available from the International AIDS Society (IAS, 2010, *JAMA* 2010;304:321–33) and European AIDS Clinical Society (EACS, 2011, Available at www.europeanaidscinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6_english.pdf). The main difference between these and the U.S. guidelines is that the EACS guidelines also recommend treatment of patients with CD4⁺ cell counts less than 500 cells/mm³ but recommend individualizing therapy for patients with counts greater than 350 cells/mm³. In addition, whereas the IAS guidelines recommend individualized treatment for patients with counts greater than 500 cells/mm³, the EACS guidelines recommend deferring treatment for this group.

6. Jakobsen MR, Tolstrup M, Sogaard OS, Jørgensen LB, Gorry PR, Laursen A, et al. Transmission of HIV-1 drug-resistant variants: prevalence and effect on treatment outcome. *Clin Infect Dis* 2010;50:566–73.

Rates of transmitted resistance in the developed world have been reported to be between 4% and 23% depending on the study population. These methods typically use a standard genotype-sequencing technique. A cohort of 61 treatment-naïve patients with new HIV infections in Denmark were examined using two different methods, a sensitive multiplex-primer-extension approach (HIV-SNaPshot) and standard commercially available genotype sequencing, to detect the prevalence of viral mutations conveying antiretroviral resistance. The experimental method, the HIV-SNaPshot, allowed a more sensitive detection of low-level resistance mutations. The results showed that 36% of patients (22/61) had a detectable mutation, which was higher than previous estimates in similar populations. The clinical relevance of this is unknown, although it reinforces the use of resistance testing before initiating ART when rapid therapy initiation is not clinically warranted.

7. World Health Organization. Priority Interventions: HIV/AIDS Prevention, Treatment and Care in the Health Sector. Version 2.0 Release July 2010. Available at whqlibdoc.who.int/publications/2010/9789241500234_eng.pdf. Accessed November 22, 2011.

This comprehensive document is the strategic plan of the World Health Organization (WHO) to guide global response to HIV/AIDS, including a primary focus on Sub-Saharan Africa. Almost two-thirds of all people with HIV infection reside in this region, and the prevalence rates in some countries are above 15%. Unlike in the developed world, heterosexual contact is the primary mode of transmission in this region. Although annual HIV infection rates have stabilized in some high-prevalence countries, in other countries (e.g., Malawi), rates continue to rise, with a concurrent increase in several sexual partnerships among men and decrease in condom use during the same period. The priority interventions are defined to guide the health care sector in providing universal access to prevention and treatment, guide clinicians to the most appropriate treatment interventions, and provide effective resources to facilitate improvement in these priority intervention areas. Prioritization begins with public awareness of HIV and education in prevention strategies. The WHO also stresses the importance of laboratory screening and treatment availability in resource-limited areas. This document will be updated with new data and resources as they become available.

8. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009;373:1352–63.

The goal of this comprehensive review was to examine the effect of early versus delayed initiation of ART on the basis of CD4⁺ cell counts. This strategic analysis included data from 15 prospective studies in which treatment-naïve patients were initiated on therapy at CD4⁺ less than 50 cells/mm³. The primary outcomes of progression to AIDS and mortality rate were examined across the data set, which was divided into adjacent CD4⁺ cell counts of 100 (e.g., 250–350, 350–450). There was a significant increase in AIDS progression in patients who had therapy deferred until CD4⁺ cell counts were below 350 cells/mm³ compared with those who had higher cell counts (hazard ratio [HR] 1.28, 95% confidence interval [CI] 1.04–1.57). Mortality rates were lower in the early treatment group, although this decrease was not statistically significant.

9. Powers KA, Ghani AC, Miller WC, Hoffman IF, Pettifor AE, Kamanga G, et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modeling study. *Lancet* 2011;378:256–68.

