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Identifying and Co-managing the HIV-infected Adult: A Guidebook for Primary Care Clinicians

Jason Leider
Albert Einstein College of Medicine

Susan F. LeLacheur
George Washington University - School of Medicine and Health Sciences

Julie G. Stewart DNP, MPH
Sacred Heart University, stewartj1270@sacredheart.edu

Identifying and Co-Managing the HIV-Infected Adult: A Guidebook for the Primary Care Clinician

NEEDS ASSESSMENT

Someone in the United States is infected with HIV every 9½ minutes[1] and more than 1 million persons in the US are currently living with the disease.[2] Since the beginning of the epidemic, primary care providers have been on the front lines of patient care. Updated screening recommendations from the CDC have given these practitioners an even greater role in HIV management, especially in regard to implementing recommended "opt-out" screening.[3] Primary care clinicians are also integral in counseling patients to reduce the risk of further HIV transmission and, for patients who test positive, providing routine health maintenance interventions, offering prophylaxis against opportunistic infections, fostering adherence to antiretroviral therapy (ART), and managing ART side effects.

This guidebook was designed to help primary care clinicians improve their performance in terms of HIV identification and co-management. Surmounting barriers to opt-out screening, making an HIV diagnosis, and preventing transmission and opportunistic infections will be discussed, as will selection of initial therapy and considerations for patients receiving ART.

REFERENCES

1. US Department of Health & Human Services, Centers for Disease Control and Prevention. *Act Against AIDS.* http://www.nineandahalf-minutes.org/get-the-facts.php. Accessed July 26, 2011.
2. US Department of Health & Human Services, Centers for Disease Control and Prevention. *HIV in the United States.* http://www.cdc.gov/hiv/resources/factsheets/us.htm. Accessed July 26, 2011.
3. Branson BM, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep.* 2006 Sep 22;55:1-17.

TARGET AUDIENCE

Nurse practitioners

LEARNING OBJECTIVES

After participating in this program, clinicians should be better able to:

- Describe the rationale for implementing "opt-out" HIV testing, as recommended by the CDC
- Address issues and potential barriers to routine screening
- Identify the signs and symptoms of acute HIV infection
- Address issues pertinent to the co-management of patients with HIV, including considerations for those receiving antiretroviral therapy

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FACULTY

Jason Leider, MD, PhD (Chair)
Associate Professor of Clinical Medicine
Albert Einstein College of Medicine of Yeshiva University
Jacobi Medical Center
Bronx, NY

Susan F. LeLacheur, DrPH, PA-C
Associate Professor of Health Care Sciences
The George Washington University School of Medicine and Health Sciences
Physician Assistant Program
The Whitman-Walker Clinic
Washington, DC

Julie Stewart, DNP, MSN, MPH, FNP-BC
Assistant Professor
Sacred Heart University Nursing Program
Nurse Practitioner
Southwest Community Health Center
Bridgeport, CT

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Susan F. LeLacheur, DrPH, PA-C has no relevant financial relationships to disclose.

Julie Stewart, DNP, MSN, MPH, FNP-BC has no relevant financial relationships to disclose.

Susan Basilico, Marjorie Hale, and **Krista Sierra**, Haymarket Medical Education, have no relevant financial relationships to disclose.

25 Philips Parkway, Suite 105
Montvale, NJ 07645
www.myCME.com

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CHAPTER 1: The Why, When, and How of Implementing Routine HIV Screening

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A new case of human immunodeficiency virus (HIV) infection is diagnosed every 9½ minutes, and an estimated 1.8 million people in the US are currently living with the disease.[1,2] Unfortunately, about 21% of people with HIV are unaware they have the infection and may not receive treatment.[3] Furthermore, a significant proportion of patients are diagnosed late in the course of the disease, when treatment is less effective and after they may have unknowingly infected others.[3]

PREVALENCE OF HIV/AIDS IN THE UNITED STATES

In the US, HIV prevalence is highest among men, who account for 74.8% of cases.[4] While whites comprise 72% of the approximately 307 million people living in the US but only 35% of the HIV population, blacks account for 13% of the US population but 46% of people with HIV.[4]

The highest prevalence of diagnosed HIV infection is among persons 25 to 44 years old (51.2%), and most cases are acquired through men having sex with men (MSM, 48%) or MSM who are also injection drug users (IDU, 5%).[4] Nearly 28% of HIV infections are transmitted through male and female high-risk heterosexual contact.[4]

Although the prevalence of HIV infection has been increasing since the 1980s, the introduction of effective antiretroviral (ARV) regimens have contributed to a decrease in AIDS diagnoses and AIDS-related deaths.[2,4,5] The most recent statistics (2008) indicate that approximately 474,000 people are living with AIDS, suggesting there has been a failure to prevent transmission of HIV in the community at large.[2]

NATURAL HISTORY OF UNTREATED HIV INFECTION

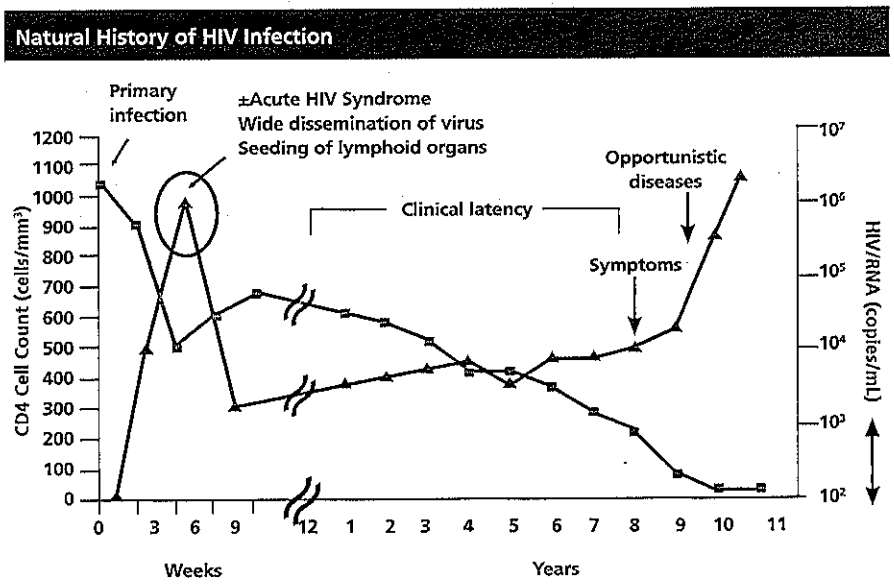
The HIV retrovirus has a remarkable capacity to replicate and mutate.[6] HIV infection is a complex disease process in which abnormal and persistent immune activation, and

dysregulation of cytokine secretion, in the presence of persistent viral replication, lead to progressive deterioration of immune function[7] (**Figure 1**).

HIV binds to CD4 cell receptors and one of two co-receptors (CCR5 or CXCR4).[6] The course of the infection varies from person to person, but in general, the virus begins to replicate rapidly about 3 to 6 weeks after it is acquired and is widely disseminated throughout the body, where it is trapped predominantly in lymph nodes.[7] During this time of high viremia, the peripheral CD4 cell count drops dramatically, and the patient may experience symptoms of an acute influenza- or mononucleosis-like syndrome. This surge in viral replication, or viral load, stimulates an HIV-specific immune response that somewhat controls the acute illness and triggers restoration of the CD4 cell count. However, the virus is not eradicated, and viral replication continues, even when plasma levels of HIV are difficult to detect.

In untreated infection, a period of clinical latency occurs over the next several years, during which the patient may be asymptomatic but the immune system continues to deteriorate as the CD4 cells become depleted. The inevitable outcome of progressive HIV disease, as the CD4 cell count continues to decline, is an AIDS-defining illness with severe or persistent constitutional symptoms, risk for an opportunistic infection, and ultimately, death.[7]

FIGURE 1.



Adapted from Fauci AS, et al. *Ann Intern Med.* 1996;124:654-663; Pantaleo G, et al. *N Engl J Med.* 1993;328:327-335.

RATIONALE FOR ROUTINE HIV SCREENING

About 56,000 new HIV infections are diagnosed each year in the US, and of these, 32,000 are transmitted through sexual exposure.[3] Of these new infections, at least 20,000 per year are due to transmission of HIV from persons who are unaware that they are infected.[3] In an effort to reach these unaware HIV-positive persons, the CDC now recommends screening all individuals in all health care settings for HIV infection, as a normal part of clinical practice and similar to screening for other treatable conditions or diseases.[8]

Currently, only about 20% of HIV infections are diagnosed during a routine check-up.[9] Furthermore, about 40% of all infections are diagnosed in "late testers," that is, persons who progressed to AIDS within 1 year of an HIV diagnosis.[5]

Knowledge of HIV serostatus can lead to a change in high-risk behaviors. A 2005 meta-analysis found that unprotected anal or vaginal intercourse during specified recall periods was reduced substantially after people became aware they were HIV-positive.[10] It should be noted, however, that prevalence and incidence data indicated that awareness of HIV diagnosis alone has not appreciably changed the rates of the epidemic.

