Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America

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EXECUTIVE SUMMARY

It has been >20 years since the first case of AIDS was identified. There has been a significant and dramatic change in the management of HIV infection since the introduction of potent antiretroviral therapy in 1996. There has also been a significant decrease in morbidity and mortality among persons living with HIV infection resulting from improved access to care, prophylaxis against opportunistic infections, and antiretroviral therapy. A working group of clinical scientists was chosen by the HIV Medicine Association of the Infectious Diseases Society of America (IDSA) to develop guidelines addressing the primary care of persons infected with HIV. The purpose of these guidelines is to assist health care providers in the primary care management of persons infected with HIV, including a description of baseline laboratory screening and adherence issues. Given the improved survival among people living with HIV infection, it is imperative that all persons in the United States be managed according to standard practices ap-propriate for the individual's age and sex regardless of HIV status. In addition, HIV-infected persons require more extensive screening and examinations than do those without HIV infection. There are increasing reports of complications associated with antiretroviral therapy that may require additional and more frequenting monitoring.

These guidelines discuss the following topics: (1) transmission of HIV infection; (2) HIV diagnosis; (3) risk screening; (4) management, with special sections concerning women and children; and (5) adherence. It is not our intent to duplicate the extensive guidelines endorsed by the United States Public Health Service, the Department of Health and Human Services, the Centers for Disease Control and Prevention (CDC), IDSA, or other accredited programs. We have referred to these guidelines where applicable, so that this document may also serve as a "guide to the guidelines" (table 1). As with previously published IDSA guidelines, we have graded our recommendations accordingly (table 2).

TRANSMISSION OF HIV

The modes of transmission of HIV—sexual contact, exposure to infected blood through sharing of injection drug use paraphernalia or receipt of contaminated blood products, and perinatal transmission—were clarified relatively early in the AIDS epidemic. In the United States, their relative importance over time is reflected

Table 1. Guidelines from various sources regarding aspects of care of HIV-infected persons.

Topic	Title	URL	Issuing agency	Reference
HIV testing and counseling	Revised Guidelines for HIV Counseling, Testing, and Referral	http://www.cdc.gov/mmwr/pdf/rr/rr5019.pdf	CDC	[1]
Risk assessment	Incorporating HIV Prevention into the Medical Care of Persons Living with HIV	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm	CDC, Health Resources and Services Administration, NIH, HIV Medicine Association of IDSA	[2]
Antiretroviral therapy for adults and adolescents	Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents	http://aidsinfo.nih.gov/guidelines	US Department of Health and Human Services	[3]
Antiretroviral therapy for pediatric patients	Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection	http://aidsinfo.nih.gov/guidelines	NIH	[4]
Antiretroviral therapy for pregnant women	Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States	http://aidsinfo.nih.gov/guidelines	US Public Health Service Task Force	[5]
Resistance testing	Antiretroviral Drug Resistance Testing in adults Infected with Human Immunodeficiency Virus type 1	http://www.iasusa.org/pub/	International AIDS Society–USA Panel	[6]
	Guidelines for the Use of Antiretroviral Agents in HIV Infected Adults and Adolescents	http://aidsinfo.nih.gov/guidelines	US Department of Health and Human Services	[3]
Opportunistic infections	Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons	http://www.cdc.gov/mmwr/PDF/rr/rr5108.pdf	US Public Health Service; IDSA	[7]
Mental health	Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner	http://www.hivguidelines.org/public_html/center/clinical-guidelines/mental_health_guidelines/mental_health_intro.htm	New York State Department of Health AIDS Institute	[8]
Sexually transmitted diseases	Sexually Transmitted Diseases Treatment Guidelines 2002	http://www.cdc.gov/std/treatment/rr5106.pdf	CDC	[9]
Immunizations	Practice Guidelines for Quality Standards for Immunization	http://www.journals.uchicago.edu/CID/journal/issues/v35n5/020679/020679.web.pdf	IDSA	[10]
Occupational exposures	Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm	US Public Health Service	[11]
Hyperlipidemia in HIV	Guidelines for the Evaluation and Management of Dyslipidemia in Human Immunodeficiency Virus (HIV)—Infected Adults Receiving Antiretroviral Therapy	http://www.journals.uchicago.edu/CID/journal/issues/v37n5/31776/31776.web.pdf	HIV Medicine Association of IDSA; Adult AIDS Clinical Trials Group	[12]
Metabolic complications in HIV	Management of Metabolic Complications Associated with Antiretroviral Therapy for HIV-1 Infection	http://www.iasusa.org/pub/Schambelan%20et%20al-JAIDS-11.1.02.pdf	International AIDS Society–USA Panel	[13]

NOTE. CDC, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America; NIH, National Institutes of Health.

Table 2. Infectious Diseases Society of America–United States Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use; should always be offered
B	Moderate evidence to support a recommendation for use; should generally be offered
C	Poor evidence to support a recommendation; optional
D	Moderate evidence to support a recommendation against use; should generally not be offered
E	Good evidence to support a recommendation against use; should never be offered
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

by the frequency of HIV risk activities among reported persons with AIDS, which has been reportable in all US states and territories.

Throughout the AIDS epidemic in the United States, male-to-male sexual contact has been the most frequently reported risk for HIV exposure among men, accounting for 59% of cumulative and 55% of recently diagnosed (calendar year 2002) AIDS cases. The second most frequently reported risk among men has been injection drug use, accounting for 24% of cumulative and 22% of recent AIDS diagnoses, followed by heterosexual contact (7% of cumulative and 6% of recent AIDS diagnoses). An additional 8% of cumulative and 6% of recent cases were diagnosed among men who reported both male-to-male sexual contact and injection drug use [14].

In 1994, heterosexual contact accounted for 51% of AIDS cases diagnosed among women, surpassing injection drug use as the predominant mode of HIV exposure. Heterosexual contact has continued to account for an increasing proportion of AIDS cases among women. From 1996 to 2002, AIDS diagnoses attributed to heterosexual contact increased from 57% to 68% of cases among women, whereas AIDS diagnoses attributed to injection drug use decreased from 40% to 29% [14].

The epidemic affects increasing proportions of women and continues to affect racial and ethnic minorities disproportionately. Between 1996 and 2002, the proportion of AIDS cases among women increased from 22% to 26%. The proportions of cases among African American persons in these 2 years were 44% and 52%, respectively, and the proportions among Hispanic persons were 20% and 17%, respectively [14].

Various studies have yielded estimates of the probability of HIV transmission by various routes. Per-act probabilities of transmission would be expected to vary considerably, depending on factors such as plasma HIV RNA level in the index case patient, presence of sexually transmitted diseases (STDs) in the index case patient or the partner, and the quantity of blood

transferred via needlestick. Nevertheless, the overall probability of becoming infected by transfusion with contaminated blood or blood products has been estimated to be 95 in 100; from mother to child, in the absence of antiretroviral therapy, as 1 in 4; by needle sharing, as 1 in 150; and by occupational needlestick exposure, as 1 in 300. The risk of infection by male-male receptive anal intercourse has been estimated as 1 in 10 to 1 in 1600; by male-to-female vaginal intercourse, as 1 in 200 to 1 in 2000; and by female-to-male vaginal intercourse, as 1 in 700 to 1 in 3000 [15].

DIAGNOSIS OF HIV INFECTION: TESTING AND COUNSELING

HIV infection is typically diagnosed by means of serological tests that demonstrate the presence of antibodies to HIV. A positive screening test result by EIA is confirmed by either Western blot or immunofluorescence assay. Rapid tests for HIV (Oraquick, OraSure Technologies; Unigold, Trinity Diagnostics), which are performed with whole-blood samples obtained by fingerstick, have recently been approved as screening tests by the US Food and Drug Administration (FDA); the Oraquick test has also been approved for plasma, serum, and oral fluid specimens. Specimens reactive in this test are termed "preliminary positive" and also require confirmatory testing.

Persons who should be offered counseling and testing include those reporting risk behaviors associated with HIV infection, those exhibiting signs or symptoms suggestive of HIV infection, and those with tuberculosis or STDs (table 3). In populations with an estimated prevalence of HIV infection of >1% (e.g., hospitalized patients in inner cities), all adults should be offered testing. All pregnant women should be offered testing because of the availability of treatment to reduce the likelihood of mother-to-child transmission as well as maintenance of health of the mother. Testing should be offered to anyone who has

Table 3. Persons who should be tested for HIV infection.

Persons with high-risk behavior
    Men who have sex with men
    Injection drug users
    Persons with multiple sex partners
    Persons who have exchanged money or drugs for sex
    Persons who have had sexual contact with an HIV-positive person or a person at risk
        for HIV infection
Persons who request testing, regardless of risk
Persons with certain medical conditions
    AIDS-defining illness
    Oral candidiasis
    Generalized unexplained lymphadenopathy
    Symptoms consistent with acute retroviral syndrome
    Any sexually transmitted disease
    Tuberculosis
    Pregnancy
    Other (e.g., pneumonia, herpes zoster, recurrent vulvovaginal candidiasis, seborrheic
        dermatitis, new-onset psoriasis, or oral hairy leukoplakia)[a]
Persons who have been sexually assaulted
Persons who have had occupational exposures

[a] The predictive value of these conditions for HIV infection may vary considerably, depending on epidemiological circumstances, but counseling and testing for HIV infection should always be considered.

been sexually assaulted. Those potentially exposed to HIV via an occupational exposure should follow the "Updated US Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis" [11] (HBV, hepatitis B virus; HCV, hepatitis C virus). Testing should also be offered to all persons requesting HIV testing for any reason.

