Annals of Internal Medicine®

In the Clinic®

Management of Newly Diagnosed HIV Infection

o field in medicine has moved as swiftly as HIV/AIDS over the past 35 years. Because of the rapid turnover of key information, this In the Clinic focuses on essential principles of care for newly diagnosed adults with HIV-1 infection and how to prevent infection in persons at risk. To ensure continued usefulness, future directions in therapy and how to access updated information on a continuous basis are emphasized.

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CME Objective: To review current evidence for screening and prevention, diagnosis and evaluation, treatment, and practice improvement of management of newly diagnosed HIV infection.

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Screening and Prevention

Diagnosis and Evaluation

Treatment

Practice Improvement

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Studies have shown that positive clinical outcomes for HIV-infected persons are a function of the clinician's experience (1, 2). Thus, nonspecialists are urged to seek expert advice and consultation from experienced HIV care providers whenever possible. HIV specialists come from many backgrounds, including infectious diseases, hematology/oncology, general internal medi-

cine, family medicine, pharmacy, and advanced-practice nursing. Thus, it is important to identify experts available in a given community. It is especially important to seek input from experienced practitioners in the setting of antiretroviral treatment failure and in cases of advanced HIV disease (AIDS) when patients are vulnerable to multiple, often simultaneous opportunistic infections (OIs).

Screening and Prevention

Who should be screened for HIV infection?

Despite a sharp decline in AIDS cases and deaths since the advent of highly active antiretroviral therapy (ART) (3), the Centers for Disease Control and Prevention (CDC) estimates that more than 1.2 million adults and adolescents in the United States are living with HIV, including 14% (1 in 7) who are unaware of their infection (4). The U.S. epidemic continues to disproportionately affect racial and ethnic minorities. and especially young men who have sex with men (MSM). Persons with undiagnosed HIV tend to be younger (13-29 years) MSM and males with high-risk heterosexual contact (4).

People at known increased risk for HIV infection include MSM; men and women having unprotected sex with multiple partners; persons who inject drugs (PWIDs) currently or have done so in the past; men and women who exchange sex for money, drugs, or other commodities or who have sex partners who do; persons with past or present sex partners who are HIV-infected, bisexual, or PWIDs; persons who engage in receptive anal sex regardless of sexual orientation; persons treated for sexually transmitted diseases (STDs); and, although now few in number, persons treated for hemophilia

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or who received a blood transfusion between 1978 and 1985. Persons who request an HIV test despite reporting no individual risk factors may also be considered at increased risk because it is likely that they have risk factors that they are unwilling or unable to disclose. Anyone who asks for an HIV test should receive one.

In 2006, the CDC recommended that everyone between the ages of 13 and 64 years should be tested for HIV on an opt-out basis at least once as part of routine health care, unless the local prevalence rate of HIV infection is below 0.1%. Because clinicians may not know this rate, the CDC recommends routine voluntary HIV screening for all patients aged 13 to 64 years in any health care setting until the diagnostic yield in a given locality has been shown to be less than 1 per 1000 patients screened (5).

"Opt-out" means that permission for HIV testing is included in the general informed consent for medical care unless, after being notified of this fact, the patient explicitly declines. Written consent and prevention counseling as required elements of HIV testing were eliminated from the 2006 recommendations. Only Nebraska and New York have laws that differ from CDC recommendations (6, 7). Also, because many adults continue sexual activity past age 64 years and 45% of HIV-infected persons are aged 50 years or older (8), testing all sexually active adults, regardless of age, is clinically appropriate.

These recommendations are based partially on the fact that risk-based testing has not been effective: Providers seldom adequately assess risk, approximately 10%-25% of persons with undiagnosed HIV are unaware of any risk factors or are uncomfortable with disclosing them, and almost half of patients are identified late in the course of disease when they can no longer receive the maximum benefit from ART

All persons at risk as well as those in the following subgroups should routinely be screened for HIV infection: those who have sex with a person of unknown HIV status; those diagnosed with and initiating treatment for tuberculosis, hepatitis B, or hepatitis C; those seeking treatment for STDs; victims of sexual assault; all pregnant women as part of routine prenatal care on an opt-out basis; all women of unknown HIV serostatus who present in labor (9, 10); infants exposed to HIV in utero; persons initiating and taking HIV pre- or post-exposure prophylaxis (PrEP, PEP); and anyone who requests testing (9). Persons whose blood or body fluid is the source of an occupational or a nonoccupational exposure should be informed of the incident, and a request to be tested for HIV should be made at the time of exposure. Assessment of potential occupational exposure to HIV should follow the U.S. Public Health Service guidelines, including PrEP provision as indicated (11, 12).

How frequently should persons at risk be tested?

All potentially high-risk persons should be retested at least annually per the 2006 recommendations. In sexually active MSM, routine testing every 3-6 months should be considered (13). Retesting at-risk pregnant women in the third trimester will identify

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those who may have seroconverted during pregnancy. The CDC recommends that all persons and their prospective sex partners be tested before entering into a new sexual relationship. Rescreening patients who are not likely to be at high risk is left to clinical judgment. Clinicians should generally maintain a low threshold for both screening and rescreening.