Finally, expanded testing may lead to HIV diagnoses when CD4 cell counts are higher and before immune function has been compromised significantly, prompting earlier initiation of treatment with antiretroviral therapy (ART).[11-13]

KEY POINTS OF REVISED CDC RECOMMENDATIONS FOR HIV TESTING

Routine voluntary testing for HIV infection is now recommended by the CDC for all patients aged 13 to 64 years in all health care settings, regardless of the clinician's assessment of patient risk.[8,14]

However, screening is not warranted if the prevalence of HIV infection in a particular community is less than 1 per 1000 patients screened (<0.1%). In contrast to previous recommendations, patients' assent to testing is performed on an "opt-out" basis, in which consent for HIV testing becomes part of the agreement for general medical care and no separate consent is required.

Persons at high risk for HIV infection should be screened at least once a year. "Opt-out" HIV screening should be included with standard prenatal screening tests for all pregnant women, not only those at high risk; repeat screening in the third trimester is recommended for women in certain areas with increased rates of HIV infection among pregnant women.

IS COUNSELING NECESSARY PRIOR TO HIV TESTING?

Because the "opt-out" approach for HIV testing has been shown to improve test acceptance, the CDC no longer recommends formal counseling prior to testing for HIV infection.[8] However, informing the patient of the HIV test allows an opportunity to provide information about the infection and high-risk activities.[14]

A pre-test discussion may include a description of the testing process, the meaning of positive and negative results, and the impact of a positive test result on the patient and the family. For patients who decline the test, counseling provides a means of addressing any misinformation about HIV infection and identifying and discussing the reasons for refusal.

THE WHY, WHEN, AND HOW OF IMPLEMENTING ROUTINE HIV SCREENING

IDENTIFYING AND OVERCOMING BARRIERS TO HIV TESTING

A number of states have laws that differ from the CDC recommendations and require written, informed consent and/or mandatory pre- and post-test counseling that impede "opt-out" testing. Currently, statutes for HIV testing in 34 states and the District of Columbia are consistent or neutral with the CDC recommendations, and legislation related to the recommendations is pending in 15 states. It is important, therefore, that health care providers are aware of local and state regulations regarding HIV testing, consent, and counseling. A useful resource is the *2011 Compendium of State HIV Testing Laws*, which is updated periodically: http://www.nccc.ucsf. edu/consultation_library/state_hiv_testing_laws.

Among providers, there is a misperception that risk-based testing for HIV infection is more cost effective than screening.[15] In addition, providers voice concerns regarding a lack of universal counseling or referral services to link newly diagnosed patients with experienced HIV providers and other clinicians.

In general, patients are accepting of HIV testing under the "opt-out" approach.[16] Nonetheless, important patient-related barriers remain.[14] Many patients refuse testing because they do not feel they are at risk for HIV infection.[17] Others may be reluctant to be tested because of the significant stigma that persists with HIV diagnosis and their concerns about confidentiality, fear of disclosure of sexual orientation or IV drug use, or rejection by friends and loved ones.[14] Patients also may have concerns that discrimination against HIV-positive individuals could affect employment and access to medical insurance. No less important is the psychological impact of a possible positive test result, which may lead to a delay in testing and initiation of treatment.

"Opt-out" Versus "Opt-in" HIV Screening

"Opt-out" screening for HIV infection, in which patient assent is implied unless the patient declines testing, implies that all patients are considered candidates for screening and includes HIV testing as part of the standard panel of laboratory tests.[8]

In contrast, "opt-in" screening requires health care providers to recommend HIV testing specifically, and patients must agree to that test specifically. In addition, "opt-in" screening assumes that clinicians have the ability to assess which patients may be at risk for HIV infection.

HIV diagnosis rates are as much as 25% higher with "opt-out" screening compared with the "opt-in" approach.[8]

CHAPTER 2: Diagnosing HIV Infection

Patients with acute HIV infection often seek medical attention from their primary care providers for the signs and symptoms of a disease that may mimic those of other illnesses.[6]

ACUTE (PRIMARY) HIV INFECTION

The symptoms of acute, or primary, HIV infection may be difficult to distinguish from community-acquired viruses, such as influenza or mononucleosis.[6] Up to 90% of persons develop an acute retroviral syndrome, usually within 2 to 4 weeks of acquiring the virus, although some patients may present with symptoms up to 3 months after exposure. The most common symptoms include low-grade fever, rash, diarrhea, nausea and vomiting, pharyngitis, and headache.[6,18] The syndrome may also be characterized by malaise, fatigue, loss of appetite, arthralgias, night sweats, and mucocutaneous ulcers in some persons (**Figure 2**).

Rash, which is a presenting symptom in about half of patients, is erythematous and maculopapular in appearance, usually over the torso and upper extremities (**Photo, page 9**).

HIV TESTS

Diagnosis of HIV infection is made by an enzyme immunoassay (EIA) that demonstrates the presence of antibodies to HIV, followed by a confirmatory Western blot test.[6,19] Several rapid immunoassays for detection of HIV antibodies have been approved by the US Food and Drug Administration and provide results in 30 minutes or less. These include Uni-Gold™ Recombigen® HIV[20], the Reveal G3® Rapid HIV-1 Antibody Test[21], the Multispot HIV-1/HIV-2 Rapid Test[22], the Clearview® Complete HIV 1/2[23] and HIV 1/2 Stat Pak®[24], and the recently approved INSTI™[25] rapid HIV antibody test, all of which use blood samples from finger stick or venipuncture. The OraQuick Advance® Rapid HIV-1/2 Antibody Test[26] uses oral fluid samples rather than blood samples.

A positive screening test result is considered "preliminary positive" and must be confirmed by the Western blot test or indirect immunofluorescence assay.[19] There are 4 possible interpretations of the 2 tests. If the results of both the EIA and Western blot test are positive, a diagnosis of HIV infection is confirmed.

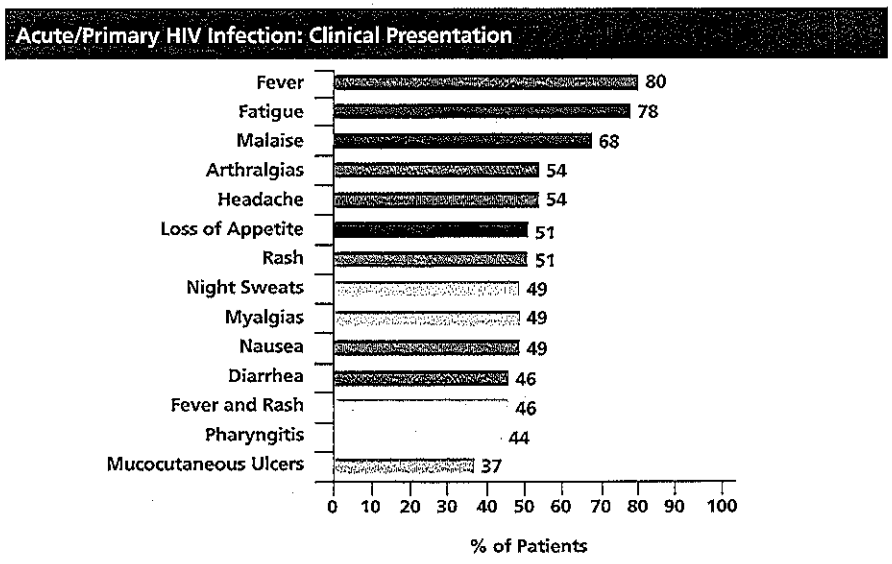
Conversely, negative results of both tests indicate the patient is not infected with HIV; however, this interpretation is not valid during the period from 2 to 8 weeks after the infection may have been acquired and antibodies to HIV have not reached detectable levels, often referred to as the "diagnostic window period."

The results of the EIA may be positive and the Western blot test, negative; in that case, the patient generally is considered not infected with HIV, unless he or she is at high risk for acquiring the infection. If the EIA results are positive but the Western blot test results are inconclusive, the patient is either not infected with HIV or is in the process of seroconversion; that is, the patient may have acquired HIV infection, but the antibodies cannot yet be detected by the Western blot test. In such a case, a polymerase chain reaction (PCR) test should be done to determine the amount of HIV RNA in the blood, or viral load, and the serologic tests should be repeated in about 1 month.

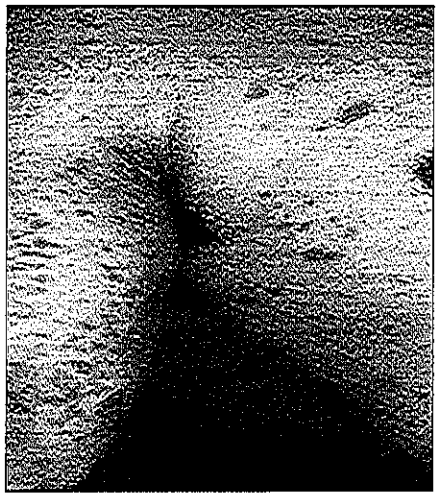
A confirmed diagnosis of HIV infection should be communicated confidentially and in person. It is important that the patient be reassured that the medications to treat HIV have advanced considerably and that life expectancy can be prolonged significantly if he or she adheres to a proposed ART regimen. It is appropriate to consult with an HIV specialist who can assist in developing a care plan at the time of diagnosis.

Additional tests are needed to characterize the infection (**Table 1**).[19] The initial CD4 cell count is used to stage HIV disease, establish the risk for specific HIV-related complications, and determine the

FIGURE 2.



Hecht FM, et al. *AIDS*. 2002;16:1119-1129.



Example of Typical Rash Associated with Acute HIV Infection.