The transmission of HIV is directly correlated with serum viral load, which may be especially high in acute

and early infection. The relative contribution of acute and early infection to overall transmission is debatable, but it is known to be a strong contributor. The authors reported that during an 8-year investigation in Malawi, 38.4% of transmitted infections were attributable to source patients with acute or early infection. Interventions in patients with HIV infection should target both early and chronic-stage infections. These data add support to the early administration of ART in patients acutely infected to help reduce the transmission burden.

10. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364:2417–28.

Traditional therapies for HCV-1 genotype, the most common in the United States, result in a sustained virologic response of around 40% to 45%. Telaprevir, a novel HCV PI, offers the first advance in HCV targets in more than 2 decades. This study was one of three published in this journal issue investigating this agent's use in populations of HCV-positive patients. This investigation was a randomized controlled trial in treatment-naïve patients that compared three groups: 48 weeks of pegIFN α plus ribavirin (standard therapy); 12 weeks of telaprevir plus standard therapy for 48 weeks; and a 4-week pegIFN α plus ribavirin lead-in period, followed by 12 weeks of telaprevir plus standard therapy for 48 weeks. Results showed significantly higher sustained virologic response in the combined telaprevir groups (75% and 69%) compared with the standard treatment arm (44%). Adverse effects of anemia, rash, and gastrointestinal effects were higher in the telaprevir groups. The additional articles providing outcomes data with telaprevir, also published in this issue, discuss efficacy in previously untreated patients and previously treated patients with long-term HCV. Information regarding ongoing studies in patients with HCV-HIV coinfection can be found at clinicaltrials.gov.

11. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195–206.

Boceprevir represents the other new addition to the HCV PI class of agents. This agent was approved by the FDA in summer 2011. This investigation was a randomized controlled trial of previously untreated patients comparing three groups. Each group received a 4-week lead-in treatment with pegIFN α plus ribavirin: pegIFN α plus ribavirin for 44 additional weeks (standard therapy); standard therapy plus boceprevir for 44 additional weeks; and standard therapy plus boceprevir for 24 weeks with those with detectable HCV RNA through week 24 continuing to complete 44 weeks. Results were analyzed on the basis of race. Among non-African Americans, the sustained virologic response was 67% to 68% success in the boceprevir arms compared with 40% for standard therapy. The sustained virologic response among African Americans, known to be significantly lower than that of whites, was 42%

to 53% in the boceprevir arm and 23% in the standard therapy group. Anemia rates were higher in the patients who received boceprevir than in those who received standard therapy (21% vs. 11%). These data provide compelling evidence for the addition of a PI to standard therapy for HCV patients who are chronically infected. An accompanying article on the use of boceprevir in previously treated patients is published in this edition. Information regarding ongoing studies in HCV-HIV-coinfecting patients can be found at clinicaltrials.gov.

12. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010;362:697–706.

The purpose of this investigation was to determine the impact of early versus delayed ART in patients with HIV-tuberculosis coinfection. Six hundred forty-two patients with coinfection were randomized to receive early integrated ART (within 4 weeks of MTB treatment); late integrated ART (more than 8 weeks after the start of MTB treatment); or ART after the completion of MTB therapy. Patients received the integrated therapy on average of day 70 of MTB treatment and the deferred therapy on average of day 260 after the initiation of MTB treatment. Overall, mortality was significantly lower in the integrated arm of the study (5.4 deaths per 100 person-years vs. 12.1 deaths per 100 person-years). As expected, the IRIS rate was higher in the integrated treatment group. This landmark study and several others have helped drive the current recommendations of initiating ART earlier during MTB therapy (less than 8 weeks) in most patients.

13. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10:251–61.

This systematic review compiled data from 54 studies with 13,103 patients who initiated ART. Of those, 1699 developed IRIS. The risk of IRIS was most associated with pre-ART CD4⁺ cell counts, with a greater risk at less than 50 cells/mm³. Patients with cytomegalovirus retinitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and MTB had the highest rates of IRIS at 37.7%, 19.5%, 16.7%, and 15.7%, respectively. The death rate in those who developed IRIS was 3.2%, with higher rates among those with cryptococcal meningitis. The authors conclude that earlier therapy initiation before immune compromise helps prevent the occurrence of IRIS.

14. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363:2587–99.

This investigation was set to determine the impact of oral PrEP with tenofovir/emtricitabine in men who have sex with men. A total of 2499 HIV-negative men

were enrolled to receive either placebo or tenofovir/emtricitabine daily. Patients were followed for a median of 1.2 years. Thirty-six patients in the treatment arm became infected, compared with 64 in the placebo arm ($p=0.005$), a reduction of 44%. Efficacy was directly correlated to reported adherence and detection of study drug. Only 3 of 34 patients with HIV infection and about 51% of subjects tested had detectable study drug. In patients with detectable study drug, HIV infection was 12 times more likely to be prevented. The CDC released guidelines in January 2011 to help clinicians determine the appropriateness of PrEP in their patient populations (MMWR 2011;60:65–8).

- Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for post-exposure prophylaxis. MMWR 2005;54:RR-9. Centers for Disease Control and Prevention. Anti-retroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States. MMWR 2005;54:RR-2.

Contrary to other guidelines with strict levels of evidence, the CDC 2005 guidelines for PeP after occupational and nonoccupational exposures are driven mostly by expert opinion. This is because of the lack of controlled trials conducted (and lack of feasibility for future study), limited setting-specific data, known effects, and comfort with ART. Significant or high-risk exposures, outlined in both guidelines, require timely evaluation and initiation of ART within 72 hours. In general, exposed patients should not receive PeP if the source person is unknown to be HIV positive. Two-drug regimens with NRTIs are indicated in low-risk exposures. Three-drug regimens are indicated in certain circumstances involving large-volume exposures of known HIV-positive source patients with high viral loads or suspected resistance. Treatment should be reevaluated at 72 hours and, if indicated, continued for 4 weeks.

- Pastakia SD, Corbett AH, Raasch RH, Napravnik S, Correll TA. Frequency of HIV-related medication errors and associated risk factors in hospitalized patients. *Ann Pharmacother* 2008;42:491–7.

Inpatient ART errors are increasingly common and potentially harmful. During a 4-month study period, investigators identified at least one error in the ART regimens of 72% (48/68) of inpatients in a single tertiary care medical center. Most of these errors occurred in the initial regimen and were considered class 2 or 3 (increased potential to cause harm). No risk factors or predictors could be identified for the presence of a single class 2 or class 3 error. However, the presence of a nonformulary ART antiretroviral agent represented almost a 2-fold increased risk of having more than one class 2 and 3 error. This stresses the importance of having coformulated products and newly available ART on hospital formularies.

- Buchacz K, Baker RK, Palella FJ Jr, Chmiel JS, Lichtenstein KA, Novak RM, et al. AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. *AIDS* 2010;24:1549–59.

The HIV Outpatient Study (HOPS) investigators studied 8070 patients in 12 HIV clinics to investigate the incidence of OIs. The time to first diagnosis of any OI and all OIs was reported in rates per 1000 person-years. Steady decline in OIs was encountered from 1994 to 2003, with the greatest decline of 89.0 from 1994 to 1997 and stabilizing at a rate of about 13.3 between 2003 and 2007. The most common OIs identified included PCP and esophageal candidiasis. The finding of most concern was the trend to OI occurrence at higher CD4⁺ thresholds, with more than 30% occurring in CD4⁺ counts greater than 200 cells/mm³. With potent ART available now for much more than a decade, these data may help direct changes in guideline-recommended antimicrobial prophylaxis. A good source for more on this topic is the 2009 CDC OI treatment and prevention guidelines for management strategies.

- Walensky RP, Wood R, Ciaranello AL, Paltiel AD, Lorenzana SB, Anglaret X, et al. Scaling up the 2010 World Health Organization HIV treatment guidelines in resource-limited settings: a model-based analysis. *PLoS Med* 2010;7:e1000382.