HIV-seronegative persons should be counseled regarding risk of acquiring HIV infection. Because of the delayed appearance of HIV antibodies in persons recently infected, high-risk activity within the past 3 months should prompt repeated serological testing at 6, 12, and 24 weeks. Symptoms of acute retroviral syndrome (fever, lymphadenopathy, sore throat, malaise, and skin rash) in a person reporting recent high-risk behavior should prompt testing for plasma HIV RNA in addition to HIV antibody testing. It should be emphasized, however, that plasma HIV RNA testing is not approved for diagnostic purposes by the FDA; false-positive results have been reported and generally suggest low levels of viremia [11]. A positive plasma HIV RNA test result should be confirmed by subsequent serological or virological testing.

HIV-infected persons should be counseled concerning the nature of their infection and the risk of transmission of HIV to others, in addition to being referred for various support services and for medical treatment. More details concerning counseling and testing can be found in CDC's counseling and testing guidelines [1].

RISK SCREENING FOR HIV-INFECTED PATIENTS

Screening

Persistent high-risk behavior has implications for the health of the patient, as well as for the risk of transmission of HIV to others. Therefore, each visit of an HIV-infected person to a health care provider should include screening for high-risk behavior (A-II).

Screening for high-risk behavior can be accomplished by a brief series of questions administered by questionnaire in the patient waiting room, by other personnel in the health care setting, or by the health care provider; an example of such a questionnaire is included in "Incorporating HIV Prevention into the Medical Care of Persons Living with HIV: Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America" [2] and is reproduced here in table 4.

In addition, patients should be queried concerning symptoms of STDs at each visit (A-I). All patients should be screened with laboratory tests for STDs at the initial encounter (A-II for syphilis, for trichomoniasis in women, and for chlamydial infection in women aged <25 years; B-II for gonorrhea and chlamydial infection in all men and women), and thereafter, depending on reported high-risk behavior, the presence of other STDs, and the prevalence of STDs in the community (B-III) (table 5). The presence of STDs indicates recent risk behavior

Table 4. Examples of screening strategies to elicit patient-reported risk for HIV transmission.

Open-ended question by clinician, similar to one of the following
  "What are you doing now that you think may be a risk for transmitting HIV to a partner?"
  "Tell me about the people you've had sex with recently."
  "Tell me about your sex life."
Screening questions (checklist) for use with a self-administered questionnaire; computer-, audio-, or
  video-assisted questionnaire; or a face-to-face interview[a]
"Since your last checkup here," or, if first visit, "Since you found out you were infected with HIV,"
  "Have you been sexually active; that is, have you had vaginal, anal, or oral sex with a partner?"
    If yes, "Have you had vaginal or anal intercourse without a condom with anyone?"
    If yes,
      "Were any of these people HIV-negative, or are you unsure about their HIV status?"
      "Have you had oral sex with someone?"
      If yes (for a male patient), "Did you ejaculate into your partner's mouth?"
  "Have you had a genital sore or discharge, discomfort when you urinate, or anal burning or
    itching?"
  "Have you been diagnosed or treated for an STD, or do you know if any of your sex partners have
    been diagnosed or treated for an STD?"
  "Have you shared drug-injection equipment (needles, syringes, cotton, cooker, water) with others?"
    If yes, "Were any of these people HIV negative, or are you unsure about their HIV status?"

NOTE. From [2]. STD, sexually transmitted disease.

[a] This checklist can be administered by the patient or clinician and should take ~4 min. A positive response to any of the screening questions should cue the clinician to have a more in-depth discussion to ensure that specific risks are clearly understood.

despite what the patient may report. In addition, STDs constitute a health problem for the patient as well as increased risk of transmission of HIV to others.

Additional details concerning risk screening of HIV-infected persons can be found in the recommendations from CDC, Health Resources and Services Administration, National Institutes of Health, and the HIV Medicine Association of IDSA [2].

Behavioral Intervention

General messages regarding risk reduction should be given at all health encounters, regardless of risk behaviors reported by the patient or perceived risk on the part of the health care provider. Such messages can be delivered by the provider, by others in the health care setting, or by educational materials (e.g., pamphlets, posters, videos) in the health care setting (A-III).

Tailored messages are critical for patients who report persistent high-risk behavior or who have symptoms or signs of STDs. In nearly all situations, the provider should offer brief counseling; in general, persons exhibiting risk behavior should also be referred to programs capable of offering more extensive intervention programs (A-I).

More details concerning behavioral intervention in the health care setting, including criteria for referrals and information regarding making and ensuring completion of referrals, can be found in the HIV prevention guidelines [2].

MEDICAL MANAGEMENT OF ESTABLISHED HIV INFECTION

History and Physical Examination

History of present illness. This should include the date of diagnosis of HIV infection and, whenever possible, the approximate date of infection, which can sometimes be estimated on the basis of prior negative test results, occurrence of symptoms suggestive of the acute retroviral infection, or timing of high-risk activities. It is critical to take a thorough medication history for patients who have already received antiretroviral therapy. The medication history is generally more helpful than the results of resistance testing in estimating resistance that has developed during treatment with prior regimens. Such a history should include not only the drug combinations taken, but also response to each regimen, including virus load and CD4 cell count, drug toxicities, adherence, and prior resistance test results. Patients should be asked whether they can recall the lowest CD4 cell count they have ever had and the highest HIV load. Every effort should be made to obtain medical records from prior health care providers. Patients should be asked about prior HIV-associated complications, including opportunistic infections, malignancies, and HIV-related symptoms.

Past medical history. Clinicians should ask about other medical conditions that might affect the choice of therapy or response to therapy, such as neuropathy, gastrointestinal disease, chronic viral hepatitis, hyperlipidemia, diabetes, or renal

Table 5. Examples of screening strategies to detect asymptomatic sexually transmitted or blood-borne infections.

First visit
  All patients
    Serological test for syphilis (i.e., nontreponemal test, such as RPR or VDRL)
    Consider urine-based (first-void specimen) NAAT for gonorrhea
    Consider urine-based (first-void specimen) NAAT for *Chlamydia* species
    Serological tests for hepatitis B and C (If hepatitis B negative, vaccinate)
  Women
    Examination of vaginal secretions for *Trichomonas* species
    Cervical specimen for NAAT for *Chlamydia* species for all sexually active women aged ⩽25 and other women at increased risk
  Patients reporting receptive anal sex
    Culture of rectal sample for *Neisseria gonorrhoeae*
    Culture of rectal sample for *Chlamydia* species
  Patients reporting receptive oral sex: culture of pharyngeal sample for *N. gonorrhoeae*
Subsequent visits
  All sexually active patients: screening tests for STDs should be repeated at least annually
  Asymptomatic persons at higher risk
    More frequent periodic screening (e.g., at 3-month to 6-month intervals) if any of the following factors are present
    Multiple or anonymous sex partners
    Past history of any STD
    Identification of other behaviors associated with transmission of HIV and other STDs
    Sex or needle-sharing partner(s) with any of the above-mentioned risks
    Developmental changes in life that may lead to behavioral change with increased risky behavior (e.g., dissolution of a relationship)
    High prevalence of STDs in the area or in the patient population

NOTE. Adapted from [2]. NAAT, nucleic acid amplification test; RPR, rapid plasma reagin; STD, sexually transmitted disease; VDRL, Venereal Disease Research Laboratory.

insufficiency. Other past medical conditions that have particular relevance for HIV-infected patients include prior chickenpox or shingles; tuberculosis or tuberculosis exposure, including results of tuberculin skin tests (TSTs); STDs; and gynecologic problems. It is important that the history also include questions about where the patient has lived and traveled. For example, patients reporting travel in areas of endemicity for histoplasmosis (Ohio and Mississippi River valleys) or coccidioidomycosis (southwestern deserts) may be at risk for reactivation disease, even after moving to areas in which the diseases are not endemic. Patients should be asked about adult vaccinations, including dates of last tetanus booster, pneumococcal polysaccharide vaccine, and hepatitis A and B vaccination.

Medications and allergies. Patients should be asked about the medications they take, including over-the-counter medications, medications taken infrequently, methadone, and dietary or herbal supplements, a number of which have been shown to interact with antiretroviral agents. A discussion of allergies should include questions about hypersensitivity reactions to prior HIV therapies, including sulfonamides, nonnucleoside reverse-transcriptase inhibitors, and abacavir.

Social, sexual, and family histories. The social history should include a discussion of the use of tobacco, alcohol, heroin, and recreational drugs, including marijuana, cocaine, and so-called "club drugs," such as MDMA ("ecstasy") and ketamine, which may interact with some antiretroviral agents. Active injection drug users should be asked about their drug-using practices, the source of their needles, and whether they share needles. It is critical to take a careful sexual history in an open, nonjudgmental manner, asking about past and current sexual practices. Risk reduction counseling can be introduced during this discussion. Counseling should focus on reduction of risk both of HIV transmission to others and of "reinfection" and infection with other sexually transmitted pathogens to the patient. Patients should also be asked about their sex partners, sexual practices (including condom use and contraceptive use), and whether their partner(s) have been informed of the patients' HIV status. Patients should be encouraged to inform their partners of their HIV status. Laws vary from state to state regarding the obligation of health care providers to notify sex partners, and clinicians should be aware of such laws in their own jurisdiction. Patients should also be specifically asked whom they have informed of their HIV status, how they have been coping with the diagnosis of HIV infection, and what

kinds of support they have been receiving. It is important to know about the patient's family, living situation, and work environment and how they have been affected by the diagnosis of HIV infection. Other pertinent information includes their housing issues, employment, and plans for having children. Family medical history, rarely relevant in the pre-HAART era, has now become important as HIV-infected patients are living longer and are developing treatment-related hyperlipidemia and diabetes. Patients should be asked whether there is a history of myocardial infarction in a first-degree relative before the age of 55 years for male relatives and the age of 65 years for women.