Many persons, especially MSM who seek preventive services for HIV, face stigma, homophobia, and discriminatory behavior; black MSM have substantially more challenges. The CDC estimates the lifetime risk for HIV as 1 in 2 among black MSM. Young black MSM are more likely not to know their HIV status, face strong socioeconomic barriers, and have smaller sexual networks (14, 15).

Daily PrEP with a single, fixeddose, antiviral combination tablet (emtricitabine/tenofovir) has been shown to reduce HIV acquisition by 92% or greater in certain at-risk populations, is considered safe, and is approved by the U.S. Food and Drug Administration for this purpose (16). An estimated 1.2 million people in the United States are eligible for PrEP, specifically 1 in 4 MSM, 1 in 5 PWIDs, and 1 in 200 heterosexuals (17). In May 2014, the U.S. Public Health Service released clinical practice guidelines as well as a clinical providers' supplement that highlights certain behavioral risk factors that are clear indications for prescribing PrEP. Although PrEP is a powerful prevention tool, 1 in 3 primary care physicians and nurses are unaware of it (17). Current studies are investigating products and delivery methods other than pills, including vaginal rings, vaginal and rectal gels, vaginal films, and long-acting injectables.

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Screening and Prevention... All sexually active persons aged 13 years or older should be offered screening for HIV on an opt-out basis at least once; high-risk persons should be retested annually. Sexually active MSM can be retested as frequently as every 3-6 months. Persons receiving PrEP should be tested every 3 months. All pregnant women should be offered opt-out HIV testing and receive immediate treatment if results are positive to prevent vertical transmission.

CLINICAL BOTTOM LINE

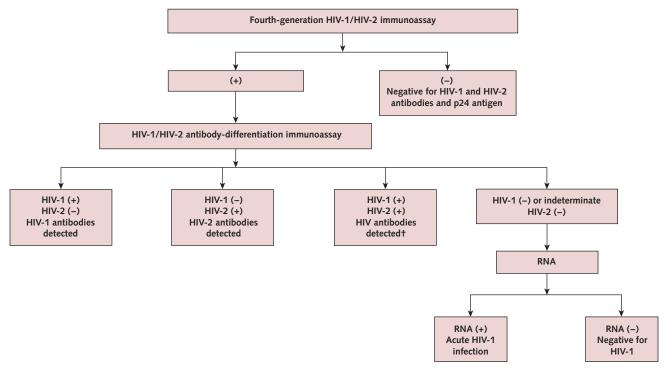
Diagnosis and Evaluation

Which tests should be used, and what is the appropriate sequence of tests to confirm a diagnosis of HIV infection?

According to the 2014 CDC guidelines on laboratory testing for HIV infection, screening starts with the fourth-generation HIV-1/2 antigen/antibody combination (HIV Ag/Ab) test (**Figure 1**) (18). The defining benefits of this test are that it eliminates the confirmatory Western blot, allows detection sooner after infection.

and decreases the "window period" before antibody conversion to as little as 10 days (19). This allows earlier initiation of ART, decreasing both morbidity and the likelihood of transmission to others, which is especially high in the setting of acute infection. Positive results are followed by an HIV-1/2 differentiation test. The fourth-generation HIV Ag/Ab test is the most accurate in medical use (>99.7% sensitivity and >99.3% specificity) and can iden-

Figure 1. Centers for Disease Control and Prevention laboratory testing for HIV diagnosis from serum or plasma.



^{*} Updated in 2014.

[†] Additional testing required to rule out HIV-1 and HIV-2 co-infection.

tify most (>80%) acute infections that would otherwise require RNA polymerase chain reaction (PCR) confirmation (19, 20). However, as with all screening tests, the predictive value of individual positive or negative results depends on local seroprevalence (21, 22). Chronic HIV infection should not be diagnosed by an HIV quantitative RNA PCR assay because of the possibility of false-positive results at low viral loads (<5000 copies/mL). The PCR assay should only be used for diagnostic purposes in the setting of acute infection. A specialist should be consulted when serologic results are inconsistent.

Several rapid tests have been approved for detection of HIV antibodies that can be performed on plasma and variably on whole blood, serum, or saliva, including a new rapid HIV-1/2 Ag/Ab test (21). Although the sensitivity and specificity of these tests are excellent, all rapid tests must be confirmed with the standard fourth-generation test (18). Data are currently insufficient to recommend a single rapid HIV-1/2 Ag/Ab test as the initial assay.

What should clinicians do if they suspect acute HIV infection but test results are negative?

The fourth-generation HIV-1/2 Ag/Ab tests can be indeterminate or negative during seroconversion ("window period"). However, in acute infection the quantity of HIV virions in the blood ("viral load") is extraordinarily high-often in the millions; thus, HIV infection can be diagnosed by a quantitative RNA PCR assay that measures the number of copies of the virus in plasma. Because acute infection often mimics mononucleosis or other acute viral illnesses, sexually active or persons at risk with a

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mononucleosis-like presentation (particularly those with a negative result on a Monospot test) should be evaluated for acute HIV infection with a quantitative RNA PCR assay (23). Proof of seroconversion typically occurs 2-6 weeks after exposure, and 99.9% of HIVinfected patients have a positive combination Ag/Ab test result by 12 weeks (18). Because risk for transmission is directly related to viral load, patients with negative results on the fourth-generation Ag/Ab test who may still be acutely infected should avoid sex until they are retested. Pregnant women who develop acute HIV infection should be rapidly referred to an HIV specialist and an obstetrician experienced in HIV disease for immediate ART (24, 25).