The WHO treatment guidelines recommend the initiation of ART when the CD4⁺ cell count drops below 350 cells/mm³. The guidelines also recommend the substitution of stavudine with tenofovir as a first-line NRTI. These investigators used the Cost Effectiveness of Preventing AIDS Complications international model to determine the priority implementation of guideline recommendation on survival in resource-limited countries. Although the change from stavudine to tenofovir as first-line NRTI and the availability of a second-line regimen for treatment failures both enhance survival at 5-year projections, the greatest benefit is seen in early administration of ART (threshold of 350 cells/mm³ vs. 200 cells/mm³). Countries that must prioritize implementation of these new guidelines should begin with earlier administration of ART, which will require further availability of CD4⁺ laboratory monitoring.

- Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;360:1815–26.

These investigators conducted two parallel analyses of 17,517 HIV-positive patients, stratifying them by CD4⁺ count at the time of ART initiation into two groups (351–500 cells/mm³ vs. greater than 500 cells/mm³). The NA-ACCORD study showed a significant reduction in mortality for patients initiating therapy at greater than 500 cells/mm³ compared with those below this threshold. These findings are in contrast to an ART-Cohort Collaboration study that failed to show a slowing of AIDS progression or a reduction in mortality in patients with early initiation (greater than 450 cells/

mm³). The overall mortality rate in these studies was relatively low, possibly confounding the results. In addition, enrolled patients with sustained CD4⁺ cell counts above 500 may represent a subpopulation of long-term nonprogressors, as discussed in this chapter.

20. Katlama C, Haubrich R, Lalezari J, Lazzarin A, Madruga JV, Molina JM, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48-week analysis of two randomized, controlled trials. *AIDS* 2009;23:2289–300.

The DUET-1 and DUET-2 randomized controlled trials were identically designed to evaluate twice-daily etravirine versus placebo in treatment-experienced patients. In addition to the study drug, each subject received boosted darunavir and optimized background therapy. Data compiled over 48 weeks showed that significantly more patients in the etravirine group achieved viral suppression (61% vs. 40%). Adverse effects were common in both groups, but rash was significantly more common in the etravirine arm, similar to other NNRTIs. Etravirine is administered twice daily and must be dose adjusted when combined with CYP 3A-active agents. These data support etravirine as an alternative therapy in treatment-experienced patients, including those with drug-resistant strains.