Review of systems. The review of systems should be thorough and comprehensive and should include questioning about common HIV infection–related symptoms, including fever, night sweats, weight loss, headaches, visual changes, oral thrush or ulceration, swallowing difficulties, respiratory symptoms, diarrhea, skin rashes or lesions, and changes in neurological function or mental status. Patients should be questioned about how their current weight compares with what they consider their normal or baseline weight. Depression is common among HIV-infected patients, and the review of systems should include questions focusing on changes in mood, libido, sleeping patterns, appetite, concentration, and memory. In the course of taking a complete history, the clinician can begin to assess the patient's level of awareness about HIV infection and treatment, evaluating the patient's educational needs, and determining the form that education and other support might take.

Physical examination. A complete physical examination should be done for all patients at the initial encounter. Special attention should be paid to examination of the skin, looking for evidence of seborrheic dermatitis, Kaposi sarcoma, folliculitis, fungal infections, psoriasis, and prurigo nodularis. The overall body habitus should be assessed, especially for patients taking antiretroviral therapy, who may have drug-related lipodystrophy, with evidence of fat accumulation (i.e., dorsocervical fat pad, increased fat around the neck, gynecomastia, or abdominal distention due to visceral fat) and/or lipoatrophy (i.e., loss of subcutaneous fat in the face, extremities, or buttocks). Funduscopic examination should be done, and for patients with advanced HIV disease (CD4 cell count, <50 cells/mm^3), it may be appropriate to refer the patient to an ophthalmologist for a slit-lamp examination while dilated to screen for cytomegalovirus (CMV) retinitis and other ocular manifestations of HIV infection. The oropharynx should be carefully examined, noting evidence of candidiasis, oral hairy leukoplakia, mucosal Kaposi sarcoma, aphthous ulceration, and periodontal disease. Although persistent generalized lymphadenopathy is common among HIV-infected patients, it does not correlate with prognosis or disease progression. Localized lymphadenopathy or hepatomegaly or splenomegaly, however, may be a sign of infection or malignancy and should be evaluated further. It is important to perform a careful anogenital examination for evidence of STDs, including condylomata and herpes simplex lesions. Examination of HIV-infected women should include careful palpation of the breasts and pelvic examination. The pelvic examination should include visual inspection of the vulva and perineum for evidence of genital ulcers, warts, or other lesions. Speculum examination is used to assess the presence of abnormal vaginal discharge or vaginal or cervical ulcers or other lesions. Papanicolaou (Pap) test should be obtained to rule out cervical dysplasia. Bimanual and rectovaginal examinations assess the presence of cervical, uterine, or adnexal tenderness or masses, as well as rectal masses. The neurological examination should include a general assessment of cognitive function, as well as motor and sensory testing. Patients in whom dementia is suspected may benefit from more sensitive neuropsychological testing.

Baseline Evaluation: Diagnostic and Screening

A number of initial laboratory studies should be done for patients presenting with HIV infection (tables 6–8).

Serological testing for HIV. Patients who have no documentation of their HIV serological test results or who were tested anonymously should undergo an additional serological test for HIV (A-III). Seropositive patients who are asymptomatic and have normal CD4 cell counts and undetectable or very low virus loads should undergo repeated serological testing. Although HIV serological testing (ELISA or HIV rapid test with confirmatory Western blot) is extremely accurate and specific, false-positive ELISA or rapid test results may occur. However, the Western blot will yield negative results in those cases. The ELISA may yield false-positive results for patients with autoimmune disorders or pregnancy.

CD4 cell counts. A CD4 cell count should be obtained and confirmed (A-II). The CD4 cell count is used to stage HIV disease, to help establish the risk of specific HIV-associated complications, to determine the need for prophylaxis against opportunistic infection, to determine the need for therapy, and to assess response to antiretroviral therapy. It is important that the clinician and patient be aware of the substantial variation in CD4 cell counts. CD4 cell counts may be affected by medications and intercurrent illnesses. It is best to obtain 2 CD4 cell counts at baseline at least 1 week apart. Although the absolute CD4 cell count is the number most often used in clinical practice, the CD4 cell percentage can also be used to assess immune function and is somewhat less variable than the absolute count. Total CD4 cell counts of 200 and 500 cells/mm^3 generally correspond to CD4$^+$ cell percentages of 14% and 29%, respectively. The use of the ratio of CD4 cells to CD8 cells is no longer advocated (C-III).

Plasma HIV RNA load. A quantitative HIV RNA determination (virus load) should be obtained (A-II). Consideration

Table 6. Diagnostic studies for patients presenting with HIV infection.

Type of test, test	Comment(s)
HIV disease characterization	
HIV antibody test	If HIV infection is not clearly documented
CD4 cell count	Estimates stage of HIV disease, need for antiretroviral therapy, and OI prophylaxis
CD4 cell percentage	Also correlates with disease stage, need for antiretroviral therapy
Serum HIV RNA (virus load)	Estimates risk of progression, need for antiretroviral therapy, and correlates with infectiousness
HIV resistance testing	Recommended at baseline for some patients; genotype preferred
Hematology	
Complete blood cell count, differential, platelets	Screening, baseline
Glucose-6-phosphate dehydrogenase	Screen for deficiency in appropriate racial or ethnic groups
Serum chemistry	
Fasting blood glucose	Screen
Electrolytes/blood urea nitrogen/creatinine	Screen for renal, acid-base problems, baseline
Alanine aminotransferase, aspartate aminotransferase, bilirubin	Screen for liver problems, baseline
Albumin	Screen for liver, nutritional status, disease stage, baseline
Alkaline phosphatase	Screen for liver, biliary, bone metabolism, baseline
Fasting triglycerides, cholesterol	Baseline for drug effects, primary care screen
Urinalysis: RBCs, WBCs, proteinuria, sediment	Screen, baseline
Microbiology: culture for sexually transmitted pathogens	Others when appropriate
Cytology: Papanicolaou test	Cervical; consider anal if indicated
Serological tests	
Anti-*Toxoplasma* IgG	
Syphilis nontreponemal serology (VDRL or rapid plasma reagin)	
Anti-cytomegalovirus IgG	
Hepatitis	Hepatitis B surface antigen, antibody to hepatitis B surface antigen or to hepatitis B core antigen, antibody to hepatitis C virus
Radiology: chest radiography	Many experienced clinicians want a recent, baseline chest radiograph for all patients; others obtain one only if there is a history of abnormalities, past pulmonary disease, or active chronic pulmonary problems
Electrocardiogram	If over 40 or otherwise indicated
Routine health maintenance: age-appropriate standard of care	

NOTE. OI, opportunistic infection; VDRL, Venereal Disease Research Laboratory.

should be given to obtaining 2 virus load determinations at baseline at least 1 week apart because of variability in test results and potential for intercurrent illnesses. Virus load testing is used to assess prognosis, determine the need for antiretroviral therapy and the type of antiretroviral therapy required, define a baseline laboratory value so that the response to therapy can be measured, and monitor response to therapy. Virus load assays include the HIV RNA PCR (Amplicor HIV-1 Monitor; Roche Laboratories), the branched-chain DNA (Quantiplex HIV RNA assay, Chiron), and the nucleic acid sequence–based amplification (Advanced BioScience Laboratories/Organon Teknika). Thresholds for detection range from 200–400 copies/mL for the standard assay to 20–75 copies/mL for the ultrasensitive assays. The standard assay should be ordered in the initial evaluation of the untreated patient. The ultrasensitive assay should be reserved for patients whose virus loads are expected to be low.

HIV resistance testing. Because drug-resistant virus can be transmitted from one person to another, patients presenting during or shortly after primary infection should be tested for transmitted drug resistance [6] (B-II). A resistance test at this stage is likely to detect the resistance pattern of the infecting virus strain. The results of early resistance assays may be useful in guiding therapy, even if treatment is deferred for many years (B-III). With time, however, resistant virus will be overgrown by wild-type virus, and resistance tests will be less sensitive in detecting acquired resistance. A baseline resistance test for a patient with chronic infection is helpful only if it yields positive results: the absence of resistance does not mean that the patient does not harbor drug-resistant virus. Resistance testing should be offered to antiretroviral-naive subjects (those who have never taken any antiretroviral medications) who are initiating therapy and who have been infected for ≤2 years and perhaps longer. It is often difficult to ascertain how long a person has been

Table 7. Screenings for specific diseases for patients presenting with HIV infection.