What symptoms and signs should prompt clinicians to consider acute or chronic HIV infection?

Acute HIV infection (also termed "acute seroconversion syndrome") is a nonspecific viral syndrome similar to mononucleosis. influenza, and hepatitis and includes the common features of fever, fatique, myalgia and arthralgia, lymphadenopathy, pharyngitis, and rash. However, the range of possible presentations is wide and encompasses neurologic syndromes (meningitis, encephalitis, radiculopathy), hepatitis, and gastrointestinal symptoms. If the patient's CD4 count drops precipitously below 200 cells/mL, he or she may present with an OI that is the hallmark of AIDS.

Approximately 40%–90% of persons who have seroconverted have symptoms (26), but not all seek medical care. Acute HIV infection is often not recognized by primary care and emergency physicians because the symptoms mimic those of other common viral illnesses (27). One

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study estimated the prevalence of acute HIV infection among patients seeking care for fever or rash as 0.5%-0.7% (28). Because viral load in plasma and genital secretions is very high, acute seroconverters have a high rate of transmission to others and thus play a disproportionate role in maintaining the epidemic. Thus, there is a significant public health benefit to identifying and treating these individuals as soon as possible (29).

Chronic HIV infection has a protean range of presentations, with some dependence on the stage of disease. Throughout the course of HIV infection, lymphadenopathy waxes and wanes and thus is not an accurate clinical marker of disease stage. In fact, many patients are diagnosed with HIV when lymph node biopsies for possible lymphoma are read as "reactive." Many have minor, nonspecific skin problems, such as folliculitis or seborrhea; recurrent episodes of candida vaginitis are frequently the first manifestation of HIV disease in women (30). Obviously, these conditions also occur in HIV-negative persons, but it is important to consider HIV infection in the differential diagnosis and recommend testing. Some laboratory abnormalities, such as an unexplained low platelet count or low lymphocyte fraction, should trigger an HIV test. Illnesses that cause disease in HIVnegative persons with intact immune responses may occur in HIV-positive persons at relatively well-preserved CD4 (T-helper) cell counts, including tuberculosis and bacterial pneumonia (especially pneumococcal disease). Oral thrush is frequently present as CD4 counts drop below 350 cells/mL. Unexplained weight loss, fever, and night sweats are common nonspecific symptoms of AIDS, which is defined by the

occurrence of one or more OIs or severe immune depletion defined by a CD4 count less than 200 cells/mL.

Many patients tolerate waning immunity fairly well until they present emergently with a serious complication that signals an AIDS diagnosis. Typically, viral loads are high in advanced disease, and CD4 counts are generally far less than 200 cells/mL. Late diagnosis is still the rule rather than the exception; in 2014, 23% of persons who tested positive for HIV in the United States were concurrently diagnosed with AIDS (29).

The most common Ols include Pneumocystis pneumonia, esophageal candidiasis, cryptococcal meningitis, and toxoplasma encephalitis. Most patients with AIDS and an acute OI are sick enough to warrant hospitalization. Interestingly, Kaposi sarcoma, the opportunistic cancer that was one of the original hallmarks of AIDS in the early 1980s, has for unknown reasons become relatively rare. However, other types of cancer, including B-cell lymphoma, Hodgkin disease, and central nervous system lymphoma, do occur in patients with AIDS.

Which laboratory tests and evaluations are indicated in a patient with newly diagnosed disease?

As measures of immune function and viral activity, respectively, CD4 cell count and HIV viral load are surrogate markers of disease with proven value for determining prognosis, clinical staging, and monitoring response to treatment (31, 32). These tests are done at the start of care and repeated at regular intervals throughout follow-up. An HIV-resistance test should be done at diagnosis because the overall