SELF-ASSESSMENT QUESTIONS

1. A 20-year-old man comes to the emergency department with a flu-like illness, rash (predominantly on his trunk), fever, and pronounced lymphadenopathy. He reports a sexual encounter 1 week prior with a male partner of unknown HIV status. He reports being an active smoker and intravenous drug user. **Which one of the following screening tests would be the best to perform in this patient?**
 - A. CD4⁺ cell count.
 - B. Rapid HIV.
 - C. Enzyme-linked immunosorbent assay (ELISA).
 - D. HIV RNA.
 2. A 29-year-old HIV-negative man comes to the clinic reporting receptive anal intercourse about 18 hours ago. His partner's HIV status was unknown. The patient inquires about postexposure prophylaxis (PeP). **Which one of the following is the best plan for this patient?**
 - A. Initiate two-drug antiretroviral therapy (ART) for 28 days.
 - B. Initiate three-drug ART for 72 hours; then de-escalate to a two-drug regimen.
 - C. Perform rapid HIV test on the source person before ART initiation for proper regimen selection.
 - D. Perform rapid HIV test and screening for hepatitis B virus (HBV) and hepatitis C virus (HCV), but do not initiate ART.
 3. A 28-year-old woman has had HIV infection for 5 years. She has decided to initiate ART because she and her husband are going to attempt to have children. Her current laboratory values include the following: CD4⁺ cell count 290 cells/mm³, HIV RNA 150,000 copies/mL, white blood cell count (WBC) 3.1 x 10³ cells/mm³, hemoglobin 10.1 g/dL, aspartate aminotransferase (AST) 40 IU/mL, and alanine aminotransferase (ALT) 36 IU/mL. She has no evidence of HCV infection, and she has received the HBV vaccine. She is an emergency medical technician working full-time and reports no illicit drug use, smoking, or alcohol abuse. **Which one of the following regimens would be the best initial choice for this patient?**
 - A. Once-daily fixed-dose abacavir/lamivudine and twice-daily zidovudine.
 - B. Once-daily fixed-dose efavirenz/tenofovir/emtricitabine.
 - C. Twice-daily fixed-dose zidovudine/lamivudine and twice-daily nevirapine.
 - D. Once-daily fixed-dose tenofovir/emtricitabine and lopinavir/ritonavir.
 4. A 36-year-old man has a CD4⁺ cell count of 165 cells/mm³ and HIV-1 RNA of 74,538 copies/mL. He recently initiated ART with tenofovir/emtricitabine/efavirenz. He has no known drug allergies, nor is he taking any other drugs. He was noted to have a glucose-6-phosphate dehydrogenase (G6PD) deficiency. **Which one of the following would be best to add to this patient's regimen for prophylaxis?**
 - A. Trimethoprim/sulfamethoxazole 160 mg/800 mg/day.
 - B. Dapsone 100 mg/day.
 - C. Atovaquone 1500 mg/day.
 - D. Azithromycin 1200 mg/week.
- Questions 5 and 6 pertain to the following case.**
- M.M. is a 39-year-old woman with chronic active HBV and HIV. She is seen in the clinic today and is eager to start treatment. Results of a complete metabolic panel are as follows: sodium 139 mEq/L, potassium 3.9 mEq/L, blood urea nitrogen (BUN) 15 mg/dL, and serum creatinine (SCr) 0.9 mg/dL; all other values were within normal limits. Her CD4⁺ count is 45 cells/mm³, her HIV RNA is 106,500 copies/mL, and she is immunoglobulin G (IgG) positive for toxoplasmosis. M.M. is known to be G6PD deficient. She has steroid-induced osteoporosis and had a single episode of oral thrush. Her current drugs include calcium 1500 mg/day plus vitamin D 400 international units/day. Documented allergies are to sulfa (rash) and chrysanthemums (facial swelling).
5. **Which one of the following is the best regimen for treatment of M.M.'s HIV-HBV coinfection?**
 - A. Tenofovir/emtricitabine, darunavir, ritonavir, and pegylated-interferon alfa (pegIFN α).
 - B. Tenofovir/emtricitabine/efavirenz.
 - C. Abacavir/lamivudine, atazanavir, ritonavir, and adefovir.
 - D. Zidovudine/lamivudine and raltegravir.
 6. **Which one of the following would be best to initiate for additional antimicrobial prophylaxis in M.M.?**
 - A. Dapsone 100 mg/day, azithromycin 1200 mg once weekly, and acyclovir 400 mg twice daily.

- B. Atovaquone 1500 mg/day and acyclovir 400 mg twice daily.
 - C. Dapsone 50 mg/day, pyrimethamine 75 mg/day, azithromycin 1200 mg once weekly, fluconazole 100 mg/day, and acyclovir 400 mg twice daily.
 - D. Atovaquone 1500 mg/day and azithromycin 1200 mg once weekly.
7. A 25-year-old man comes to the clinic requesting preventive HIV therapy. He is currently single and discloses that he had four male partners in the past 6 months, with his last encounter 3–4 weeks ago. He uses condoms for anal intercourse but rarely for oral intercourse. The patient has found several potential partners online and will be meeting all of them for a weekend getaway in 2 weeks. He has no specific medical history, he tested HIV negative 9 months ago, and he is currently taking no long-term drugs. The patient did experience the flu this past week but did not seek specific medical care. **In addition to counseling on sexually transmitted diseases and proper condom use, which one of the following would be best for this patient?**
- A. Initiate tenofovir/emtricitabine once daily with counseling on proper adherence.
 - B. Initiate darunavir/ritonavir once daily with counseling on proper adherence.
 - C. Perform rapid HIV test; if results are negative, initiate tenofovir/emtricitabine once daily and counsel on proper adherence.
 - D. Perform ELISA, obtain HIV RNA, and counsel on avoiding high-risk behavior.