Disease or pathogen, test	Comment(s)
CMV: anti-CMV IgG	Consider if CMV-negative blood is available, in population with <75% prevalence of CMV; if CMV negative, and transfusion becomes necessary, use CMV-negative blood products
Hepatitis	
Hepatitis B surface antigen	Screen for chronic or active hepatitis B virus infection
Antibody to hepatitis B surface antigen or antibody to hepatitis B core antigen	Consideration for hepatitis B vaccine
Antibody to hepatitis C virus	Screen for chronic hepatitis C virus infection
Total antibody to hepatitis A virus	Screen for hepatitis A vaccine, baseline
Syphilis: nontreponemal test (rapid plasma reagin or VDRL)	
Neisseria gonorrhoeae	
Culture of samples from orifices if appropriate	
Nucleic acid amplification test of urine	
Chlamydia species	
Culture of samples from orifices if appropriate	
Nucleic acid amplification test of urine	
Toxoplasmosis	
Anti-*Toxoplasma* serum IgG	If results are positive, provide primary prophylaxis when CD4 cell count is <100 cells/mm^3. If results are negative, counsel on avoidance of infection (avoidance of undercooked meat and avoidance or proper handling of cat feces)
Tuberculosis: tuberculin skin testing	If tuberculin skin test result is negative or unknown; if result is positive (>5 mm of induration), obtain chest radiograph; if symptomatic, obtain sputum for acid-fast bacteria smear and culture

NOTE. CMV, cytomegalovirus; VDRL, Venereal Disease Research Laboratory.

infected, and consideration should be given to testing when the duration is uncertain and the expected regional prevalence of resistance is >5% [6] (B-II). Resistance testing should be done for patients experiencing virological failure to guide changes in antiretroviral therapy, and resistance testing should always be done during pregnancy [6] (A-II).

Complete blood cell (CBC) count and chemistry panel. A CBC count and chemistry panel should be obtained (A-III). Anemia, leukopenia, and thrombocytopenia are common in HIV-infected persons and are readily detected with a CBC count. The CBC count is also used to calculate the total CD4 lymphocyte count. A chemistry panel is an important tool in the evaluation of the patient's nutritional status and to assess renal and liver function. The CBC count and the chemistry panel also provide baseline information that is necessary before the initiation of therapeutic agents that may have myelosuppressive or hepatotoxic effects or require dose adjustment for patients with renal dysfunction.

Glucose-6-phosphate dehydrogenase (G6PD). G6PD deficiency is a genetic condition that predisposes to hemolysis following exposure to oxidant drugs. The drugs most commonly used to treat HIV-infected patients that can lead to hemolysis in G6PD-deficient patients are dapsone, primaquine, and sulfonamides. Although there are many variants of G6PD

deficiency, the most common are Gd_{A-}, which is found in 10% of black men and 1%–2% of black women, and Gd_{med}, which is found predominantly in men from the Mediterranean, India, and Southeast Asia. The hemolysis associated with Gd_{med} can be life-threatening, whereas patients with the Gd_{A-} variant have milder, more self-limited hemolysis that may not preclude the use of the oxidant drugs. Screening for G6PD deficiency is recommended either at baseline or before initiating therapy with an oxidant drug for patients with the susceptible racial or ethnic background (B-III).

Tuberculosis screening. HIV-infected patients should be tested for *Mycobacterium tuberculosis* infection [7] by TST applied on the volar surface of the forearm by the Mantoux (intradermal injection) method with an intermediate-strength PPD (0.1 mL containing 5 TU) (A-I) [16, 17]. For an HIV-infected person, an induration of ≥5 mm is considered a positive result and should prompt chest radiography and evaluation for possible tuberculosis [18]. Annual testing should be considered for those who have negative results by TST but are at high risk for exposure to tuberculosis. Repeated testing should also be considered for those who had negative TST results but who have subsequently experienced an increase in the CD4 cell count due to antiretroviral therapy and thus may have restored sufficient immunocompetence to mount a pos-

Table 8. Tests of questionable or no value in initial evaluation of patient presenting with HIV infection.

Test	Comment(s)
Anergy testing	Most experts believe anergy testing is nonspecific and insensitive and is not useful in guiding clinical management
Serum lactic dehydrogenase level assessment	Some clinicians use this as a nonspecific indicator of "something going on" to motivate more aggressive evaluation of minimally symptomatic persons; elevations suggest pulmonary process or lymphoma, but other indicators usually provide clues
Erythrocyte sedimentation rate assessment	Some clinicians use this as a non-specific indicator of "something going on" to motivate more aggressive evaluation of minimally symptomatic persons
Serum cryptococcal antigen assessment	Not useful in routine screening; consider for symptomatic patient (fever and/or headache) with CD4 cell count of <100 cells/mm^3
Culture of blood for acid-fast bacilli	Not useful in routine screening unless patient is symptomatic with CD4 cell count of <50 cells/mm^3
Serological tests for herpes simplex virus	Not typically recommended; however, some experts do recommend type-specific serological testing for herpes simplex virus type 2 for both men and women

itive reaction (B-III). A TST should be performed any time there is concern of a recent exposure. HIV-infected persons who are close contacts of persons with infectious tuberculosis should be treated for latent *M. tuberculosis* infection—regardless of their TST results, age, or prior courses of treatment—after the diagnosis of tuberculosis has been excluded (A-II). Routine anergy testing is no longer recommended because of the variability of reagents and its poor predictive value and because prophylaxis given to anergic persons has been shown to prevent few cases of tuberculosis [19]. If someone was vaccinated with bacille Calmette-Guérin, he or she may have a positive TST result. This reaction may be due to the vaccine itself or to latent *M. tuberculosis* infection; therefore, further workup to exclude tuberculosis with consideration of therapy for latent infection is warranted.

Serological testing for **Toxoplasma gondii.** All HIV-infected patients should be tested for prior exposure to *T. gondii* [7] by measuring anti-*Toxoplasma* IgG (B-III). *Toxoplasma*-seronegative adults, representing 70%–90% of the US population, should be counseled on how to avoid new infection, primarily through the proper preparation of meat and the appropriate handling of cat feces (B-III). Serological testing should be repeated for previously seronegative persons if the CD4 cell count decreases to 100 cells/mm^3 and if they are unable to take trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (C-III). If *Toxoplasma* serological tests yield positive results, the patients should be managed according to the guidelines [7]. Although serological tests for *Toxoplasma* can never be used to diagnose or exclude toxoplasmosis, a seronegative patient with a space-occupying lesion of the CNS is less likely to have toxoplasmosis than is a seropositive patient.

Viral hepatitis screening. HIV-infected patients should be screened for evidence of prior HBV infection [7] by determination of hepatitis B surface antigen (HBsAg), antibody to HBsAg (HBsAb), and, possibly, antibody to hepatitis B core

antigen (HBcAb) (A-III), and those who remain susceptible should be vaccinated against HBV (B-II). Partners of persons who are positive for HBsAg should be offered vaccination. Patients who are negative for HBsAg and HBsAb but positive for HBcAb should be screened for chronic HBV infection by determination of HBV load (PCR for HBV DNA) (C-III) [20–22]. There are no data to support vaccination against HBV for persons who are positive for HBcAb only. HIV-infected persons should be screened for HCV infection with a test for HCV antibody (B-III). Positive test results should be confirmed by measurement of HCV RNA by PCR (A-II) [23]. HCV RNA should also be measured for HCV-negative persons with unexplained liver disease, because ~6% of HIV-positive persons do not develop HCV antibodies. Hepatitis A vaccine is safe for use in HIV-infected patients and should be considered for patients without prior exposure (negative for total antibody to hepatitis A virus) (B-III). Prevaccination screening is cost-effective when there is a seroprevalence of hepatitis A virus of >30% in the population being screened. Hepatitis A vaccination should be administered to all nonimmune patients who are coinfected with HCV because of the increased risk of fulminant hepatitis A in HCV-positive persons (B-III).

Screening for infections with CMV and other herpesviruses. Patients at lower risk of CMV infection (i.e., populations other than men who have sex with men or injection drug users, who may be assumed to be CMV positive) should be tested for latent CMV infection [7] by serological testing for anti-CMV IgG (B-III). Although seroprevalence of CMV among HIV-infected persons is high, the identification of seronegative patients allows for the use of CMV-negative or leukocyte-reduced blood products when transfusions are needed, thus reducing the risk of iatrogenic CMV infection. It may also be valuable to determine anti-varicella IgG for the minority of patients who are unable to give a history of chickenpox or shingles. Patients who are seronegative should receive postexposure prophylaxis with varicella zoster immune globulin as

soon as possible after exposure to a person with chickenpox or shingles (A-III). Serological testing for other herpesvirus infections is not usually recommended, because it has no diagnostic or therapeutic applications, although some experts do recommend type-specific testing for herpes simplex virus type 2 for both men and women [2].

STD screening. HIV-infected persons who are asymptomatic for STDs, regardless of risk behavior, should be screened at the initial visit [9] for syphilis (A-II) and for gonorrhea and chlamydial infection (B-II). Women should have a pelvic examination and should have a wet mount examined for *Trichomonas* species (A-II). A variety of screening tests for gonorrhea and chlamydial infection are available, including nucleic acid amplification tests, nucleic acid hybridization tests, and culture. Periodic follow-up screening should be considered depending on reported risk behavior, the presence of other STDs, and the prevalence of STDs in the community (B-III) (table 5).