Recommended Laboratory Tests for Newly Diagnosed HIV Infection*

- HIV tests: HIV serology; CD4 cell percentage and absolute number (requires concomitant CBC and differential); plasma HIV RNA level; HIV genotype (resistance test)
- Possible additional HIV tests: HLA-B*5701 if considering abacavir; coreceptor tropism assay if considering CCR5 entry inhibitor
- Other key tests: CBC with differential; serum chemistries to include measurement of electrolytes, renal and hepatic function, fasting blood glucose or hemoglobin A_{1c} level, fasting lipid level, and vitamin D level and complete urinalysis
- Co-infection and comorbidity tests: Screening for tuberculosis by purified protein derivative or interferon-y-release assays (QuantiFERON [Qiagen] or T-SPOT [Oxford Immunotec]) and, if positive, chest radiography; screening for syphilis, chlamydia, and gonorrhea; screening for viral hepatitis (hepatitis B surface antigen and antibody, hepatitis B core antibody, hepatitis A IgG, hepatitis C antibody); cervical Papanicolaou (Pap) test, and anal Pap test if indicated
- Possible additional co-infection and comorbidity tests: Pregnancy test in women of childbearing age before starting or changing antiretroviral therapy; total and free testosterone in men with fatigue, weight loss, depression, loss of libido, absence or diminished frequency of erection on awakening, erectile dysfunction, or evidence of reduced bone mineral density; testosterone level in women with loss of libido; glucose-6-phosphate dehydrogenase for persons of Mediterranean ancestry who may have absolute enzyme deficiency; toxoplasma IgG; cytomegalovirus IgG, varicella-zoster IgG in persons without a history of chickenpox or shingles; dual-energy x-ray absorptiometry for bone mineral density, as indicated
- Women should receive a Pap smear twice in the first year of care and then annually if initial results are negative. Although there is increased risk for anal dysplasia and carcinoma among MSM with human papillomavirus infection, anal cytologic screening is not yet the standard of care.
- CBC = complete blood count; MSM = men who have sex with men.
- * Adapted from reference 40.

rate of resistant infection is 10%-17% (33). Risk for anal dysplasia and carcinoma is increased among MSM with human papillomavirus infection. Although anal cytologic screening is not yet the standard of care, many HIV clinics offer such testing. Testing for a variety of co-infections and other causes of comorbidity is also indicated (see the Box: Recommended Laboratory Tests for Newly Diagnosed HIV Infection) (24).

Diagnosis and Evaluation... Diagnosis of established (chronic) infection by HIV-1/2 Ag/Ab screening is highly sensitive and specific, and this test is among the most reliable in medical practice. If acute HIV infection is suspected but results are negative or indeterminate, HIV quantitative RNA PCR assay should be used for diagnosis because seroconversion has not yet occurred; on retesting 4-12 weeks later, results of the standard serologic test will be positive. Patients often present late in the course of HIV disease (AIDS), and careful evaluation for OIs and cancer is important in this setting.

CLINICAL BOTTOM LINE

What are the goals of ART and the principles of treatment?

Because HIV cannot be cured, the primary goal of therapy is to reduce morbidity and prolong length and quality of life. This is accomplished by maximally and durably suppressing the HIV load

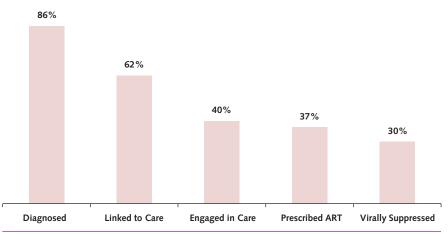
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Prognosis in HIV-1 infection predicted by the

Figure 2. Care continuum for the 1.2 million persons in the United States who live with HIV.



Adapted from reference 36. ART = antiretroviral therapy.

below the limit of detection (currently <20 copies/mL, or "undetectable" in common parlance) and improving immune function by increasing the CD4 cell count. This goal was once limited to previously untreated patients but now also applies to treatmentexperienced patients with drug resistance and/or intolerance. Increasingly better-tolerated drugs that are highly active against multidrug-resistant HIV are available. Achieving these goals requires individualization of therapy and encouragement of patients to adhere to treatment; it also has the public health benefit of preventing transmission to sex partners and neonates (vertical transmission) (34, 35). The care continuum for people living with HIV in the United States is shown in Figure 2 (36).

The START (Strategic Timing of Antiretroviral Treatment) study was the first large, international, randomized clinical trial showing that earlier treatment can decrease serious AIDS events (tuberculosis, Pneumocystis pneumonia, and AIDS-related cancer) as well as serious non-AIDS-defining events (other types of cancer, cardiovascular disease, and renal and liver disease) and death (36).

The cornerstone of HIV treatment is the use of multiple agents directed against different steps in the HIV life cycle, to both in-

crease the effectiveness of treatment and prevent or delay emergence of resistance mutations. Typically, this is a combination of 3 drugs from at least 2 of 6 current drug classes. Maximum suppression of virus replication to undetectable levels ("virologic success") in a treatment-naive patient usually occurs in the first 4-24 weeks of treatment. Predictors of virologic success include regimen potency, lower baseline viral load, higher baseline CD4 cell count, rapid response of viremia to treatment, and adherence to therapy (24). The vast majority of patients can achieve this goal, although success rates in clinical practice tend to be lower than the approximate 85%-90% seen in clinical trials. "Virologic failure" is defined as repeated measures of viral load greater than 200 copies/ mL; repeated measures are key in determining treatment failure because some patients may have transient viral load increases, known as "blips." These individuals may then resuppress without any clinical consequences, resistance development, or change in ART. Most blips are small (50-100 copies/mL), and multiple studies have reported that they are relatively common, occurring in 20%-60% of patients (37, 38).

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Treatment is lifelong, and interruptions should be assiduously avoided. Both randomized and cohort studies have shown that interrupting therapy not only portends a poorer outcome for HIV disease but also increases risk for non-HIV-associated end organ disease (cardiac, renal, hepatic) and cancer (33). This morbidity may be due in part to inflammation that results from chronic, lowlevel viremia even when infection is well-controlled.