Questions 8–10 pertain to the following case.

G.J. is a 31-year-old woman (weight 65 kg, height 48 inches) admitted to the medical ward secondary to a compromised respiratory status. She reports a 2-week history of cough and chest pain that has steadily worsened. G.J.'s platelet count is 123,000 cells/mm³, lactose dehydrogenase 400 IU/L, SCr 1.1 mg/dL, and BUN 24 mg/dL. Her partial pressure of oxygen in arterial blood is 76 mm Hg. G.J.'s most recent CD4⁺ count was 41 cells/mm³, and she is known to be IgG positive for toxoplasmosis. Chest radiography shows bilateral infiltrates with a ground-glass appearance. She is placed on supplemental oxygen with a 3L nasal cannula; subsequently, her oxygen saturation is 98%. On examination, it is also noted that she has esophageal candidiasis. Proper diagnostics are initiated.

8. **Which one of the following is the best empiric therapy for G.J.'s pulmonary infection?**

- A. Trimethoprim/sulfamethoxazole 400 mg intravenously every 8 hours and prednisone 40 mg twice daily to taper.
 - B. Levofloxacin 750 mg intravenously daily, clindamycin 600 mg intravenously every 6 hours, and primaquine 30 mg orally daily.
 - C. Atovaquone 750 mg orally twice daily, dapsone 100 mg/day, ceftriaxone 1 g intravenously daily, and azithromycin 500 mg intravenously daily.
 - D. Trimethoprim/sulfamethoxazole 300 mg intravenously every 6 hours and levofloxacin 750 mg intravenously daily.
9. **Which one of the following is best for G.J.'s esophageal candidiasis?**
- A. Amphotericin B 40 mg intravenously daily.
 - B. Fluconazole 200 mg intravenously daily.
 - C. Nystatin 100,000 units orally four times/day.
 - D. Micafungin 150 mg intravenously daily.
10. G.J. completes current antimicrobial treatment and is being discharged after a 3-week hospitalization. A repeat CD4⁺ count is 146 cells/mm³. **For which one of the following opportunistic infections (OIs) would it be best for her to receive prophylaxis?**
- A. *Mycobacterium avium* complex (MAC), *Pneumocystis jiroveci* pneumonia (PCP), and toxoplasmosis.
 - B. MAC and toxoplasmosis.
 - C. PCP only.
 - D. Candidiasis, MAC, and toxoplasmosis.
11. A 24-year-old woman with a history of nonadherence has documented antiretroviral resistance. Her CD4⁺ count is 180 cells/mm³ and HIV RNA is 41,300 copies/mL. After tropism testing, it is determined she has an R5-tropic virus. Her new regimen will include tenofovir/emtricitabine (3A4 neutral), darunavir and ritonavir (3A4 inhibitor), etravirine (3A4 inducer), and maraviroc. She is also receiving omeprazole 20 mg/day. **Which one of the following maraviroc dosages is best for this patient?**
- A. 150 mg twice daily.
 - B. 300 mg twice daily.
 - C. 600 mg twice daily.
 - D. 800 mg once daily.
12. A 24-year-old man (weight 68 kg) is admitted to the inpatient ward with pancytopenia, prolonged diarrhea, and overall fatigue and malaise. Initial blood cultures and bone marrow aspirate are positive for *Mycobacterium* spp., later identified as MAC. He has a CD4⁺ count of 33 cells/mm³ and an HIV