Serological testing for syphilis . A nontreponemal test for syphilis, such as a rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test, should be done at baseline (A-II) and repeated periodically, depending on the patient's risk behavior and presence of other STDs (B-III). Biologically false-positive test results are not uncommon and can be excluded with a confirmatory test (i.e., fluorescent treponemal antibody absorption test [FTA-ABS] or microhemagglutination test for antibodies to *T. pallidum* [MHA-TP]). False-positive results of RPR and VDRL tests are generally of low titer. Opinions vary on the need for lumbar puncture for HIV-infected patients with evidence of syphilis. Most authorities would recommend that a lumbar puncture be done for all HIV-infected patients with latent syphilis (>1 year's duration), or for patients with early syphilis (<1 year) when accompanied by neurological signs or symptoms or when standard therapy with benzathine penicillin cannot be used (B-III). Patients who experience a therapeutic failure should also undergo lumbar puncture (B-III). Unfortunately, the interpretation of CSF findings can be difficult, because the VDRL tests of CSF are insensitive and the mononuclear pleocytosis and elevated CSF protein level characteristic of neurosyphilis are also common manifestations of HIV infection.

Human papillomavirus (HPV) screening. Women should have a Pap test at the initial evaluation (A-I). Liquid-based cytology is the preferred approach for HPV testing [24].

Men who have sex with men are at increased risk of anal high-grade squamous intraepithelial lesions (SILs) and may be at increased risk for anal cancer. Anal cytological screening of HIV-infected men who have sex with men has not yet become standard of care but is now being done for high-risk persons in some health care centers and may become a useful preventive measure in the near future. Additional studies of screening and treatment programs for anal high-grade SILs need to be carried out before recommendations for routine anal cytological screening can be made [7].

Fasting lipid profiles. Because many antiretroviral agents cause increases in cholesterol and triglyceride levels, blood should be drawn at baseline from fasting HIV-infected patients for determination of lipid profiles, especially for patients who are about to start therapy [12, 13] (B-III). Follow-up testing and response to therapy should be in accordance with current National Cholesterol Education Program guidelines [12, 13, 25].

Testosterone levels. HIV-infected men are at risk for hypogonadism, especially with more advanced disease. Whether antiretroviral therapy ameliorates or contributes to this condition is unclear. Clinicians should consider drawing blood in the morning for determination of serum total and free testosterone levels in patients who complain of fatigue, weight loss, loss of libido or erectile dysfunction, or depressive symptoms (C-III). A total testosterone level that is low or in the low end of the normal range establishes the diagnosis; however, if the results are normal, determination of a free testosterone level is required to determine whether hypogonadism is present.

Chest radiography. HIV-infected patients are susceptible to a variety of pulmonary complications and infections. A baseline chest radiograph may be useful, in part for detection of asymptomatic tuberculosis (B-III). Injection drug users are especially likely to have radiographic abnormalities that may be mistaken for infiltrates. A radiograph obtained when the patient is asymptomatic may be useful for comparison during the evaluation of future respiratory complaints, especially if the patient has a history of pulmonary disease.

Other laboratory tests. Other tests that may be indicated, depending on the age and sex of the patient, include urinalysis, electrocardiography, determination of thyroid-stimulating hormone, colonoscopy, or mammography. Routine testing for cryptococcal infection by determination of serum cryptococcal antigen or for disseminated *Mycobacterium avium* complex infection by culture of blood for acid-fast bacilli is not recommended (D-III). These are tests for acute disease and should be reserved for symptomatic patients with advanced immunodeficiency or suggestive clinical findings.

Special Considerations for Women

Women with HIV infection have the same reproductive health needs, concerns, and illnesses as do women without HIV infection. In addition, they may have gynecologic problems that are associated epidemiologically with HIV infection because of common risk factors, such as sexual behavior or drug use. Finally, certain gynecologic problems may be more common or more severe because of HIV-associated immunosuppression. In one study of 292 HIV-infected women, almost 50% had ⩾1 incident gynecologic problem discovered with serial assess-

ments [26]. Both prevalence and incidence of gynecologic problems are high in HIV-infected women throughout their disease course.

As part of the initial assessment, a comprehensive gynecologic history should be obtained, including menstrual history; sexual practices; contraception history and current use; male or female condom use and consistency of use; previous sexually transmitted and other genital tract infections; prior abnormal Pap test results, including evaluation and treatment; history of gynecologic surgery or other illnesses (e.g., uterine fibroids, endometriosis, and infertility); and current gynecologic symptoms (e.g., abnormal vaginal discharge, abnormal vaginal bleeding or amenorrhea, and pelvic pain).

More in-depth discussion about childbearing early in the course of HIV care is indicated if the patient expresses desire for future pregnancy, she is not trying to conceive but is not using appropriate contraception, or she expresses uncertainty about reproductive plans. The goal is to ensure informed decisions about contraception and to offer preconception counseling if pregnancy is desired. Patients should explicitly be asked to communicate with their provider if their plans change, when they are ready to consider pregnancy, or when they have questions related to reproduction.

Women with HIV infection or at increased risk for HIV infection have high rates of adult sexual and physical abuse and frequent history of childhood sexual abuse. The prevalence of depression is twice as high among women as among men in general and is more prevalent in HIV-infected persons and in the setting of violence or victimization. As part of the initial evaluation and at periodic intervals, providers should assess the presence of depression and domestic violence in women by means of direct questions or validated screening tools (B-III). A basic pregnancy history should also be included: number of pregnancies and outcomes (miscarriage, abortion, ectopic pregnancy, stillbirth, and preterm or term live birth), significant obstetrical complications, and number of living children and their HIV and general health status. Obstetrical issues, such as preconception counseling and care, antiretroviral management during pregnancy for maternal care, prevention of perinatal transmission, and decision-making about mode of delivery, are covered in detail in the US Public Health Service perinatal HIV guidelines [5]. Women who are HIV positive should be instructed not to breast-feed, given the risk of transmitting HIV to the infant.

Pregnancy testing. Approximately 80% of HIV-infected women are of childbearing age and may become pregnant intentionally or unintentionally. Because of issues related to perinatal HIV transmission, the potential impact of HIV and treatment on mother, fetus, and pregnancy course, and the life-threatening nature of ectopic pregnancy, health care providers should question female patients about interval menstrual

history and sexual and contraceptive practices at each visit. Pregnancy testing should be considered in the following situations: missed menses (unless using levonorgestrel implants or depot medroxyprogesterone acetate), irregular bleeding (unless using levonorgestrel implants or depot medroxyprogesterone acetate), new onset of irregular bleeding after prolonged amenorrhea while using levonorgestrel implants or depot medroxyprogesterone acetate, new-onset pelvic pain, enlarged uterus or adnexal mass on examination, before institution of new therapies, or at the patient's request. Pregnancy tests can be done on blood or urine, with the latter often available as rapid tests for use onsite in clinics. Most pregnancy tests in current use yield positive results before the first missed menses with normal intrauterine pregnancy.

Gynecological evaluation for cervical cancer screening and prevention. Abnormal cervical cytology is 10- to 11-fold more common among HIV-infected women than among HIV-uninfected women and is associated with the presence of HPV infection and the degree of immunosuppression [26]. Both the CDC and the Agency for Health Care Policy and Research recommend that HIV-infected women have a Pap test as part of their initial evaluation and that this should be repeated once within the first year after diagnosis (A-I). If the results are normal, annual Pap tests are indicated (A-II). More frequent Pap tests should be considered in the following circumstances: if there is a previous history of an abnormal Pap test, after treatment for cervical dysplasia, in women with symptomatic HIV infection, and in women with HPV infection. HIV-infected women who have had a hysterectomy, particularly if they have had a history of abnormal cervical cytology before or at the time of the hysterectomy, are at increased risk for SIL on vaginal cytological testing and should undergo regular screening with Pap tests [27]. Although the appropriate interval for screening has not been established, it is reasonable to follow guidelines similar to those for screening women who have not undergone a hysterectomy [24].

Pap test results should be reported according to the Bethesda System [28]. The results should include a statement on specimen adequacy and general categorization (negative for intraepithelial lesion or malignancy, epithelial cell abnormality, or other). Specimens that are reported as unsatisfactory for evaluation should be repeated. The presence of epithelial cell abnormalities (atypical squamous cells [ASC], SIL, glandular cell abnormalities, and squamous cell carcinoma) requires further evaluation. Women with ASC (both ASC-US [ASCs of unknown significance] and ASC-H [ASCs cannot rule out high-grade squamous intraepithelial lesion]), atypical glandular cells, SIL (low-grade or high-grade), or squamous carcinoma noted by Pap testing should undergo colposcopy and directed biopsy (A-II). Newer Pap test screening techniques that use liquid-based media appear to increase sensitivity, decrease the number

of tests with inadequate sampling, and reduce, but not eliminate, false-negative results; they also offer the possibility of direct testing for HPV on collected specimens. They are more expensive than conventional Pap tests. There are no current data examining the utility of these tests among HIV-positive women.

Mammography. Breast cancer is the second leading cause of death due to cancer in US women. It does not appear to have an increased prevalence among women with HIV infection, although unusual clinical presentations and rapid progression have been reported in the setting of HIV infection, suggesting that breast cancer may behave more aggressively in HIV-infected women [29, 30]. At present, breast screening by mammography for women with HIV infection should follow standard guidelines. Mammography should be performed every 1–2 years for women 40–50 years of age and annually after the age of 50 years (A-I). Mammography should be done before the age of 40 years for women with a history of breast cancer, with a first-degree relative or multiple other relatives with a history of premenopausal breast cancer or breast and ovarian cancer, or with a persistent palpable mass or other suspicious finding on examination [31].