"Viral load correlates with the severity of HIV infection and can be used to estimate the risk for progression and to determine the need for ART."

need for prophylaxis against opportunistic infections (OIs). The CD4 cell count is also used as a guide for the initiation of antiretroviral therapy (ART) and to monitor the response to treatment. Current recommendations suggest obtaining 2 baseline CD4 cell counts at least 1 week apart. The CD4 cell percentage can be used in lieu of the CD4 cell count to assess immune function. In general, total CD4 cell counts of 200 and 500 cells/mm^3 correspond to CD4 cell percentages of 14% and 29%, respectively.

Viral load, measured quantitatively as HIV RNA copies/mL, correlates with the severity of HIV infection and can be used to estimate the risk for progression and to determine the need for ART.

Because HIV has the capacity to mutate and develop resistance to antiretroviral agents, drug-resistant HIV infection can be transmitted from person to person.[19] A baseline HIV genotype resistance test should be performed during acute HIV infection or shortly afterward because it may be helpful in selecting an appropriate ART regimen, even if treatment will not be initiated immediately.

TABLE 1.

Additional Tests for Diagnosing and Monitoring HIV Infection.[19]

Test	Purpose of Test
CD4 cell count and percentage	• Assess immune function • Assess disease stage • Determine need for prophylaxis against opportunistic infection • Determine need for ART • Monitor response to ART
HIV RNA level (viral load)	• Assess risk for disease progression • Determine need for ART • Monitor response to ART
HIV genotype resistance test	• Assess risk for transmitted resistance

ART, antiretroviral therapy.

CHAPTER 3: Clinical Approach to the Patient Newly Diagnosed With HIV Infection

The first step in the care of the newly diagnosed HIV-positive patient is to conduct a thorough history and physical examination.[19] A comprehensive assessment should include:

- The history of the present illness (including approximate date of acquisition)
- Past medical history
- Prescription and over-the-counter medications

TABLE 2.

Baseline Laboratory Studies for the Patient Newly Diagnosed With HIV.[13,19]

- Complete blood count with differential
- Fasting lipid profile
- Fasting plasma glucose level
- G6PD (if at risk)
- Serum chemistries
  - ALT, AST, bilirubin levels
  - Albumin level
  - Alkaline phosphatase level
  - Electrolytes, BUN, creatinine
- Urinalysis
  - –RBC
  - –WBC
  - –Proteinuria
  - –Sediment levels
- Coinfection/comorbidity screening
  - –Chest x-ray
  - –Hepatitis B and C serologies
  - –*Toxoplasma* IgG
  - –*Cytomegalovirus* IgG and other herpes virus
  - –Screening for other STDs (syphilis, gonorrhea, *Chlamydia*, *Trichomonas*, HPV)
  - –Tuberculin skin test
  - –Pap smear in women; anal cytology in MSM and all patients with a history of cytological abnormalities

HIV, human immunodeficiency syndrome; IgG, immunoglobulin G; G6PD, glucose-6-phosphate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; STDs, sexually transmitted diseases; HPV, human papillomavirus; MSM, men who have sex with men.

- Allergies (including any history of hypersensitivity reactions to medications)
- Social and family histories (including tobacco, alcohol, and illegal drug use)
- Sexual history[19]

Baseline laboratory tests recommended for newly diagnosed patients are outlined in **Table 2**.[13,19]

With the exception of tuberculosis and STD screening, the tests should be repeated periodically before and after the initiation of ART, as indicated in **Table 3**.[13]

The reproductive health needs of women with HIV infection are no different from those of otherwise healthy women.[19] However, the prevalence of gynecologic problems is high throughout the course of HIV disease, and immunosuppression contributes to these problems being more common or severe (see **Special Considerations for Women With HIV,** below).[19]

Special Considerations for Women With HIV.[19]

- *Contraception and Preconception Care*: All HIV-infected women of childbearing age should be advised regarding effective contraception to prevent unintended pregnancy or referred for preconception counseling if pregnancy is desired. All medications for women at risk for pregnancy should be reviewed carefully to minimize the risk for reproductive toxicity.
- *Pregnancy Testing*: Women with HIV infection in the following circumstances should be tested for pregnancy: missed menses, irregular bleeding, new onset of irregular bleeding or pelvic pain, enlarged uterus or adnexal mass on examination, before initiating new medications with potential risks for a pregnant woman or fetus, or at the patient's request.
- *Cervical Cancer Screening and Prevention*: A cervical Pap smear should be performed at the initiation of care, after 6 months, and, if normal, yearly thereafter. Abnormal Pap smear results should prompt further examination by colposcopy and directed biopsy, and treatment as needed.
- *Breast Cancer Screening*: Mammography should be performed annually in women >50 years of age, and women 40 to 49 years old should be assessed individually for breast cancer risk and informed of the potential benefits and risks of screening mammography.
- *Menopause*: Routine use of hormone replacement therapy (HRT) currently is not recommended for women with HIV infection. HRT may be considered in women with severe menopausal symptoms but prescribed at the lowest effective doses and for a limited period of time.
- *Maternal-to-Fetal HIV Transmission*: Pregnant women should be treated for HIV infection, regardless of virologic or immunologic status, and infants exposed to HIV in utero should receive ARV post-exposure prophylaxis and undergo HIV diagnostic testing at 14 to 21 days, 1 to 2 months, and 4 to 6 months of age. HIV-infected infants should undergo HIV genotype resistance testing and initiate ART in the first year of life regardless of CD4 cell count, viral load, or clinical status.

ARV, antiretroviral.

CLINICAL APPROACH TO THE PATIENT NEWLY DIAGNOSED WITH HIV INFECTION

TABLE 3.

Laboratory Monitoring Schedule Before and After Initiation of ART.[13]

Laboratory Study	Follow-up Before ART	At ART Initiation or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated
CD4+ cell count	every 3-6 mo	X		X	In clinically stable patients with suppressed viral load, can be measured every 6-12 mo		X	X
HIV RNA	every 3-6 mo	X	X	X			X	X
Resistance testing		X					X	X
Hepatitis B serology		Prior to all ART						X
CBC with differential	every 3-6 mo	X	if on ZDV	X				X
Blood chemistries	every 6-12 mo	X	X	X				X
Fasting plasma glucose	if normal, annually	X		if abnormal at last measurement	if abnormal at last measurement			X
Fasting lipid profile		X	X			X		X
ALT, AST, bilirubin	every 6-12 mo	X	X	X				X
Urinalysis		X				X		X
Pregnancy test	if starting EFV							X

ART, antiretroviral therapy; HIV, human immunodeficiency virus; CBC, complete blood count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ABC, abacavir; ZDV, zidovudine; EFV, efavirenz.

CHAPTER 4: Overview of Antiretroviral Therapy

There are 4 key goals for initiating antiretroviral therapy (ART):[13]

- Reduce HIV-related morbidity and prolong the duration and quality of survival
- Restore and preserve immune function
- Achieve maximal and durable suppression of plasma HIV viral load
- Prevent HIV transmission

Viral suppression and recovery of immune function may delay or prevent cardiovascular disease, kidney disease, liver disease, and malignancies.[13] In addition, viral suppression may decrease inflammation that is associated with cardiovascular and other end-organ damage reported in HIV-infected patients. Achieving viral suppression requires the use of ART regimens with 3 drugs from 2 or 3 different classes. Thus, it is crucial that any patient beginning ART should be willing and able to commit to lifelong treatment, understand the benefits and risks of therapy, and understand the importance of adherence.[13]

CURRENT GUIDELINES FOR ANTIRETROVIRAL THERAPY

The US Department of Health and Human Services issued updated guidelines for the initiation of ART in treatment-naïve patients in January 2011.[13] The guidelines continue to recommend earlier initiation of therapy, that is, starting treatment in all patients with a history of an AIDS-defining illness or with a CD4 cell count <350 cells/mm^3.[13] ART also should be initiated in patients with HIV-associated nephropathy and patients with hepatitis B co-infection in whom treatment for hepatitis B virus is indicated, regardless of CD4 cell count.

The guidelines include a recommendation to initiate therapy in patients with CD4 cell counts between 350 and 500 cells/mm^3, based on panel members' strong-to-moderate (55% vs. 45%) recommendation.[13] In addition, 50% of the panel members favored initiating a ntiretroviral therapy for patients with CD4 cell counts >500 cells/mm^3, with the other 50% considering it optional.

Early initiation of ART significantly reduces the risk for AIDS progression or death (P=0.035) and the time to AIDS progression or death (P=0.02), according to a recent study by the AIDS Clinical Trials Group (ACTG).[27] There was no increase in adverse events or loss of virologic response associated with early ART compared with deferred treatment.

Finally, early initiation has the potential to reduce ART-related toxicity.[28] In a cohort of the HIV Outpatient Study (HOPS), patients who began ART at higher pre-ART CD4 cell counts (>349 cells/mm^3) were less likely to develop renal insufficiency, distal polyneuropathy, or lipoatrophy during ART than those with lower pre-ART CD4 cell counts.

In contrast, there are deleterious consequences to deferring or interrupting ART, including an increased risk for death, end-organ disease, and drug toxicity. In the Strategies for Management of Antiretroviral Therapy (SMART) study,

"Early initiation of antiretroviral therapy (ART) significantly reduces the risk for AIDS progression or death, and may reduce ART-related toxicity."