Prevention of transmission is another goal of treatment: By decreasing the viral load in blood and genital secretions, treatment reduces infectiousness to others (35).

The HPTN 052 trial demonstrated a 93% reduction in HIV transmission among serodiscordant couples when the HIV-infected partner received ART and was virologically suppressed (35). This study established the concept of "treatment-asprevention"-the goal of improving the "cascade of care" so that as many HIV-infected persons as possible are virologically suppressed to greatly reduce the likelihood of infecting others.

Treatment-as-prevention is critical to containing the HIV epidemic because an effective vaccine remains elusive after more than 30 years of investigation.

What should guide the selection of ART?

The U.S. Public Health Service treatment guidelines classify combination regimens as "recommended," "alternative," and "other" for nonpregnant adolescents and adults and "preferred" and "alternative" for pregnant women (24). Choosing among them is a matter of balancing drug susceptibility, convenience (pill burden, dosing frequency, food requirements, use of acid suppressants), potential adverse effects and drug interactions, adherence potential, and patient desire (see the **Box:** Treatment for Adults and Pregnant Women) (24). Other factors to consider during selection of an initial regimen include pregnancy or the potential to become pregnant and comorbid conditions (cardiovascular disease, drug dependence, liver or renal disease, psychiatric condition, hepatitis B or C, tuberculosis). Alternative regimens are chosen on the same basis when the preferred approaches are not effective, when they have limitations for certain populations, or when there are fewer supporting data than for the recommended regimens. "Other" regimens, when compared with recommended or alternative regimens, have decreased virologic activity, limited supporting data in large comparative trials, poorer tolerance and more toxicity, higher pill burden, increased potential for drug interaction, or limitations in certain populations.

All antiretrovirals have the potential for short- and long-term adverse effects; the first few weeks are generally the most difficult. Subjective adverse effects usually improve with time. With current well-tolerated regimens, many patients do not have any adverse effects.

How should clinicians monitor patients receiving ART?

The frequency of evaluation should be driven by disease stage and response to therapy.

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^{37.} Lee PK, Kieffer TL, Siliciano RF, Nettles RE. HIV-1 viral load blips are of limited clinical significance. J Antimicrob Chemother. 2006;57:803-5. [PMID: 16533823]

^{38.} Nettles RE, Kieffer TL, Kwon P, Monie D, Han Y, Parsons T, et al. Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART. JAMA. 2005; 293:817-29. [PMID: 15713771]

Treatment for Adults and Pregnant Women*

Recommended for nonpregnant adults

INSTI-based:

- DTG/ABC/3TC.
- DTG + TDF/FTC or TAF/ FTC
- EVG/c/TAF/FTC
- EVG/c/TDF/FTC
- RAL + TDF/FTC or TAF/ FTC

PI-based: DRV/r (once daily) + TDF/FTC or TAF/FTC

Preferred for pregnant women

PI-based:

- ATV/r + ABC/3TC or TDF/ FTC or TDF/3TC
- DRV/r (twice daily) = ABC/3TC or TDF/FTC or TDF/3TC

INSTI-based: RAL + ABC/3TC or TDF/FTC or TDF/3TC

3TC = lamivudine; ABC = abacavir; ATV = atazanavir; c = with cobicistat for pharmacokinetic boosting; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; PI = protease inhibitor; r = with ritonavir for pharmacokinetic boosting; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

* Adapted from reference 24. Italics indicate coformulation of 2 or 3 drugs as a single tablet. ABC must not be used in patients with positive results on HLA-B*5701 testing because it indicates potential for hypersensitivity reaction. Results should be reviewed before the drug is started

Viral load should be measured 2-8 weeks after therapy is initiated to reassure both the physician and patient that the infection is responding and that the patient is adherent. Viral load and

CD4⁺ cell counts are both important prognostic indicators and key means of monitoring health. They disclose different aspects of the patient's health status and thus have complementary value. The viral load measures how well HIV replication is being suppressed, but it is important for patients to understand that "undetectable" (viral load below the assay's limit of detection) does not mean "cured." The CD4⁺ cell count and percentage reflect the restoration of immune function as measured by recovery of T-helper cells, but an increase in CD4⁺ cells–even to normal levels-does not indicate complete restoration of immunocompetence because there are other HIV-associated immune defects that are not measured routinely. The CD4 percentage is a better tool to monitor long-term response because it is measured directly, whereas the total CD4 cell count is derived from the concurrent complete blood count and differential and thus can vary widely, even on the same day.

In general, asymptomatic persons should have interval testing of markers (CD4 cell count, viral load) every 3-6 months (30). However, after 2 years of therapy with consistently suppressed viral loads and clinical stability, testing and visits every 6 months and annual checks of the CD4 cell count are usually adequate. Standard laboratory tests (urinalysis, renal and hepatic function, and lipid and glucose levels) should be repeated at similar intervals, depending on baseline values, drug regimen, and comorbidities.

In patients who are symptomatic at entry to care, monitoring certain clinical variables is useful to reassure both the patient and the physician. These include weight gain, increased energy level, resolution of minor skin problems and thrush, and improvement in other signs and symptoms.