Special Considerations for Children >13 Years Old

Perinatal HIV infection is for the most part a preventable disease if pregnant women receive antiretroviral therapy as outlined in the "Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1–Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States" [5]. The transmission rate has been reported to be <1% in women who achieve undetectable HIV loads while being treated with HAART. Usually, HIV-infected infants have normal physical examinations, although a number of perinatal conditions are comorbid problems because of other maternal risk factors. These include fetal alcohol syndrome, prematurity, opioid withdrawal, and symptoms from other perinatal infections, including congenital syphilis and CMV, HCV, and HBV infection. *P. jiroveci* pneumonia was the presenting opportunistic infection in most infants before routine HIV prenatal testing programs and the introduction of trimethoprim-sulfamethoxazole prophylaxis. Older children with perinatally acquired HIV infection may be asymptomatic in the first 2–3 years of life but then began to present with frequent "common" bacterial infections (otitis media, sinusitis, pneumonia, and sepsis osteomyelitis) progressing to failure to thrive and wasting syndrome. In the United States, the diagnosis of perinatal HIV infection is typically made within the first 6 months of age through routine screening of children born to known HIV-infected mothers. The diagnosis of HIV secondary to vertical transmission in older children is uncommon.

A number of diagnostic issues set apart perinatal HIV infection from adult disease. Maternal IgG crosses the placenta, and infants have positive results of serological assays because of maternal infection independent of their infection status. In the case of HIV infection, maternally derived antibody can result in positive results of ELISAs and Western blot assays for up to 18 months of age. Diagnosis of active HIV infection in the infant can be differentiated from HIV exposure by a PCR assay for HIV DNA. When 2 PCR assays are performed 1 month apart, with 1 assay after 4 months of age, the sensitivity and specificity is >98%. Once the diagnosis of perinatal HIV infection is made by detection of HIV DNA by PCR, HIV RNA PCR assays are subsequently used to monitor virus load. Perinatally HIV-infected infants have higher virus loads than do adults, reflecting primary infection, but as in adults, the virus load response to antiretroviral therapy is a strong predictor of prognosis.

There are also age-specific differences in CD4 cell counts, with infants having higher absolute counts than adults. From birth through 12 months of age, the normal CD4 cell count is >1500 cells/mm^3; between 2 and 5 years, it is >1000 cells/mm^3; only after 6 years of age do normal CD4 cell counts compare with adult counts of >500 cells/mm^3. The percentage of CD4 cells that define as normal, moderate, or severe immunosuppression are the same for infants and children as for adults. Periodic monitoring of CD4 cell counts is an important predictor of treatment response and prognosis.

In addition to HIV infection, clinicians should screen pregnant women for other infections, including syphilis and HBV, HCV, and group B streptococcal infections, to determine whether to evaluate and/or treat the newborn. In the United States, there is a single FDA-approved rapid HIV test, with others soon to be available. These rapid tests are useful for women who present in labor without having been tested during the prenatal period, so that antiretroviral therapy can be administered to the mother and infant. Increasingly, infants are born to antiretroviral-experienced mothers who may have received multiple combination regimens, including all major classes of antiretroviral drugs. Unfortunately for HIV-infected children born to these mothers, there are no data to guide selection of newborn antiretroviral drug treatment regimens on the basis of maternal HIV resistance testing. Although it may be prudent to take resistance of maternal virus into consideration, present pediatric antiretroviral treatment guidelines do not address this issue [4].

Staging of Disease

Adults. The most widely used system for staging HIV disease is the 1993 revision of the CDC's AIDS Surveillance Case Definition for Adolescents and Adults [32]. HIV disease is a continuous spectrum. These stages are used for determining re-

sources, especially those from governmental sources, research, epidemiology and prognosis. According to this system, individuals are assigned a stage according to a 3×3 matrix consisting of 3 CD4 cell count categories and 3 clinical categories (table 9).

CD4 cell count categories are as follows: category 1, CD4 cell count of ≥500 cells/mm³ or ≥29%; category 2, CD4 cell count of 200–499 cells/mm³ or 14%–28%; category 3, CD4 cell count of <200 cells/mm³ or <14%. Clinical categories are as follows: category A is documented HIV infection, asymptomatic, including persistent generalized lymphadenopathy, or acute HIV infection. Category B is symptomatic disease, with conditions not listed in clinical category C, including conditions that are attributed to HIV infection or indicative of a defect in cell-mediated immunity or considered to have a clinical course or management that is complicated by HIV infection. This includes conditions such as bacillary angiomatosis, persistent or recurrent thrush, poorly responsive vulvovaginal candidiasis, moderate to severe cervical dysplasia, constitutional symptoms (such as fever [temperature, 38.5°C] or diarrhea of >1 month's duration, oral hairy leucoplakia), herpes zoster (>1 episode or >1 dermatome), idiopathic thrombocytopenic purpura, listeriosis, pelvic inflammatory disease, and peripheral neuropathy. Category C is the AIDS indicator condition. Once a category C condition has occurred, the person remains in category C.

According to the 1993 case definition for AIDS, persons with stage A3, B3, C1, C2, or C3 infection have CDC-defined AIDS. Specifically, anyone with either an AIDS indicator condition or a CD4 cell count of <200 cells/mm³ has AIDS. Once a diagnosis of AIDS has been made, for surveillance purposes, it is not negated by subsequent developments (e.g., persons given a diagnosis of AIDS on the basis of a CD4 cell count of <200 cells/mm³ are still considered to have AIDS if their CD4 cell count subsequently increases to ≥200 cells/mm³, perhaps in response to antiretroviral therapy), even though the relevance of the diagnosis may then be more historical than clinical. Many states use the CDC classification as a criterion for accessing social services.

Although reporting requirements for HIV infection vary from state to state, all cases of AIDS must be reported to the local health department. Accurate and complete reporting is important to ensure that adequate resources are available, because the amount of federal AIDS funding received by a city or community is frequently based on the number of reported cases from that region.

Children. The CDC pediatric clinical and laboratory classification system [33] parallels the adult HIV case definition. The major modification is the recognition that 3 age-related CD4 cell categories define levels of immunosuppression (table 10).

Table 9. Centers for Disease Control and Prevention (CDC) staging system for classification of HIV-infected persons.

CD4 cell count, cells/mm³ (CD4 cell percentage)	CDC classification		
	A[a]	B[b]	C[c]
≥500 (≥29%)	A1	B1	C1
200–500 (14%–28%)	A2	B2	C2
<200 (<14%)	A3	B3	C3

NOTE. From [32].
[a] Asymptomatic, persistent generalized lymphadenopathy, or acute HIV infection.
[b] Symptomatic (not A or C).
[c] AIDS indicator condition.

There is no acute HIV syndrome recognized in pediatric patients as there is in adults. Infants and children are more likely to present with common bacterial infections, chronic diarrhea with failure to thrive, or acute encephalopathy rather than the illnesses seen in adults defined in categories B or C.

Schedule of Evaluations for Care

Adults. The frequency of evaluation depends in part on the stage of HIV disease and in part on the rate at which disease is progressing. As a general rule, both the CD4 cell count and the virus load determine the frequency with which monitoring is needed. Asymptomatic patients with normal CD4 cell counts and low virus loads can be monitored infrequently, repeating virus load measurements every 3–4 months and CD4 cell counts every 3–6 months (B-III). CBC counts and chemistry panels should also be monitored to assess medication toxicity if the patient is given prophylaxis for opportunistic infections and/or antiretroviral therapy. The frequency of monitoring is dependent on the medications in addition to the stage of disease. For example, transaminase levels should be monitored every 2 weeks during the first 8–12 weeks of treatment with nevirapine. Once therapy has been initiated, the response to therapy should be monitored 4–8 weeks later with a repeated virus load determination. Once the virus load has become undetectable, laboratory tests can then be obtained at 3–4-month intervals to monitor for drug toxicity and to assess response to therapy [3]. The virus load and CD4 cell count should not be measured within 2–3 weeks of an illness or immunization. CD4 cell counts should be followed both for assessment of antiretroviral efficacy and to determine the need for prophylaxis against opportunistic infections (A-II). Pap tests should be repeated yearly (A-II). Screening tests for STDs and TSTs should be repeated periodically depending on behavioral risk and possible exposure to patients with tuberculosis (B-III). Testing for hepatitis should be repeated if suspected exposure occurs in a patient who was not previously immune. Patients who were previously seronegative for CMV should be retested if their CD4 cell count

Table 10. Centers for Disease Control and Prevention scheme for defining level of immunosuppression in HIV-infected pediatric patients.

Category	CD4 cell count, cells/mm³ (CD4 cell percentage), by age		
	0–12 months	1–5 years	>6 years
Normal	>1500 (>25%)	>1000 (>25%)	>500 (>25%)
Moderate	750–1499 (15%–24%)	500–999 (15%–24%)	200–499 (15%–24%)
Severe	<750 (<15%)	<500 (<15%)	<200 (<15%)

decreases to <50 cells/mm³. Patients who have IgG to CMV detected should undergo funduscopic examinations by a qualified ophthalmologist once their CD4 cell count decreases to <50 cells/mm³. Patients who were previously seronegative for *Toxoplasma* species should be retested if their CD4 cell count decreases to <100 cells/mm³ and if they are not receiving trimethoprim-sulfamethoxazole for prophylaxis against *P. jiroveci* pneumonia (C-III). Vaccinations for pneumococcal infection, influenza, and hepatitis should be offered as indicated.