ART was deferred until the CD4 cell count decreased to <250 cells/mm^3, then continued until the CD4 cell count increased to >350 cells/mm^3; treatment was resumed when the CD4 cell count again fell to <250 cells/mm^3.[29] Compared with continuous ART, episodic treatment increased the risk for all-cause mortality (P=0.007), serious opportunistic disease (P<0.01), and major cardiovascular, renal, or hepatic disease (P=0.009), but did not reduce the risk for ART-associated adverse events.

ANTIRETROVIRAL AGENTS AVAILABLE IN THE US

At least 20 ARV agents in 6 therapeutic classes are available for the treatment of HIV in the US; each class uses a different mechanism to interrupt the HIV life cycle.[13,30]

Fusion inhibitors (FIs) prevent virus particles from attaching to the host cell membrane, blocking entry into CD4 T cells.[31]

Chemokine co-receptor 5 antagonists (CCR5 antagonists) specifically block access of the virus to the CD4 receptor. Other classes of ARV agents inhibit enzymes needed for HIV replication.

Nucleotide (or nucleoside) reverse transcriptase inhibitors (NRTIs) and *non-nucleoside reverse transcriptase inhibitors (NNRTIs)* interrupt the reverse transcription of viral RNA into double-stranded HIV DNA within the host cell.

Integrase strand transfer inhibitors (INSTIs) block the action of the enzyme required for HIV DNA to combine with host cell DNA in the cell nucleus.

Lastly, *protease inhibitors* (PIs) block the splicing of HIV messenger-RNA into smaller units and the formation of new viral proteins.

The specific agents approved for use in the US are listed in **Table 4**; the agents in boldface are most often used in the primary care setting.[6]

Preferred and alternative combination regimens currently recommended for patients naïve to ART are listed in **Table 5**; the various combinations are based on their virologic efficacy, tolerability and toxicity profiles, and ease of use.[13] Some ARV agents are available as fixed-dose combinations that reduce pill burden and frequency of dosing, factors that may promote adherence.[13]

The regimens combine ARV agents with different mechanisms of action to maximize the potential for optimal and durable virologic response, with minimal toxicity. The preferred regimens are NNRTI-, PI-, or INSTI-based with 2 NRTIs added.

PERIODIC FOLLOW-UP AND EVALUATION

Because management of HIV involves a lifelong commitment to ART on the part of the patient and ongoing monitoring on the part of the provider, it is critical for the patient and provider to

formulate and agree on a long-term disease management plan in order to maximize outcomes.[9]

The frequency of follow-up visits and monitoring depends at least in part on the stage of the disease, the rate at which it is progressing, and any clinical problems the patient may be experiencing.[19] For example, asymptomatic patients with low viral load and normal CD4 cell counts need infrequent monitoring, with routine evaluations carried out every 3 to 6 months. However, patients requiring prophylaxis for opportunistic infections may need to be monitored more frequently for medication toxicity.

For patients who have begun ART, follow-up with the primary care provider at 1, 2, and 4 weeks is recommended.[19] These clinic visits provide opportunities to discuss the results of serologic and clinical laboratory tests, assess adherence, identify psychosocial issues related to the disease and its therapy or personal relationships, and emphasize the need to practice birth control and prevent disease transmission.

OPTIMIZING ADHERENCE

One key reason that only 40% to 50% of patients with HIV in some clinical practices achieve maximal and durable suppression of HIV replication is suboptimal adherence to the treatment regimen; this is particularly true among patients on initial therapy.[19]

Adherence to ART is a major determinant of the degree and duration of viral suppression, and, therefore, clinical outcomes.[32] Durable suppression of viral replication requires at least 95% adherence to the regimen, but only one third of patients with HIV or AIDS achieve this level of adherence.

TABLE 4.

Antiretroviral Medications Approved for Use in the US.[13]

FI	
Enfuvirtide	ENF
CCR5 Antagonist	
Maraviroc	MVC
NRTIs	
Abacavir	**ABC**
Didanosine	ddI
Emtricitabine	**FTC**
Lamivudine	**3TC**
Stavudine	d4T
Tenofovir	**TDF**
Zalcitabine	ddC
Zidovudine	ZDV
NNRTIs	
Delavirdine	DLV
Efavirenz	**EFV**
Nevirapine	NVP
Etravirine	ETR
Rilpivirine	RPV
INSTI	
Raltegravir	**RAL**
PIs	
Atazanavir	**ATV**
Darunavir	**DRV**
Fosamprenavir	FPV
Indinavir	IDV
Lopinavir	**LPV**
Nelfinavir	NFV
Ritonavir	**RTV**
Saquinavir	SQV
Tipranavir	TPV

*Some agents are available in fixed-dose combinations.
Drug names in **boldface** are commonly used in the primary care setting.
FI, fusion inhibitor; CCR5, chemokine co-receptor 5; NRTI, nucleotide (nucleoside) reverse transcriptase inhibitor; NNRTI, non-nucleotide (nucleoside) reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor.

It is important for clinicians to recognize the patient-, provider-, and regimen-related factors that can contribute to nonadherence, and to develop strategies that will optimize compliance (see **Table 6**).[19]

TABLE 5.

Preferred and Alternative Antiretroviral Regimens for Treatment-naive Patients With HIV Infection.[13]

Preferred Regimens	
NNRTI-based:	EFV/TDF/FTC
PI-based:	ATV/r + TDF/FTC **or** DRV/r + TDF/FTC
INSTI-based:	RAL + TDF/FTC
For pregnant women:	LPV/r + ZDV/3TC
Alternative Regimens	
NNRTI-based:	EFV + (ABC or ZDV)/3TC **or** NVP + ZDV/3TC
PI-based:	ATV/r + (ABC or ZDV)/3TC **or** FPV/r + either (ABC or ZDV)/3TC or TDF/FTC **or** LPV/r + either ABC or ZDV/3TC or TDF/FTC

Notes:

- 3TC may be substituted for FTC and vice versa.
- EFV should not be used during the first trimester of pregnancy or in women trying to conceive or who are not using effective and consistent contraception.
- ATV/r should not be used in patients who require >20 mg of omeprazole equivalent per day.
- NVP should not be used in patients with moderate to severe hepatic impairment, in women with pre-ART CD4 cell counts >250 cells/mm^3, or in men with pre-ART CD4 cell counts >400 cells/mm^3.
- ABC should be used with caution in patients with high risk for cardiovascular disease or with pretreatment viral load >100,000 copies/mL.
- Once-daily LPV/r is not recommended in pregnant women.

NNRTI, non-nucleotide (nucleoside) reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; EFV, efavirenz; TDF, tenofovir; FTC, emtricitabine; ATV/r, ritonavir-boosted atazanavir; DRV/r, ritonavir-boosted darunavir; RAL, raltegravir; LPV/r, ritonavir-boosted lopinavir; ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine; ABC, abacavir; FPV, fosamprenavir.

TABLE 6.

Factors Contributing to Suboptimal Adherence to ART and Strategies to Aid Adherence.[19]

Factors that negatively affect adherence:

- Lack of education about HIV infection
- Denial, anxiety, or depression
- Alcohol or drug use
- Poor social situation
- Inadequate health insurance
- Number of medications or pill burden
- Frequency of dosing
- Stringent dosing requirements
- Presence of side effects
- Poor clinician-patient relationship

Multifaceted strategies that promote adherence:

Patient-focused

- Screen for and treat depression, substance/alcohol abuse
- Stabilize support system
- Address negative perceptions of ART
- Use appropriate educational materials
- Offer educational sessions about ART
- Identify someone to assist with adherence

Provider-focused

- Develop adherence-focused activities
- Develop warm, caring patient-clinician relationship
- Provide a user-friendly practice
- Use a multidisciplinary care team
- Schedule intensive and frequent visits in first month of treatment

Regimen-focused

- Prescribe simpler regimens
- Individualize regimens
- Choose regimens with fewer side effects
- Manage side effects proactively
- Assess patient's understanding of regimen

CHAPTER 5: Clinical Considerations Related to Antiretroviral Therapy

Although most patients tolerate antiretroviral therapy (ART), all antiretroviral (ARV) drugs can cause adverse effects that are common reasons for nonadherence and switching or discontinuing therapy.[13] The development of newer regimens for treatment-naïve patients has reduced the rates of treatment-limiting side effects, offering a means to maximize effectiveness, maintain viral suppression, and improve immune function. Class-specific adverse events are well documented, and each agent is associated with specific adverse events.[33] In addition, certain individuals may be predisposed to adverse effects of ARV agents. These events may be precipitated by the use of concomitant medications, comorbid conditions or co-infections, or drug-drug interactions.[13]

COMMON AND/OR SERIOUS ADVERSE EVENTS ASSOCIATED WITH ANTIRETROVIRAL THERAPY

A wide range of adverse effects are associated with ART.[33] Common but mild adverse effects that occur early in most ARV regimens include gastrointestinal effects (nausea, vomiting, diarrhea), which may be transient or persist throughout therapy.

The features of other serious adverse effects associated with specific ARV classes are outlined in **Table 7.**

DRUG-DRUG INTERACTIONS

Potential interactions among ARV agents and interactions between these agents and other drugs should be taken into consideration when selecting a regimen.[13] Most drug-drug interactions are mediated through induction or inhibition of drug metabolism in the liver through the cytochrome P (CYP) 450 system.

While a complete listing of possible interactions between ARVs and other drugs is beyond the scope of this guidebook, key interactions are detailed here. Specific drug-drug interactions can be found in the US Department of Health and Human Services publication, *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf).