RNA of 35,350 copies/mL. His laboratory values include SCr 1.4 mg/dL and BUN 34 mg/L. He has an allergy to sulfa (hives). His last prescribed ART regimen included tenofovir/emtricitabine/efavirenz, although he reports being nonadherent. **Which one of the following is best for management of this patient's OIs?**

- A. Azithromycin 600 mg, rifabutin 300 mg twice daily, ethambutol 1200 mg/day, and atovaquone 1500 mg/day.
- B. Clarithromycin 500 mg twice daily and dapsone 100 mg/day.
- C. Atovaquone 1500 mg/day; defer MAC therapy until CD4⁺ count is greater than 50 cells/mm³.
- D. Azithromycin 1200 mg/week and dapsone 100 mg/day.

13. A 31-year-old man was recently admitted to the medical ward with severe headache and photophobia. He has a CD4⁺ count of 15 cells/mm³ and HIV RNA of 105,350 copies/mL. His current laboratory values are SCr 1.0 mg/dL, BUN 17 mg/L, AST 25 IU/mL, ALT 38 IU/mL, hemoglobin 10.3 g/dL, platelet count 167,000 cells/mm³, and WBC 2.9 x 10³ cells/mm³. He has no drug allergies. He reports being off antiretrovirals for several years and does not recall his previous regimen. A lumbar puncture is performed, and a cerebrospinal fluid stain is positive for yeast. Given the high suggestion of cryptococcal disease, amphotericin B 60 mg intravenously daily and flucytosine 1500 mg orally every 6 hours are initiated. After 2 weeks of induction therapy, the patient is discharged to continue fluconazole and is initiated on tenofovir/emtricitabine, darunavir and ritonavir, and raltegravir with scheduled clinic follow-up. Three weeks after initiating ART, he begins to experience fever, fatigue, and lymphadenopathy, prompting a visit to the emergency department. **Given the concern for immune reconstitution inflammatory syndrome (IRIS), which one of the following is best for this patient?**

- A. Discontinue ART and fluconazole and provide symptomatic care as needed.
- B. Continue ART, discontinue fluconazole, and initiate prednisone 60 mg/day.
- C. Discontinue ART, initiate prednisone 60 mg/day, and reinstate induction therapy for cryptococcal disease.
- D. Continue ART and fluconazole and provide symptomatic care as needed.

14. A nurse from the outpatient clinic reports to employee health. She states she had a self-inflicted subcutaneous puncture wound through her gloved hand 1 hour earlier after giving HBV vaccine to a known patient with HIV infection. The needle

was not bloody, although the nurse bled from the puncture wound. The source patient's most recent laboratory values show a CD4⁺ count of 345 cells/mm³ and HIV RNA of less than 50 copies/mL, controlled on a regimen consisting of tenofovir/emtricitabine and lopinavir/ritonavir. The exposed nurse is very anxious and seeks advice on proper PeP. **Which one of the following is best for this health care worker?**

- A. Initiate two-drug therapy for 28 days.
- B. Initiate two-drug therapy pending rapid HIV testing on the nurse and discontinue if results are negative.
- C. Initiate three-drug therapy for 28 days.
- D. PeP is not recommended at this time.

15. Your institution is a 300-bed community hospital in a rural area of the Southeastern United States, which is a high-prevalence area for HIV. Given the CDC recommendations for universal screening, hospital administration is requesting an update to the current policy for testing in the emergency department. **Which one of the following would be the best testing approach?**

- A. All patients aged 13–64 should be routinely screened after providing written consent to testing.
- B. High-risk patients should be screened at least annually.
- C. All patients aged 13–64 should be routinely screened with an approved antibody-based screening test (e.g., ELISA or rapid test).
- D. Patients presenting with symptoms consistent with acute HIV syndrome or OI should be routinely screened (e.g., HIV RNA).