Pediatric patients. HIV-exposed newborns should be observed closely for signs and symptoms of HIV infection, for comorbid conditions, and for confirmatory laboratory diagnosis. HIV-negative babies and children should have clinical visits as per standard of care. Older perinatally infected infants and children are observed every 3 months but more frequently if ill. HIV-infected infants and children require immunizations that are modified somewhat by their HIV infection. Vaccination against chickenpox should be given only to asymptomatic, nonimmunosuppressed children. Children with severe immunosuppression should not receive measles-mumps-rubella vaccine. All HIV-infected children should be vaccinated against pneumococcal disease and influenza. With diagnosis and aggressive antiretroviral treatment, perinatal HIV infection has changed from an acute fatal illness to a chronic condition. As with adults, appropriate use of combination antiretroviral drugs, with routine monitoring of adherence, immune status, virus load, and viral resistance, has become part of routine care for pediatric HIV patients. With such careful and close management, the mortality and morbidity of pediatric HIV infection has significantly decreased in countries with the resources to support such care.

Metabolic Complications of Antiretroviral Therapy

The major metabolic abnormalities that complicate the management of HIV infection include serum lipid abnormalities, morphological changes (fat accumulation and lipoatrophy), dysregulation of glucose metabolism, lactic acidemia, and reduced bone mineral density. It is currently unknown whether these observed changes are all components of a single syndrome related to treatment of HIV infection or if they have different etiologies. Concern has been expressed about the long-term cardiovascular morbidity in patients who experience increases in atherogenic serum lipids, insulin resistance or dysglycemia, and body fat redistribution, but as of yet this risk is undefined. Recent guidelines have been developed to assist clinicians in the identification and management of lipid abnormalities and metabolic complications [12, 13].

Morphological or body shape changes. Lipoatrophy is defined as the loss of subcutaneous fat in the face, arms, legs, and/or buttocks. Patients often note the appearance of more prominent superficial veins on the extremities, which is caused by a loss of subcutaneous fat that normally surrounds the veins. Fat accumulation is defined as an increase in visceral (intrabdominal) fat, peripheral lipomas, and/or an enlarged dorsocervical fat pad. In addition, breast enlargement presumed to be secondary to fat deposition has been described in both men and women; however, the composition of the increased breast tissue is unknown. Patients may develop a mixed syndrome, or they may have predominantly fat accumulation or lipoatrophy alone.

Fat accumulation appears to be associated with protease inhibitor therapy, although there are well-documented cases of dorsocervical fat deposits in patients who received only nucleoside analogue therapy. Other risk factors include longer duration of HIV infection and of antiretroviral therapy. Women appear to be at an increased risk for fat accumulation, compared with men, possibly because of differences in baseline body composition. Lipoatrophy has been associated with nucleoside analogue therapy, as well as with combined nucleoside analogue and protease inhibitor therapy. Although the etiology of lipoatrophy is unclear, accumulating evidence suggests that it is linked to nucleoside analogue–induced mitochondrial toxicity and may be most strongly associated with use of stavudine, which appears to be more toxic to mitochondrial DNA than are other nucleoside reverse-transcriptase inhibitors (NRTIs). Men appear to be at higher risk for lipoatrophy than are women in some studies, possibly because of differences in baseline body composition.

Dual-energy x-ray absorptiometry has been used in research studies to evaluate regional body composition. It cannot distinguish subcutaneous from visceral fat, but it can compare limb fat with truncal fat. CT scanning at L4/5 can be used to

assess visceral fat and can quantitate subcutaneous fat. The body mass index assesses lean body mass but cannot assess fat redistribution. Anthropometry (measurements of skin fold thickness and circumference of the waist and hip) may be the least costly evaluation, but it does not differentiate subcutaneous from visceral fat and requires training to perform. These tools, including bioelectrical impedance analysis, are not currently recommended for clinical practice. Routine measurements of body weight and patient self-report of body shape changes are sufficient for clinical practice. At the current time, there are no approved interventions for the treatment of fat accumulation and or lipoatrophy.

Lipid abnormalities. Increases in triglyceride levels and decreases in high-density lipoprotein (HDL) cholesterol levels are common among patients with untreated advanced HIV infection. Antiretroviral therapy is associated with increases in total cholesterol and triglyceride levels. HDL cholesterol levels may increase with nonnucleoside reverse-transcriptase inhibitor therapy [34]. Fasting lipid levels should be monitored prior to and within 4–6 weeks after starting antiretroviral therapy (B-III). Patients with abnormal lipid levels should be managed according to the National Cholesterol Education Program guidelines [25], with special consideration, as discussed in the lipid guidelines, for persons with HIV infection [12].

Abnormalities of glucose metabolism. Insulin resistance and impaired glucose tolerance have been reported in upwards of 50% of patients treated with protease inhibitors in several series [35, 36]. This is in contrast to the lower incidence of new-onset diabetes (similar to type 2 diabetes), which has been reported in 1%–6% of HIV-infected patients treated with protease inhibitors [37, 38]. Fasting glucose levels should be measured prior to and during antiretroviral therapy. At the current time, routine monitoring of insulin levels and/or oral glucose tolerance testing is not recommended (C-III). Weight loss and regular exercise should be recommended for obese patients. Switching from protease inhibitors to other agents may lead to resolution of hyperglycemia and diabetes, although this is not feasible for all patients. Whenever possible, treatment of protease inhibitor–induced diabetes should include the use of an insulin-sensitizing agent (metformin or thiazolidinediones), because the mechanism of hyperglycemia is insulin resistance.

Lactic acidosis. Lactic acidosis is produced by accumulation in the body of lactic acid, which is a by-product of the anaerobic glycolysis pathway. The syndrome occurs when body tissues are deprived of oxygen through dehydration, sepsis, and other clinical situations, resulting in a low perfusion state or impairment of mitochondrial aerobic metabolism. It has also been described in association with NRTI antiretroviral therapy [39]. NRTIs are known to inhibit mammalian mtDNA polymerase-γ, resulting in insufficient oxidative metabolism and adenosine triphosphate production, and it is through this mechanism that lactic acidemia is thought to occur. Some 8%–21% of patients treated with NRTIs may have hyperlactatemia (serum venous lactate level of >2 mmol/L); the incidence of severe lactic acidemia is 1%–2% [40]. Stavudine is the drug most frequently associated with increased lactate levels [41], presumably because of its effects on mtDNA. Zidovudine and didanosine can also cause hyperlactatemia, whereas abacavir, lamivudine, and tenofovir disoproxil fumerate are thought to be the least toxic to mitochondria and thus the least likely to increase lactate levels. Pregnant women may be at increased risk of lactic acidosis and liver damage. The combination of didanosine and stavudine has been associated with increased risk of lactic acidosis and liver disease and should be avoided, especially during pregnancy.

The clinical manifestations of hyperlactatemia without acidosis (normal arterial pH) are variable and nonspecific. Some patients are asymptomatic, and others may report fatigue, nausea, vomiting, abdominal pain, and/or diarrhea. Transaminase abnormalities are common, usually because of hepatic steatosis that often accompanies lactic acidosis. Severe NRTI-related lactic acidosis has been associated with hypotension, altered mental status, hepatic steatosis, and death [42]. Mortality is common with venous lactate levels of >10 mmol/L. Pancreatitis, neuropathy, myopathy, bone marrow suppression, lipodystrophy, and osteopenia may be related to chronic lactic acidemia [43–45]. Patients starting NRTI therapy should be made aware of the symptoms of lactic acidemia and asked to report them promptly to their health care provider. A serum venous lactate level should be determined in the setting of unexplained but consistent symptoms. If abnormal, the measurement should be repeated, and arterial blood gas measurement should be considered. There is no rationale for ordering these laboratory studies for asymptomatic patients, either at the time of initiation of NRTI therapy or during the course of antiretroviral treatment (E-II). Discontinuation of NRTI drugs is recommended for symptomatic patients with a venous lactate level of >5 mmol/L (B-II). For patients with a level of 2–5 mmol/L, close monitoring is advised. No intervention is necessary for patients with a level of <2 mmol/L. Lactic acidemia will generally resolve once the offending drug(s) is stopped [46, 47]. The safety of resuming NRTI treatment in this setting has not been established.

Bone disorders. Premature osteopenia and osteoporosis (excessive bone loss compared with sex-matched controls) as well as osteonecrosis with avascular necrosis of the hips have been described in HIV-infected patients. Bone mineral density in healthy adults is determined by age (decreases over time), race (greater in black than in white subjects), sex (greater in male than in female subjects; decreases following menopause), and weight (greater in heavier people). Factors that accentuate bone loss include immobility, cigarette smoking, excessive al-

cohol use, chronic renal failure, hyperthyroidism, and long-term corticosteroid treatment. Osteopenia is generally asymptomatic; osteoporosis may present with fractures of the vertebrae, forearms, or hips. Bone mineral density is measured by dual-energy x-ray absorptiometry of the spine, hip, and form. Osteopenia is defined by a t-score (standard deviations from mean value for young sex-matched controls) between −2.5 and −1; osteoporosis is defined by a t-score of less than −2.5. Avascular necrosis of the hips may be asymptomatic or present with progressive pain with ambulation.