- Rifabutin and rifampin, used for the treatment of tuberculosis, are strong inducers of CYP 450 enzymes. Concurrent administration of these agents with PIs, NNRTIs, the INSTI raltegravir, or the CCR5 antagonist maraviroc can decrease plasma concentrations of and exposure to the ARV agent and result in treatment failure. As a result, co-administration of all PIs with rifampin is contraindicated. The only NNRTI that is not contraindicated for use with rifampin is efavirenz, and co-administration with maraviroc is not recommended. Virologic response to raltegravir should be monitored closely if used concomitantly with rifampin. Rifabutin is a less potent inhibitor of the CYP 450 system and may be used with some PIs or NNRTIs, or maraviroc, with dose adjustment of the ARV agent; no dose

(continued on page 22)

TABLE 7.

Common and/or Serious Adverse Effects of Various ART Agents.[13]

Adverse Effect	NRTIs	NNRTIs	PIs	INST	CCR5 Antagonist
GI disturbances	ddI, ZDV: nausea, vomiting > other NRTIs ddI: pancreatitis		All PIs: nausea, vomiting, diarrhea, most common with NFV, LPV/r > other PIs		
CNS effects		EFV: somnolence, insomnia, abnormal dreams, dizziness, impaired concentration			
Bone marrow suppression	ZDV: macrocytic anemia, neutropenia				
Peripheral neuropathy	d4T > ddI and ddC (can be irreversible) d4T: rare reports of Guillain-Barré-like syndrome				
Hepatotoxicity	Most NRTIs ddI: noncirrhotic portal hypertension with prolonged exposure ZDV, d4T, ddI: steatosis	NVP: severe hepatic toxicity associated with rash or symptoms of hypersensitivity. Risk greater in women with CD4 cell count >250 cells/mm³ or men with CD4 cell count >400 cells/mm³.	All PIs: varying degrees of drug-induced hepatitis and hepatic decompensation TPV/r: higher frequency of hepatic effects than other PIs IDV, ATV: jaundice due to direct hyperbilirubinemia		

TABLE 7. (continued)

Common and/or Serious Adverse Effects of Various ART Agents.[13]

Adverse Effect	NRTIs	NNRTIs	PIs	INST	CCR5 Antagonist
Nephrotoxicity	TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, urinary phosphate wasting, non-anion gap metabolic acidosis		IDV: ↑ serum creatinine, pyuria, hydronephrosis or renal atrophy IDV, ATV: stone or crystal formation		
Rash		All NNRTIs	ATV, DRV, FPV		MVC
Stevens-Johnson syndrome/ toxic epidermal necrosis	ddI, ZDV: reported cases	NVP > DLV, EFV, ETR NVP: Women, blacks, Asians, Hispanics at greater risk	FPV, DRV, IDV, LPV/r, ATV: reported cases		
Hypersensitivity reaction (excluding rash or Stevens-Johnson syndrome)	ABC: Screen for HLA-B*5701 prior to initiation of therapy. Most reactions occur in first 6 weeks of treatment. Symptoms (constitutional symptoms, skin rash, GI distress, dyspnea, arthralgias) worsen with continuation of ABC. Rapid onset of severe symptoms with rechallenge.	NVP: Hypersensitivity syndrome with hepatotoxicity and rash; may also have constitutional symptoms, arthralgias, facial edema, blood dyscrasias, lymphadenopathy, renal dysfunction. Risk greater in women with CD4 cell count >250 cells/mm³ or men with CD4 cell count >400 cells/mm³.			

TABLE 7. (continued)

Common and/or Serious Adverse Effects of Various ART Agents.[13]

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	CCR5 Antagonist
Bleeding events			All PIs: ↑ spontaneous bleeding; hematuria in hemophilia TPV: reports of intracranial hemorrhage		
Myopathy	ZDV			RAL: ↑ CPK, muscle weakness, and rhabdomyolysis	

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; ABC, abacavir; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; DLV, delavirdine; DRV, darunavir; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FPV, fosamprenavir; ritonavir-boosted fosamprenavir; FTC, emtricitabine; IDV, indinavir; LPV/r, ritonavir-boosted lopinavir; MVC, maraviroc; NFV, nelfinavir; NVP, nevirapine; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir; TPV, tipranavir; ZDV, zidovudine; CNS, central nervous system; CPK, creatine phosphokinase; GI, gastrointestinal.

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adjustment of raltegravir is necessary if used concomitantly with rifabutin.

- PIs can increase plasma concentrations of statins and are contraindicated for use with lovastatin and simvastatin; all ritonavir-boosted PIs are contraindicated for use with pitavastatin. The lowest possible dose of atorvastatin should be administered, and patients should be monitored carefully. Dose adjustment of other statins is warranted for co-administration with ritonavir-boosted PIs. In addition, patients should be advised of the symptoms of rhabdomyolysis.
- Co-administration of ritonavir-boosted PIs may decrease plasma concentrations of some antidepressants but increase concentrations of tricyclic antidepressants, necessitating dose titration of the antidepressant.
- Dexamethasone should be used with caution with all PIs because PI plasma concentrations may decrease.
- Fluticasone plasma concentrations can increase significantly in the presence of any ritonavir-boosted PI and lead to adrenal insufficiency; therefore, fluticasone should not be used unless the potential benefits outweigh the risk for systemic adverse effects.
- For patients taking the PI atazanavir and/or the newly approved NNRTI rilpivirine, protein pump inhibitors (PPIs) should not be co-administered, and H_2-receptor antagonists should be used with caution.
- ARV agents have been reported to decrease plasma concentrations of ethinyl estradiol or increase levels of progestin in oral contraceptives (OCs), thereby decreasing the efficacy of OCs or increasing the risk for adverse effects related to their components. Alternative or additional methods of contraception are recommended if OCs are used with most unboosted and ritonavir-boosted PIs and NNRTIs. OCs and the CCR5 antagonist maraviroc, however, are safe to use in combination.
- Concomitant use of ritonavir-boosted PIs with warfarin may increase or decrease plasma concentrations of warfarin, requiring close monitoring of the international normalized ratio (INR) and warfarin dose adjustment as needed.
- Several benzodiazepines are metabolized via the CYP 450 system, and co-administration with some PIs and NNRTIs can increase plasma levels of the benzodiazepine. In particular, midazolam and triazolam are contraindicated for use with all PIs and with efavirenz.
- For patients treated with a PDE5 inhibitor for erectile dysfunction, plasma concentrations may be increased by co-administration of any PI or decreased by concomitant use of an NNRTI, requiring dose adjustments. The use of any ritonavir-boosted PI with the PDE5 inhibitor sildenafil for the treatment of pulmonary arterial hypertension is contraindicated.
- Interactions also can occur between ARV agents and narcotics used to treat opioid dependence. The effects of methadone on the CYP 450 system and gastric emptying can reduce methadone levels and diminish the effectiveness of the ARV agent, and the methadone dose may need to be increased. Conversely, no dose adjustment of buprenorphine is necessary for concomitant use with ritonavir-boosted PIs, NNRTIs, or NRTIs; however, clinical monitoring is appropriate. Buprenorphine should not be co-administered with unboosted atazanavir due to the possibility of reduced atazanavir plasma concentrations. No dose adjustment of either buprenorphine or methadone is necessary, however, when co-administering NRTIs.
- Plasma concentrations of anticonvulsants may be altered if co-administered with ARV agents. Co-administration of PIs may increase concentrations of carbamazepine but decrease concentrations of lamotrigine or phenytoin, and levels of the PI may decrease substantially. Concomitant use of NNRTIs may decrease the plasma concentrations of both the NNRTI and the anticonvulsant. Plasma concentrations of the CCR5 antagonist maraviroc may decrease in the presence of an anticonvulsant. Plasma levels of the anticonvulsant and ARV agent should be monitored and doses adjusted accordingly.
- St. John's wort should not be used concomitantly with any PI or NNRTI, or maraviroc, due to potentially reduced levels of the ARV agent.

CLINICAL CONSIDERATIONS RELATED TO ANTIRETROVIRAL THERAPY

Table 8 provides a list of specific non-ARV agents that should not be co-administered with PIs, NNRTIs, and the CCR5 antagonist due to the potential for serious drug–drug interactions.

LONG-TERM METABOLIC CONSEQUENCES OF ART

Long-term administration of ART can lead to several major abnormalities in glucose, lipid, and fat metabolism, lactic acidemia, and loss of bone mineral density (BMD).[19]

Metabolic syndrome reportedly is present in up to 25% of patients receiving ART and 10% of HIV-infected patients developed new-onset diabetes within 4 years of beginning therapy.[34]

Among the ARV classes, PIs specifically induce insulin resistance, particularly indinavir and ritonavir-boosted lopinavir. The risk for developing diabetes is also

TABLE 8.