What other management strategies should be incorporated into care?

With prolonged survival now the expectation (39), all routine preventive and health maintenance strategies for adults and adolescents are warranted. These include appropriate immunizations (with special limitations on live vaccines based on CD4 cell count); smoking cessation; control of hypertension and hyperlipidemia; minimizing cardiovascular risk factors by regular exercise and a nutritious diet; preventing obesity; evaluating at-risk patients for decreased bone mineral density; and screening for cancer (cervical, anal, breast, colon, prostate) as well as screening for infectious diseases as appropriate, including tuberculosis, hepatitis B, and hepatitis C. There are no formal recommendations for yearly anal Pap screening; however, the CDC and the HIV Medicine Association state that anal cytologic screening in HIV-infected MSM may become a useful preventive measure and anal Pap tests should be considered (40). The AIDS Institute of the New York State Department of Health has published guidelines for yearly screening for MSM, women with a history of cervical cancer, and persons with a history of anogenital warts (41).

Aside from ART, what approaches are appropriate for prevention and treatment of OIs and other infections?

Initiation of prophylaxis for OIs is determined by the absolute CD4 cell count. As discussed, HIV-infected patients are vulnerable to AIDS-defining OIs, such as *Pneumocystis* pneumonia, as their CD4 counts approach and

decrease below 200 cells/mL. As the CD4 count decreases below 75 cells/mL, the risk extends to include OIs associated with endstage AIDS, such as disseminated *Mycobacterium avium* complex and cytomegalovirus retinitis. Conversely, once a patient's CD4 count is sustained above 200 cells/mL for at least 3 months, primary prophylaxis as well as long-term maintenance therapy for various OIs ("secondary prophylaxis") can safely be discontinued (30).

Which immunizations are indicated?

Persons with HIV should receive vaccination for pneumococcal disease when they are initially diagnosed. They should also receive the routine vaccinations recommended for all adults; however, some vaccines should not be given when the CD4 count is below 200 cells/mL, and some need to be repeated (see the **Box:** Recommended Immunizations for HIV-Infected Adults) (24).

How should clinicians counsel patients to decrease risk for transmission?

At the initial visit and subsequent intervals, plans for conception must be discussed with both men and women. HIV-infected persons who plan to have children should be counseled about safe conception and prevention of vertical transmission. All HIVinfected persons should use male or female condoms as appropriate for barrier protection; abstinence may be an option for some. Seronegative partners of infected persons should be routinely tested for HIV every 6-12 months and counseled to seek immediate care if they develop symptoms of acute seroconversion, such as a mononucleosis- or flu-like illness (23).

- 39. Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, et al; Agence Nationale de Recherches sur le Sida et les Hepatites Virales (ANRS) CO8 APROCO-COPILOTE Study Group. HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. J Acquir Immune Defic Syndr. 2007;46:72-7. [PMID: 17621240]
- 40. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Accessed at http: //aidsinfo.nih.gov /contentfiles/lvguidelines /adult_oi.pdf on 16 March 2017.
- 41. New York State Department of Health. HIV clinical resource: human papillomavirus (HPV). Accessed at www.health.ny.gov/diseases/aids/providers/standards/support_services_providers/docs/primary_care.pdf on 17 March 2017.

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Recommended Immunizations for HIV-Infected Adults*

Streptococcus pneumoniae:

13-valent conjugate (PCV13)—all patients at entry to care; when CD4 count >200 cells/mL, then 23-valent polysaccharide (PPV23) at least 8 weeks after receiving PCV13; then single PPV23 in 5 years and again at age 65 years, not to exceed 3 lifetime doses

Influenza vaccine (inactivated):All patients, annually

Hepatitis A vaccine series: All MSM; patients with or at risk for chronic hepatitis B and/or C infection, such as those who inject drugs; and patients with chronic liver disease

Hepatitis B vaccine series: All susceptible patients. Check hepatitis B surface antigen 6 months after third dose and revaccinate as needed (consider using double dose for repeated vaccination)

Human papillomavirus series: All patients through age 26 years; 3 doses

Varicella vaccine series: All susceptible patients with CD4 count >200 cells/mL

Tetanus/diphtheria/pertussis vaccine: All patients; then boost with tetanus/diphtheria vaccine every 10 years

Meningococcus: All MSM. If never vaccinated, use 2-dose primary series of MenACWY conjugate vaccine at an interval of at least 2 months, and revaccinate every 5 years

Other vaccines: Other vaccines should be administered according to ACIP guidelines. Live viral vaccines should not be given to HIV-infected patients with CD4 count <200 cells/mL

ACIP = Advisory Committee on Immunization Practices; MSM = men who have sex with men.

* Adapted from reference 40. The most up-to-date information can be found at the ACIP's Web site: www.cdc.gov /vaccines/hcp/acip-recs /vacc-specific/index.html.