Two cross-sectional studies found osteopenia in 38% and 62% of HIV-infected patients receiving combination antiretroviral therapy [48, 49]. Several mechanisms have been proposed by which NRTIs and protease inhibitors may lead to premature bone loss, but none has been proven. Interference of vitamin D metabolism by protease inhibitors and lactic acidemia related to NRTI therapy have been suggested as contributing factors [50, 51]. However, HIV infection itself, rather than its treatment, may also be in part responsible for osteopenia [52]. The prevalence of and predisposing factors to avascular necrosis of the hips in HIV-infected patients are unknown.

Patients taking antiretroviral therapy who have other risk factors for premature bone loss should consider undergoing bone densitometry at baseline (B-III). Calcium and vitamin D supplementation should be prescribed, and patients should be encouraged to exercise regularly and to not smoke cigarettes. If baseline bone densitometry shows osteopenia or osteoporosis, intervention with a bisphosphonate or other medical therapy should be considered. A follow-up study 1–2 years later to monitor the response to therapy is advised. Baseline bone densitometry is recommended for all women over the age of 65 years and for postmenopausal women under the age of 65 years who have 1 or more additional risk factor(s) for accelerated bone loss. Routine screening for osteoporosis in other HIV-infected patients cannot be recommended at this time (D-III). Routine radiographic monitoring for avascular necrosis in asymptomatic persons is not advised, but for patients presenting with hip pain or other large joint pain, MRI is the preferred method of diagnosis. Patients should be reminded of the health benefits of regular exercise and adequate calcium and vitamin D intake. They should also be counseled regarding cigarette smoking and excessive alcohol consumption. The use of biphosphonates and androgens has not been adequately studied in HIV-infected patients. Most patients with symptomatic avascular necrosis require hip replacement.

ADHERENCE TO ANTIRETROVIRAL THERAPY

The long-term effectiveness of HAART is dependent on achieving a maximum and durable suppression of viral replication. Unfortunately, in some clinical practices, as few as 40%–50% of patients achieve this therapeutic goal [53, 54]. The primary reason for failure to achieve maximum suppression of virus load, particularly among patients taking initial regimens, is suboptimal adherence to medications [55–57]. Because of this pivotal role that adherence plays in the success of treatment, it is essential that clinicians be knowledgeable about how to assist patients with optimizing their adherence to HAART. Factors having a negative impact on adherence are described in table 11.

Several recent studies have shown that >95% adherence is necessary to achieve a nondetectable virus load in >80% of treated patients [57, 58]. Research examining adherence to medications for other chronic illnesses has found that most patients take ~50% of their prescribed doses [59, 60]. Average adherence to HAART has been found to be higher, generally ~70%–80% [57, 61, 62]. Unfortunately, given what we know about the correlation between virological suppression and adherence, these rates of adherence are not high enough, emphasizing the need for a plan to measure and optimize adherence.

It is important to use a specific method for measuring adherence to HAART in clinical practice (A-III). Clinicians should avoid making assumptions about patients' adherence, because these assumptions are usually incorrect [63]. Ideally, the adherence measurement strategy should be easily incorporated into clinical care, be inexpensive, and be helpful in assessing both baseline adherence and the effectiveness of adherence interventions. Adherence to HAART can be measured by a variety of methods. The most commonly used methods in clinical trials are patient self-report and electronic medication monitoring devices, such as medication event monitoring systems. Other possible ways to assess adherence include pill counts and checking pharmacy refill records. No single method has been established as the reference standard for measuring adherence; all have advantages and disadvantages. Once a method has been chosen, it should be used consistently to monitor each patient's adherence at each visit.

Efforts to improve adherence in patients taking HAART have

Table 11. Factors that have a negative impact on adherence to medications.

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

several different components. First, it is important to assess patient readiness and commitment to therapy before initiating HAART. If readiness appears low, HAART should be deferred while efforts such as education and time to address concerns or barriers are undertaken to improve the patient's readiness. When therapy is begun, a regimen should be carefully chosen that has the highest likelihood of patient adherence on the basis of regimen characteristics and patient preferences. At the time that HAART is started, adherence interventions chosen on the basis of the patient's specific needs and situation should be provided. In general, information regarding the effectiveness of specific interventions to improve adherence to HAART is limited. An individualized and flexible approach is essential. However, from studies of other chronic diseases, we know that interventions that are multifaceted and repetitive are most likely to result in improvements in adherence [64, 65], such as the strategies discussed below.

Patient-Focused Adherence Strategies

Several patient factors have been found to consistently predict lower adherence to HAART. These factors are heavy alcohol use, active injection or other illicit drug use, depression, lack of belief in the benefits of the medications, and low literacy [56, 66–72]. In addition, the patient's social situation can have an impact on his or her ability to consistently adhere to medications. For persons whose lives are chaotic, who have unstable or no housing, or who have poor social support, adherence will be more challenging and will often be suboptimal [56, 70, 71]. The following strategies may be helpful in modifying these patient factors that influence adherence.

- Screen all patients for depression before initiation of HAART; if depression is found, treat and stabilize depression before initiating HAART.
- Screen patients for substance abuse and alcohol abuse, and encourage treatment. If a patient is unwilling to discontinue substance abuse but is committed to beginning HAART, use a variety of strategies to enhance his or her ability to successfully adhere to treatment. Consider placing the patient in a directly observed therapy program, if available, or in a setting in which medications will be directly administered, such as a halfway house.
- Do all that you can to assist in stabilizing the patient's living situation and social support system. Begin by establishing a clear understanding of his or her housing arrangement, the stability of that situation, and the patient's significant others. Collaborate with a case manager or social worker to effectively address these issues.
- Assess the patient's beliefs and perceptions about HAART. Consider the use of a support group, peer educator, or "treatment buddy" if the patient has negative perceptions of HAART or does not believe that the medications will work.

- When providing educational materials for patients, be mindful of their reading skills and primary language. Whenever possible, provide dosing schedules that maximize the use of pictures, especially photographs of the medications. Assess the patients' primary-language reading skills before giving materials in that language as well.
- Offer structured individualized or group educational sessions about antiretrovirals, how they work, the importance of adherence, and strategies for adherence. These have been found to be effective in a number of studies and settings and can be administered by a nurse, health educator, peer counselor, pharmacist, or other staff members, either on a one-on-one basis or in a group setting.
- With the patient's help, identify a family member, friend, or partner who will assist with and help take responsibility for the patient's medication taking and adherence. This will serve to enhance social support while enhancing adherence.

Focus on potentially modifiable patient factors in an effort to enhance the patients' likelihood of adherence. Never use personal characteristics that patients are unable to change as a reason for withholding HAART. Instead, use any such factors that cause concern as a reason to provide even more intensive adherence-related supports.

Regimen-Focused Adherence Strategies

HAART regimen characteristics can affect patients' adherence to their regimen. This includes the complexity of the regimen, side effects, and the "fit" with the patient's lifestyle and daily routine [73–75]. Given this, the following regimen focused adherence strategies are recommended:

- Prescribe simpler HAART regimens. Focus on constructing regimens that involve fewer pills and fewer doses and that minimize food-dosing restrictions.
- Individualize HAART regimens; work with each patient to choose a regimen that is tailored to his or her lifestyle and schedule. Avoid adopting a "one-regimen-fits-all" philosophy. Get the patient involved in choosing and individualizing the regimen.
- Choose regimens with fewer side effects. Whenever possible, avoid prescribing medications known to frequently cause very unpleasant side effects.
- Proactively manage side effects. Let patients know what side effects may be experienced and how each side effect will be managed if it occurs.

No matter how simple or complex the regimen is, make sure patients understand exactly how to take their medications. Confusion is an important cause of suboptimal adherence. Providing a dosing schedule with photographs of the medications and helping patients to correctly fill a medication organizer with their new medications are 2 strategies that will help decrease

confusion. One can assess a patient's understanding of the regimen by having them say the regimen back to the provider. Be open to patients' requests to change their HAART regimen because of side effects.

Provider-Focused Adherence Strategies

The quality of the patient-provider relationship has been found to influence adherence to HAART [76]. In addition, the patients of more experienced HIV providers are more likely to have excellent adherence [67]. It is reasonable to conclude that this is because the highly experienced providers have consistent strategies for enhancing adherence that are used with all patients. Given this, the following provider and clinical care site focused adherence strategies are recommended:

- Develop a set of adherence-focused activities that are provided for each patient, including an assessment of readiness for HAART, education regarding importance of adherence and consequences of nonadherence, an individualized dosing-instruction sheet with photographs of medications, structured follow-up measurements of adherence, and problem-solving for adherence-related difficulties that are identified.
- Give patients the time and opportunity to develop a warm, caring patient-provider relationship with you, even if they are not yet receiving HAART or do not feel ready to begin receiving HAART.
- Try to make your clinical site as user-friendly as possible. Make it easy for patients to call and obtain answers to questions and to come in at short notice if problems develop.
- Utilize a multidisciplinary care team, if possible, so that other providers, such as nurses, case managers, pharmacists, and peer counselors, will be available to coordinate some of the adherence-related activities.
- Schedule intensive and frequent visits during the month after initiation of HAART. Focus on identifying and solving adherence problems and difficulties with medication tolerance. These visits can also be used to obtain early measures of adherence and to reinforce the correct dosing schedule.

Acknowledgments

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