16. A 34-year-old man with productive cough, night sweats, pronounced lymphadenopathy, and a 15-pound weight loss during the past month is admitted to the internal medicine ward. He is placed on respiratory isolation and receives a tuberculin skin test, chest radiography, and sputum sample for acid-fast bacilli (AFB) smear, and cultures are ordered. Chest radiography is highly suggestive of granulomatous disease, and the AFB smear returns positive. Four-drug therapy with isoniazid, rifampin, ethambutol, and pyrazinamide is initiated. Results of an HIV ELISA return reactive and are later confirmed with Western blot. Laboratory results show his CD4⁺ cell count is 168 cells/mm³, and his HIV RNA is greater than 100,000 copies/mL. **Which one of the following is the best time to initiate ART in this patient?**

- A. After 1 week of *Mycobacterium tuberculosis* (MTB) therapy.
 - B. After MTB therapy is narrowed to two-drug therapy.
 - C. After MTB therapy is complete.
 - D. After 4 weeks of MTB therapy.
17. A 54-year-old man receives a diagnosis of HIV infection and, 6 weeks later, presents to the clinic to begin ART. His baseline laboratory values are CD4⁺ count 388 cells/mm³, HIV RNA 121,000 copies/mL, SCr 0.7 mg/dL, BUN 20 mg/L, AST 45 IU/mL, ALT 28 IU/mL, hemoglobin 11.3 g/dL, platelet count 337,000 cells/mm³, and WBC 8.9 x 10³ cells/mm³. He has a documented allergy to sulfa (rash). His current daily regimen includes hydrochlorothiazide 25 mg, esomeprazole 40 mg, and pravastatin 80 mg. **Which one of the following ART regimens would be best for this patient?**
- A. Tenofovir/emtricitabine, atazanavir, and ritonavir.
 - B. Zidovudine/lamivudine and rilpivirine.
 - C. Tenofovir/emtricitabine and raltegravir.
 - D. Abacavir/lamivudine and efavirenz.
18. After total hip replacement for avascular necrosis, a 38-year-old man is transferred to the orthopedic ward. He has a history of HIV infection and has been successfully controlled (CD4⁺ 419 cells/mm³, HIV RNA less than 50 copies/mL) on an ART regimen of tenofovir/emtricitabine/efavirenz. He is placed on a morphine patient-controlled analgesia pump and docusate. While rounding on the antimicrobial stewardship team, you proactively review his regimen and ensure the appropriate regimen is reinitiated. **Which one of the following risk factors for ART error in hospitalized patients will most likely be encountered in this patient?**
- A. Coformulated products not on formulary.
 - B. Concurrent hepatic dysfunction.
 - C. Surgery.
 - D. Tenofovir as part of ART regimen.
19. A 45-year-old man is seen in the clinic today with an apparent case of oral candidiasis. He reports being completely adherent to his current regimen of zidovudine/lamivudine, darunavir, and ritonavir. For the past 2 months, his CD4⁺ has declined to 285 cells/mm³ (from 350 cells/mm³), and his HIV RNA has increased to 1750 copies/mL (previously undetectable). **Which one of the following would be the most feasible way to evaluate adherence in this patient?**
- A. Perform therapeutic drug monitoring for darunavir serum concentrations.
 - B. Obtain a complete blood cell count and refill history at pharmacy.
 - C. Obtain a complete metabolic panel and refill history at pharmacy.
 - D. Ask the patient to bring drug bottles to the next clinic visit and perform a pill count.
20. A 23-year-old woman comes to the sexually transmitted disease clinic inquiring about measures to help prevent HIV acquisition. She admits to a monogamous relationship with a known HIV-positive man. She acknowledges that they use condoms regularly, and she is tested every 6 months as recommended by her primary care physician. **Which one of the following is most appropriate for this patient?**
- A. Start tenofovir/emtricitabine once daily and provide adherence counseling.
 - B. Start applying nonoxynol-9 gel before each sexual encounter.
 - C. Obtain partner's ART regimen and resistance profile to determine appropriate prophylactic regimen.
 - D. Encourage continued appropriate condom use and partner's adherence to ART.