Pregnant HIV-positive women should be given combination ART at the time of HIV diagnosis and during pregnancy, with intravenous zidovudine administration during labor and delivery and prophylactic medication given to the neonate for the first 4-6 weeks. Currently recommended ART for pregnant women is summarized in the **Box** (Treatment for Adults and Pregnant Women). In the United States, breastfeeding should be avoided because formula is readily available and breast milk can transmit HIV. Vaginal delivery is safe for women with a prenatal viral load less than 1000 copies/ mL; women with higher viral loads should have a cesarean section. This approach has decreased vertical transmission of HIV to fewer than 1% of babies born to infected mothers in the United States (25, 42). The rate of congenital malformations as captured by the Antiretroviral Pregnancy Registry does not differ from that of the background population rate; however, some women may prefer to delay ART until the second trimester.

At every visit, the physician should ask about symptoms of STDs and discuss risk-reduction behaviors and strategies. PWIDs should be counseled never to reuse or share syringes, needles, other equipment, or water used for drug preparation. Equipment that is planned to be shared should be cleaned with 10% bleach. Use of sterile water or water from a reliable source is preferred for drug preparation. PWIDs should clean the injection site with a new alcohol swab and not lick the needle. PWIDs should be referred to syringe services programs, if available.

The CDC recommends administration of triple-drug therapy for 4 weeks to health care and laboratory workers and all other per-

^{42.} Thea DM, Steketee RW, Pliner V, Bornschlegel K, Brown T, Orloff S, et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. New York City Perinatal HIV Transmission Collaborative Study Group. AIDS. 1997;11: 437-44. [PMID: 9084790]

sons who have had penetrating injury, such as a needlestick from an HIV-positive patient or a patient of unknown serostatus (12).

What are the special gynecologic and obstetric considerations for women diagnosed with HIV?

Because gynecologic problems are common and cervical carcinoma is an AIDS-defining condition, complete gynecologic and obstetric history, comprehensive gynecologic assessment at entry to care, interval examination, and Pap smears are indicated. Pregnancy does not accelerate the course of HIV disease, and vertical transmission can be prevented. All pregnant women should ideally be comanaged with an obstetrician experienced in HIV disease and have viral load testing at regular intervals throughout the pregnancy to guide the choice of delivery method (25).

When should an HIV specialist be consulted?

An HIV specialist should be consulted for persons with a late presentation in order to start ART

and prevent, diagnose, and manage Ols and opportunistic cancers; a baseline genotype indicating drug-resistant HIV; persistently elevated viral loads indicating virologic failure; clinical deterioration regardless of virologic response; the potential for antiretroviral toxicity that affects health, quality of life, and functioning and/or adherence; potential drug-drug interactions necessitating a change in therapy; and ART begun during treatment of an acute OI or other illness requiring hospitalization. A specialist should also be consulted if the primary provider is not comfortable with the patient's management for any reason. Although a recent study has shown benefit to starting ART during therapy for most acute Ols, experience managing multiple potential drug interactions and toxicities is required in this setting as well as to determine the optimal timing of ART initiation to avoid immune reconstitution syndrome, indicated by acute symptoms or frank illness due to the rapid return of immune competence (24, 43).

Treatment... ART is the cornerstone of HIV care and should be initiated at or near diagnosis and as soon as the patient understands what is involved and indicates readiness. There are 6 preferred therapeutic options and several alternatives, which allows individualization of treatment. Short- and long-term adverse effects and drug-drug interactions should be anticipated and managed proactively. Prophylaxis and treatment of Ols are integral to HIV care and are determined by the absolute CD4 cell count. With increased life expectancy, health care maintenance and prevention of common age-related illnesses, such as cardiovascular disease, have become important. Immunization to prevent other infections is essential. HIV-infected women should not be discouraged from having children; with ART, healthy pregnancies and prevention of vertical transmission are possible.

CLINICAL BOTTOM LINE

43. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, 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. [PMID: 19440326]

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Practice Improvement

What measures do U.S. stakeholders use to evaluate the quality of care for HIV-infected patients?

The National HIV/AIDS Strategy has defined the following goals: 1) to reduce the number of persons who become infected, 2) to increase access to care and optimize health outcomes for persons living with HIV, and 3) to reduce HIV-related health disparities (39). The Health Resources and Services Administration has developed the HIVQUAL-US program to facilitate quality improvement through measurement of key quality indicators described for the entire range of HIV care (44).

What do professional organizations recommend regarding the care of HIV-infected patients?

There is a wealth of resources from professional organizations, such as the HIV Medicine Association of the Infectious Diseases Society of America (which last updated its evidence-based primary care guidelines for HIVinfected persons in 2013) (45) and the American Academy of HIV Medicine, which periodically updates its Fundamentals of HIV Medicine (46). Several guidelines from the U.S. Public Health Service are listed in the Tool Kit. The recommendations contained in this overview largely reflect these guidelines, with some amendments by the authors based on clinical experience.

- 44. HIVQUAL_US. Accessed at http://hivqualus.org on 17 March 2017.
- 45. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA; Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;58:1-10. [PMID: 24343580]
- 46. Hardy WD, ed. Fundamentals of HIV Medicine New York: Oxford Univ Pr: 2017.