Non-Antiretroviral Drugs That Should Not Be Administered With PIs, NNRTIs, or CCR5 Antagonist.[13]

ARV Agent	Cardiac Agents	Statins	Antimycobacterials	GI Drugs	Psychotropics	Herbs	Others
PIs							
Atazanavir + ritonavir	None	Lovastatin Pitavastatin Simvastatin	Rifampin Rifapentine	Cisapride	Midazolam Triazolam	St. John's wort	Alfuzosin Irinotecan Salmeterol Sildenafil (for PAH)
Darunavir + ritonavir, Lopinavir + ritonavir	None	Pravastatin Lovastatin Pitavastatin Simvastatin	Rifampin Rifapentine	Cisapride	Midazolam Triazolam	St. John's wort	Alfuzosin Salmeterol Sildenafil (for PAH)
Fosamprenavir + ritonavir	Flecainide Propafenone	Lovastatin Pitavastatin Simvastatin	Rifampin Rifapentine	Cisapride	Midazolam Triazolam	St. John's wort	Alfuzosin Salmeterol Sildenafil (for PAH)
Ritonavir	Amiodarone Flecainide Propafenone Quinidine	Lovastatin Pitavastatin Simvastatin	Rifampin Rifapentine	Cisapride	Midazolam Triazolam	St. John's wort	Alfuzosin Sildenafil (for PAH)

TABLE 8. (Continued)

Non-Antiretroviral Drugs That Should Not Be Administered With PIs, NNRTIs, or CCR5 Antagonist.[13]

ARV Agent	Cardiac Agents	Statins	Antimycobacterials	GI Drugs	Psychotropics	Herbs	Others
Saquinavir + ritonavir	Amiodarone Dofetilide Flecainide Lidocaine Propafenone Quinidine	Lovastatin Pitavastatin Simvastatin	Rifampin Rifapentine	Cisapride	Midazolam Triazolam	St. John's wort	Alfuzosin Salmeterol Sildenafil (for PAH)
Tipranavir + ritonavir	Amiodarone Flecainide Propafenone Quinidine	Lovastatin Pitavastatin Simvastatin	Rifampin Rifapentine	Cisapride	Midazolam Triazolam	St. John's wort	Alfuzosin Salmeterol Sildenafil (for PAH)
NNRTIs							
Efavirenz	None	None	Rifapentine	Cisapride	Midazolam Triazolam	St. John's wort	None
Etravirine	None	None	Rifampin Rifapentine	None	None	St. John's wort	Carbamazepine Phenobarbital Phenytoin Clopidogrel
Nevirapine	None	None	Rifapentine	None	None	St. John's wort	Ketoconazole
CCR5 Antagonist							
Maraviroc	None	None	Rifapentine	None	None	St. John's wort	None

PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; CCR5, chemokine co-receptor 5; GI, gastrointestinal.

increased in patients treated with NRTIs, specifically zidovudine, stavudine, and didanosine; atazanavir, with or without ritonavir, has not been found to alter insulin sensitivity.

In addition to drug-specific insulin resistance, changes in glucose metabolism may be related to ART-induced dyslipidemia and lipodystrophy, as well as effects on pancreatic ß-cell insulin production.[34]

The ARV-associated dyslipidemic pattern features high low-density lipoprotein cholesterol (LDL-C) and triglycerides, and low high-density lipoprotein cholesterol (HDL-C).[19,34] This pattern of dyslipidemia is highly atherogenic, and coupled with insulin resistance, vascular inflammation, and other risk factors increases the risk for premature cardiovascular disease (CVD).

All ritonavir-boosted PIs induce dyslipidemia, and the changes can occur as early as 2 weeks after initiation of therapy. The increases in triglycerides are more profound with ritonavir-boosted lopinavir than ritonavir-boosted darunavir or atazanavir. The NNRTI efavirenz and NRTIs zidovudine, stavudine, and didanosine induce lipid abnormalities, and the changes are more pronounced in dual NRTI/NNRTI combination regimens.

Lipodystrophy is characterized by peripheral fat loss (lipoatrophy) in the face, limbs, and buttocks, as well as fat accumulation (lipohypertrophy) in the abdomen and breasts and over the dorsocervical spine.[33] NRTI therapy is associated with lipoatrophy, particularly with stavudine and zidovudine, while lipohypertrophy has been observed with NNRTIs (primarily efavirenz), PIs, and the INSTI raltegravir.[13] Lipoatrophy is more likely to occur when an NRTI is combined with efavirenz rather than a boosted PI.

Lactic acidemia is a rare but serious syndrome that can occur during treatment with the NRTIs zidovudine, didanosine, and stavudine due to their disruptive effects on mitochondrial DNA replication.[33] Because lactic acidosis can cause liver failure, cardiac dysrhythmias, and potentially death, patients taking NRTIs who complain of nausea, weight loss, fatigue, diminished exercise tolerance, or tachypnea should be evaluated for elevated lactic acid levels and elevated anion gap.

Osteopenia or *osteoporosis* resulting from decreases in bone mineral density (BMD) can occur in patients taking regimens that combine NRTIs with either NNRTIs or PIs.[13] The NRTI tenofovir is associated with a greater loss of BMD than other agents in this class. Although the need to measure BMD in all patients on ART has not been established, evaluation with dual-energy x-ray absorptiometry (DEXA) should be considered in patients taking corticosteroids, postmenopausal women, and patients with other risk factors for osteoporosis.[33]

CHAPTER 6: Managing Opportunistic Infections and HIV Complications

The introduction of antiretroviral therapy (ART) has had a profound influence on the reduction of mortality due to opportunistic infections (OIs) in the HIV-infected population.[35]

However, OIs contribute to considerable hospitalization and death in the US for several reasons. For many of the more than 250,000 persons with HIV who are unaware of their infection, the signs and symptoms of an OI are the first indication of their disease.[3,35] Even patients who are aware of their HIV status may refuse ART for psychological or socioeconomic reasons.[35] Finally, patients who are prescribed ART may not achieve an adequate virologic or immunologic response due to poor adherence, suboptimal pharmacokinetics, or biological factors.

HIV infection and OIs are interrelated, in that HIV-related immunosuppression allows opportunistic pathogens to invade otherwise healthy tissues.[35] Common OIs in HIV-infected patients can adversely alter the natural history of HIV infection by increasing the viral load and accelerating the progression of the disease. However, vaccination and chemoprophylaxis against specific pathogens can prevent a number of OIs, reduce the rate of HIV progression, and indirectly delay or reduce the occurrence of subsequent OIs.

CAUSES AND TYPES OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS

As HIV progresses over time and CD4 cell counts decline—and particularly when the CD4 cell count falls below 500 cells/mm^3, a host of viruses, bacteria, fungi, and protozoa can cause disease in virtually every organ system:[36]

- Viral pathogens: cytomegalovirus, herpes simplex, and varicella-zoster
- Bacterial pathogens: *Mycobacterium tuberculosis, Mycobacterium avium complex* (MAC), *Streptococcus pneumoniae, Haemophilus* sp., *Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella* sp., *Campylobacter* sp.
- Fungal pathogens: *Pneumocystis carinii, Candida* sp., *Cryptococcus* sp.
- Protozoal pathogens: *Toxoplasma gondii,* microsporidia, cryptosporidia, isospora, *Leishmanias* sp., *Trypanosoma cruzi*

Different OIs typically occur at different stages of disease.[35] The most common OI that develops when the CD4 cell count remains above 500 cells/mm^3 is vaginal candidiasis (see **Table 9**).

Patients with CD4 cell counts between 200 and 500 cells/mm^3 are likely to develop oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis (TB), recurrent community-acquired pneumonia (particularly streptococcal pneumonia), and herpes simplex or varicella-zoster infection.[36]

A further decline in CD4 cell count to <200 cells/mm^3 indicates that HIV infection has progressed to AIDS, predisposing the patient to *Pneumocystis jiroveci* pneumonia, cryptococcal meningitis, histoplasmosis, cryptosporidial or isospora GI infection, toxoplasmosis, extra-pulmonary TB, and disseminated herpes viral infection, histoplasmosis, or cryptococcosis. Patients with a CD4 cell count of <50 cells/mm^3 are at risk for multi-organ

invasion by the bacterial *Mycoplasma avium* complex (MAC) or infection of the eyes by *Cytomegalovirus*.

HIV-infected patients are more susceptible to infection with *Mycobacterium* tuberculosis than healthy individuals at all stages of the disease, since CD4 cell count is not a reliable predictor of increased risk for the disease.[35]

Furthermore, viable tubercule bacilli can persist for years after the immune response limits replication as latent TB infection. Current guidelines for the management of OIs in patients with HIV recommend that all patients be screened for TB infection at the time of diagnosis and every 6 to 12 months thereafter, using the tuberculin skin test with purified protein derivative. A positive response is indicated by an induration >5 mm or larger on the skin 48 to 72 hours after the test; however, patients with very low CD4 cell counts may have a diminished response (anergy) and should be retested after starting ART and the CD4 cell count increases to >200 cells/mm^3. The standard treatment for latent TB infection is a 9-month course of isoniazid 300 mg/day with pyridoxine 25 mg/day to prevent isoniazid-related peripheral neuropathy.

Appropriate measures to prevent common OIs include vaccination or antimicrobial prophylaxis.[35] Initiation of primary prophylaxis against certain bacterial infections is based on specific CD4 cell thresholds that can predict when these infections are likely to occur (see **Table 9**). Regardless of CD4 cell count, immunization is recommended for patients for whom there is no evidence of immunity, and for patients at risk for exposure to certain pathogens, according to the recommended immunization schedule in **Table 10**.

TABLE 9.