In the Clinic Tool Kit

Management of Newly Diagnosed HIV Infection

Guidelines

https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html

Vaccine guidelines from the Advisory Committee on Immunization Practices.

https://www.cdc.gov/hiv/guidelines/testing.html Centers for Disease Control and Prevention (CDC) recommendations for HIV testing of adolescents, adults, and pregnant women.

https://www.cdc.gov/hiv/risk/pep/index.html 2016 guidelines on pre- and posteexposure prophylaxis from the CDC.

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/

Guidelines for adults and adolescents from the National Institutes of Health (NIH).

https://aidsinfo.nih.gov/guidelines/html/3/perinatal -guidelines/0/#

Guidelines for perinatal care and prevention of vertical transmission from the NIH.

https://aids.nlm.nih.gov/

HIV-related topics from the NIH.

www.who.int/hiv/pub/guidelines/en/ Guidelines from the World Health Organization,

Guidelines from the World Health Organization, including self-testing and partner notification.

Patient Information

https://www.cdc.gov/hiv/basics/index.html HIV basics from the CDC.

https://www.aids.gov/hiv-aids-basics/ Information on federal HIV programs, funding, and services for newly diagnosed patients.

https://www.cdc.gov/hiv/pdf/prep_gl_patient _factsheet_acute_hiv_infection_english.pdf Information from the CDC.

www.mayoclinic.org/diseases-conditions/hiv-aids/basics/definition/con-20013732

Many useful pages from the Mayo Clinic for the patient or health care provider concerning HIV.

http://hivinsite.ucsf.edu/InSite?page=li-04-22 Comprehensive information from the University of California, San Francisco.

www.aidsmap.com/translations/es/Folletos-Booklets/page/1412531/

Booklets to help patients with HIV in several languages.

Patient Information

WHAT YOU SHOULD **KNOW ABOUT NEWLY DIAGNOSED HIV INFECTION**

What Is HIV?

HIV (human immunodeficiency virus) makes it difficult for your body to fight infection. When the immune system becomes badly damaged, HIV develops into AIDS (acquired immunodeficiency syndrome). There is no cure for HIV or AIDS, but highly effective treatment is available and, if used regularly, can permit people of all ages with HIV infection to live a normal lifespan. Treatment of a pregnant woman with HIV infection prevents her baby from becoming infected.

HIV is passed through bodily fluids, such as blood, semen, and breast milk, in the following ways:

- By having anal and/or vaginal sex with an HÍVinfected person, especially without using a condom

 By sharing needles with an HIV-infected person
- By being stuck by a needle or sharp object contaminated with HIV
- From mother to child during pregnancy, birth, or breastfeeding.

What Are the Warning Signs?

Acute HIV occurs 2 to 4 weeks after you become infected. Symptoms may be mild, and you may not even notice them. Common symptoms are similar to the flu and may include fatigue (tiredness); sore throat; swollen glands in the neck, armpits, and groin; fever; and rash.

Chronic HIV infection is the second stage, during which symptoms may not appear again for many years. When they do, they may include swollen lymph nodes, shingles, and anemia or low platelets. Vaginal yeast infections may keep coming back. However, these problems also occur in people who do not have HIV infection.

Who Should Be Tested?

Health care professionals should offer HIV testing to anyone who requests it, and everyone should be tested at least once. All pregnant women should also be offered testing, usually twice during the pregnancy. If you are at high risk for HIV infection, you should be offered testing at least once a year. People who are at high risk for getting HIV are:

- Men who have sex with men
- Men and women who have unprotected sex with many people
 • Persons who currently or in the past have used
- injection drugs
- Men and women who pay or receive money for sex
- Men or women who receive anal sex
- People being treated for other sexually transmitted diseases (STDs)
- People who were treated for hemophilia or had blood transfusions between 1978 and 1985 in



the United States or in countries where donated blood has not been screened for HIV

People with high-risk sex partners.

You should talk to your doctor about taking HIV preexposure prophylaxis (PrEP) if you are not infected with HIV but are at high risk. PrEP involves taking HIV medicines every day and is highly effective. Whether to use postexposure prophylaxis (PEP) should be discussed with your doctor if a high-risk exposure occurs, such as a condom breaking during sex.

How Is It Diagnosed?

HIV can be diagnosed through blood and saliva tests, most of which can detect HIV between 2 and 12 weeks after infection.

How Is It Treated?

HIV is controlled by a combination of at least 3 drugs, known as antiretroviral therapy (ART). You must take them for the rest of your life to stay healthy.

Talk to your doctor about other things you can do to help stay healthy, such as eating nutritious foods and getting all recommended immunizations.

Questions for My Doctor

- How will HIV affect my day-to-day life?
- What is the best treatment for me?
- Does the treatment have side effects?
- How can I avoid spreading HIV to others?
- How active can I be?
- Can I have sex despite the infection?
- How often should I see my doctor?
- Can HIV be prevented?If I think I've been exposed to HIV, what should I do?

For More Information



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MedlinePlus

https://medlineplus.gov/hivaids.html **Centers for Disease Control and Prevention**

www.cdc.gov/actagainstaids/basics U.S. Department of Health and Human Services

www.aids.gov/hiv-aids-basics