Opportunistic Infections Associated With HIV, According to CD4 Cell Count and Appropriate Prevention and Prophylaxis Measures.[35,36]

CD4 Cell Count	Opportunistic Infection	Prevention/Prophylaxis Measures
Any CD4+ cell count	Influenza Pneumococcal pneumonia Hepatitis A and B Tetanus	Immunization*
	Herpes simplex virus or varicella zoster virus infection	Acyclovir **or** famciclovir **or** valacyclovir
	Vaginal candidiasis	
200 to 500 cells/mm^3	Recurrent bacterial pneumonia (especially streptococcal)	
	Pulmonary TB	
	Oral candidiasis	
<200 cells/mm^3	*Pneumocystis jiroveci* pneumonia	TMP/SMX **or** dapsone **or** atovaquone **or** aerosolized pentamidine
	Disseminated herpes virus infection	
	Disseminated histoplasmosis/cryptococcosis	
	Extra-pulmonary TB	
	Cryptosporidiosis/isosporiasis/microsporidiosis	
<100 cells/mm^3	Toxoplasmosis	TMP/SMX **or** dapsone/pyrimethamine†
<50 cells/mm^3	*Mycobacterium avium* complex disease	Azithromycin **or** clarithromycin

*See immunization schedule in **Table 10**.
†Prophylaxis only if patient tests positive for Toxoplasmosis IgG.
HIV, human immunodeficiency virus; TMP/SMX, trimethoprim/sulfamethoxazole; TB, tuberculosis

TABLE 10.

Immunization Schedule for HIV-infected Adults.[35]

	Age Group		
Vaccine	19-49 years	50-64 years	≥65 years
Influenza*	1 dose annually		
Pneumococcal*	1 dose (every 5 years)		
Hepatitis A†	2 doses		
Hepatitis B*	3 doses (0, 1-2, 4-6 months)		
Meningococcal†	1 or more doses		
Measles, mumps, rubella*	Do not administer to severely immunosuppressed persons		
Varicella*	Do not administer to severely immunosuppressed persons		
Tetanus, diphtheria, pertussis (Td/Tdap)*	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years		1 Td booster every 10 years

*Recommended for all patients who lack evidence of immunity (eg, lack of documentation of vaccination or no evidence of prior infection)
†Recommended if a medical, occupational, lifestyle, or other risk factor is present
Td, tetanus, diphtheria
Tdap, tetanus, diphtheria, pertussis

CHAPTER 7: Additional Tools and Resources

To facilitate the application of the knowledge attained through this guidebook to your individual clinical practice, listed below are some helpful Web links. These sites contain resources designed to improve the identification and initial management of patients with HIV, facilitate initial management decisions, and aid in the provision of patient education.

Additional resources, as well as video vignettes that demonstrate initiating a discussion with a patient about opt-out screening and delivering a positive HIV test result, can be found at: **www.myCME.com/HIVresources.**

AIDS EDUCATION AND TRAINING CENTERS: NATIONAL RESOURCE CENTER

http://www.aids-ed.org

This Web site contains a vast array of references (mostly free of charge) for clinicians and patients on all aspects of HIV management, from diagnosis and treatment to patient education and psychosocial issues.

AIDS INFONET

http://www.aidsinfonet.org/

Comprehensive, regularly updated collection of fact sheets on clinical topics in HIV, available in English and Spanish, in print-friendly and downloadable formats.

AIDS MEDS

http://aidsmeds.com

Information regarding HIV-related medications for patients, including a drug interactions calculator.

AMERICAN ACADEMY OF HIV MEDICINE (AAHIVM)

http://www.aahivm.org/

The AAHIVM supports the HIV care provider and the profession by providing continuing medical education; credentialing HIV specialists, HIV experts, and HIV pharmacists; providing practice-management information; advocating on behalf of the HIV care provider at the federal and state levels for issues relevant to clinical and professional support; and advancing health care resources for HIV-infected patients.

HEALTH RESOURCES AND SERVICES ADMINISTRATION

http://ask.hrsa.gov

The HRSA Web site offers numerous publications on HIV/AIDS management, including *Psychological and Socio-Medical Aspects of AIDS/HIV* and *A Guide to the Clinical Care of Women With HIV.*

JOHNS HOPKINS MEDICINE HIV "POC-IT" GUIDE

http://www.hopkinsguides.com/hopkins/ub/index/Johns_Hopkins_HIV_Guide/All_Topics

Edited by Joel E. Gallant, MD, MPH, this online guide provides evidence-based, clinical decision resources for health care providers who treat patients with HIV. The content is easily accessible and frequently updated.

HIV INSITE

http://hivinsite.ucsf.edu

Provided as an educational service by the University of California, San Francisco, this free resource provides comprehensive, up-to-date information on HIV/AIDS treatment, prevention, and policy.

NATIONAL ASSOCIATION OF PEOPLE WITH AIDS (NAPWA)

http://www.napwa.org
(866) 846-9366

Advocates on behalf of people living with HIV/AIDS and provides treatment referrals.

NATIONAL HIV/AIDS CLINICIANS' CONSULTATION CENTER

(800) 933-3413

The National HIV Telephone Consultation Service (Warmline) offers clinicians free, up-to-the-minute HIV clinical information and individualized expert case consultation across the broad range of clinical HIV/AIDS problems. The Warmline is staffed by clinicians experienced in HIV care who can help you provide the best possible care to your HIV-positive patients.

US CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

HIV Screening. Standard Care Program.
Free Tools for HIV Screening.
http://www.cdc.gov/hiv/testing/HIVStandardCare/tool.htm

(800) CDC-INFO (800-232-4636)

Information and materials to help health care providers screen their patients for HIV. Features provider materials, such as an annotated guide to the revised CDC recommendations; and patient-education materials in English and Spanish.

Prevention IS Care Program
www.cdc.gov/PreventionISCare
(800) CDC-INFO (800-232-4636)

Information for providers and educational materials for people living with HIV/AIDS. Features provider materials, such as screening charts; patient education materials in English and Spanish; HIV/AIDS data and statistics; and links to online training and support services.

REFERENCES

1. US Department of Health & Human Services, Centers for Disease Control and Prevention. *Act Against AIDS.* http://www.nineandahalfminutes.org/get-the-facts.php. Accessed April 25, 2011.

2. Centers for Disease Control and Prevention. *HIV Surveillance Report. Diagnosis of HIV Infection and AIDS in the United States and Dependent Areas, 2009.* Vol. 21. http://www.cdc.gov/hiv/surveillance/resources/reports/. Published February 2011. Accessed April 11, 2011.

3. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. *AIDS.* 2006;20:1447-1450.

4. 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;53:619-624.

5. Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report, 2006.* Vol. 18. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2008:1-55. http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed August 4, 2011

6. Romanelli F, Matheny SC. HIV infection: the role of primary care. *Am Fam Physician.* 2009;80:946-952.

7. Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. *Ann Intern Med.* 1996;124:654-663.

8. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep.* 2006;55(RR-14):1-17.

9. Lampe M. HIV Screening in health-care settings: new approaches and new paradigms. In: Centers for Disease Control and Prevention. *HIV Testing Practices. Supplement to HIV/AIDS Surveillance, 2000-2003.* http://www.cdc.gov/hiv/topics/perinatal/resources/meetings/2007/pdf/Lampe_Guidelines_Q&A.pdf. Accessed March 28, 2011.

10. Marks G, Crepaz N, Senterfitt JW, et al. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr.* 2005;39:446-453.

11. Hader S. A "modern response" to a "modern epidemic": HIV/AIDS in the District of Columbia. Presented at the 16th Conference on Retroviruses and Opportunistic Infections; Montreal, Quebec, Canada; 2009. Abstract 57.

12. Castel A, Samala R, Griffin A, et al. Monitoring the impact of expanded HIV testing in the District of Columbia using population-based HIV/AIDS surveillance data. Presented at the 17th Conference on Retroviruses and Opportunistic Infections; San Francisco, CA; 2010. Abstract 34.

13. National Institutes of Health. US Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* January 10, 2011. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf. Accessed April 12, 2011.

14. Mahoney MR, Fogler J, Weber S, Goldschmidt RH. Applying HIV testing guidelines in clinical practice. *Am Fam Physician.* 2009;80:1441-1444.

15. Bartlett JG, Branson BM, Fenton K, Hauschild BC, et al. Opt-out testing for human immunodeficiency virus in the United States: progress and challenges. *JAMA.* 2008;300:945-951.

16. Burke RC, Sepkowitz KA, Bernstein KT, et al. Why don't physicians test for HIV? A review of the US literature. *AIDS.* 2007;21:1617-1624.

17. *Survey of Americans on HIV/AIDS.* 2006 Kaiser Family Foundation. Menlo Park, CA. http://www.kff.org. Accessed April 4, 2011.

18. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS.* 2002;16:1119-1129.

19. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:651-681.

20. Uni-Gold™ Recombigen® HIV [package insert]. St. Louis, MO: Trinity Biotech USA; September 2004.

21. Reveal G3® Rapid HIV-1 Antibody Test [package insert]. Halifax, Nova Scotia, Canada: MedMira Laboratories, Inc.; February 2001.

22. Multispot HIV-1/HIV-2 Rapid Test [package insert]. Redmond, WA: Bio-Rad Laboratories; December 2004.

23. Clearview® Complete HIV 1/2 [package insert]. Princeton, NJ: Inverness Medical; November 2008.

24. Clearview® Complete HIV 1/2 Stat Pak® [package insert]. Princeton, NJ: Inverness Medical; January 2009.

25. INSTI™ HIV-1 Antibody Test. [package insert]. Chicago, IL: Biolytical Laboratories; October 2010.

26. OraQuick Advance® Rapid HIV-1/2 Antibody Test [package insert]. Bethlehem, PA: OraSure Technologies, Inc.

27. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One.* 2009;4:e5575. Epub 2009 May 18.

28. Lichtenstein KA, Armon C, Buchacz K, et al. and the HOPS Investigators. Early, uninterrupted antiretroviral therapy is associated with improved outcomes in the HIV Outpatient Study (HOPS) cohort. Presented at the 13th Conference on Retroviruses and Opportunistic Infections; Denver, Colorado; February 5-8, 2006. Abstract 769.

29. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4 count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355:2283-2296.

30. Chen LF, Hoy J, Lewin SR. Ten years of highly active antiretroviral therapy for HIV infection. *Med J Aust.* 2007;186:146-151.

31. Nisole S, Saïb A. Early steps of retrovirus replicative cycle. *Retrovirology.* 2004;1:9.

32. World Heath Organization (WHO). Human immunodeficiency syndrome and autoimmune deficiency syndrome. In: *Adherence to Long-Term Therapies—Evidence for Action.* Geneva, Switzerland; 2003:96-106. Available at: http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed April 7, 2011.

33. Montessori V, Press N, Harris M, et al. Adverse effects of antiretroviral therapy for HIV infection. *CMAJ.* 2004;170:229-238.

34. Samaras K. Metabolic consequences and therapeutic options in highly active antiretroviral therapy in human immunodeficiency virus-1 infection. *J Antimicrob Chemother.* 2008;61:238-245.

35. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207.

36. Luber AD. Pharmacotherapy of human immunodeficiency virus infection. In: Koda Kimble MA, Young LL, Aldridge, BK, et al (eds.). *Applied Therapeutics: The Clinical Use of Drugs,* Chapter 69. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

POSTTEST

To participate in this activity at no charge, please read the CE digest and complete the posttest. Fill in your answers on the answer key on page 35 and fax or mail to NPACE, 209 W. Central Street, Ste. 228, Natick, MA 01760 or fax to 508-907-6425. Your certificate will be mailed to you in 4 to 6 weeks.

1. **The US Centers for Disease Control and Prevention recommends routine HIV testing for which group?**
   a. Persons at high risk for HIV infection
   b. Pregnant women in the third trimester
   c. Health care providers, regardless of practice setting
   d. Patients aged 13 to 64 in all health care settings

2. **What is the most common symptom of acute HIV?**
   a. Malaise
   b. Low-grade fever
   c. Loss of appetite
   d. Night sweats

3. **Which initial test is used to stage HIV disease and to establish the risk for specific HIV-related complications?**
   a. CD4 cell count
   b. ELISA
   c. Western blot
   d. Viral load

4. **A CBC with differential should be done 2 to 8 weeks after antiretroviral therapy (ART) initiation if a patient is receiving**
   a. Abacavir
   b. Indinavir
   c. Zidovudine
   d. Nevirapine

5. **Even if they do not meet the current criteria for initiation of therapy, ART should be initiated in what group?**
   a. Men who have sex with men
   b. Pregnant women
   c. Intravenous drug users
   d. Persons with HIV+ sexual partners

6. **Which drug class is associated with spontaneous bleeding and hematuria in patients with hemophilia?**
   a. Nucleoside reverse transcriptase inhibitors
   b. Non-nucleoside reverse transcriptase inhibitors
   c. Integrase strand transfer inhibitor
   d. Protease inhibitors

7. **Pharmacokinetic interactions between NRTIs include increased concentrations of didanosine when co-administered with**
   a. Emtricitabine
   b. Stavudine
   c. Tenofovir
   d. Zalcitabine

8. **Co-administration of all PIs with which drug is contraindicated?**
   a. Amitriptyline
   b. Rifampin
   c. Progestin
   d. Warfarin

9. **NRTI therapy is associated with lipoatrophy; this is particularly true with**
   a. Stavudine
   b. Didanosine
   c. Abacavir
   d. Lamivudine

10. **Patients with a CD4 cell count of <50 cells/mm³ are at risk for multi-organ invasion by which of the following?**
    a. Pulmonary tuberculosis
    b. *Pneumocystis jiroveci* pneumonia
    c. Toxoplasmosis
    d. *Mycobacterium avium* complex

ANSWER AND EVALUATION SHEET

Participate online to receive your certificate instantly at **www.myCME.com/HIV11**. Or you can submit your Answer Sheet/Evaluation form via mail to: Nurse Practitioner Associates for Continuing Education, 209 W. Central Street, Ste. 228, Natick, MA 01760, or fax to: 508-907-6425. For any questions related to receiving credit through the online system, please contact Susan Basilico at 201-799-4857.

Please print clearly. (All information is confidential)

Please type or print clearly

First name	Last name	Degree	Specialty
Mailing address			
City	State	ZIP + 4-digit code	
Phone	Fax	E-mail address	

The amount of time I spent on this activity was _____ (max of 60 minutes).

Exam Answer Darken the circle with the correct answer to each question in the CME/CE activity.

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ					
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ					

Program Evaluation

1. How would you rate this activity overall?
   (5 = excellent, 1 = poor; please circle one)
   5 4 3 2 1

2. In your opinion, did you perceive any commercial bias?
   ❑ Yes ❑ No If yes, please specify:_____

3. Do you intend to make changes in your practice as a result of this activity? ❑ Yes ❑ No
   If yes, please explain: _____

4. What barriers, if any, do you anticipate encountering as you make changes in your practice?

5. Do you feel that the information in this activity was based on the best evidence available? ❑ Yes ❑ No
   If no, please explain: _____

6. Do you feel each of the learning objectives listed on page 2 was met?

Objective 1	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 2	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 3	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 4	❑ Yes	❑ Partially	❑ No	❑ N/A

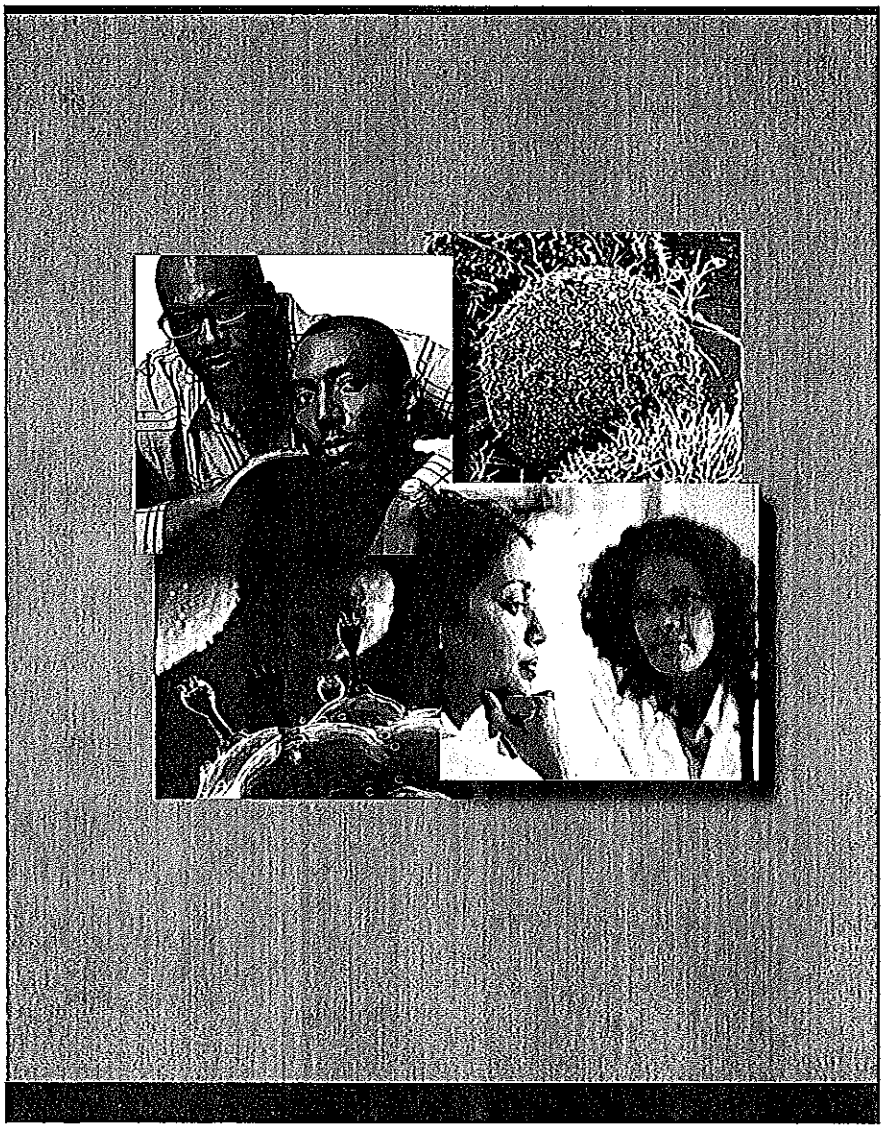
7. Which of the following competency areas do you feel have been improved as a result of this activity? (Mark all that apply.)
   ❑ Patient care ❑ Professionalism
   ❑ Practice-based learning ❑ Medical knowledge
   ❑ Systems-based practice ❑ Communication skills

8. Do you feel you need further education on this topic?
   ❑ Yes ❑ No
   If yes, please specify: _____
   If no, please explain: _____

9. Please rate the content of this activity
   (5 = excellent, 1 = poor; please circle one)
   a. Timely, up to date? 5 4 3 2 1
   b. Relevant to your practice? 5 4 3 2 1

10. Please make suggestions for future programs.

11. General Comments.



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