Annals of Internal MedicineT

# In the ClinicT

Prevention and Initial Management

of HIV Infection

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ince July 2017, when In the Clinic last addressed management of HIV infection, there have been meaningful improvements in

our ability to prevent HIV and to manage patients living with HIV. New approaches to preexposure prophylaxis and more effective treatments have made the elimination of HIV infection a feasible goal. The federal “Ending the HIV Epidemic” initia- tive aims at a 90% reduction in new HIV diagnoses by 2030. This article provides updated information on how clinicians should use these improvements to manage their patients who are at risk for HIV infection or are newly diagnosed with HIV.

CME/MOC activity available at Annals.org.

Screening and Prevention

Other Management

Strategies Initial Evaluation Antiretroviral Therapy Practice Improvement

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In 2019, the U.S. Department of Health and Human Services implemented the “Ending the HIV Epidemic” (EHE) initiative, with the 2-step goal of reduc- ing the number of new infections by 75% by 2025 and 90% by 2030. This initiative has 4 pillars: identifying all HIV-infected persons, starting them quickly on suppressive treatment, pre- venting new infections, and respond- ing promptly to new outbreaks. All

## Screening and Prevention

Who should be screened for HIV? Despite a sharp decrease in HIV/AIDS cases and deaths since the advent of highly active antiretroviral therapy (ART) in the mid-1990s, 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, 13% of whom are unaware of their infection (1, 2). The

U.S. epidemic continues to dispropor- tionately affect Black/African American and Latinx communities—especially young men who have sex with men— and others who have limited access to health care, especially in the Southeast. With the introduction of syringe services programs in the 1990s, HIV incidence among people who inject drugs decreased progressively until stalling around 2013–2014 and then increasing by 11% from 2016 to 2018 (3, 4) as a consequence of the current injection drug use epidemic.

In 2006, the CDC recommended that everyone between the ages of 13 and 64 years who has ever been sexually active should be tested for HIV on an opt-out basis at least once as part of routine health care (5). “Opt-out” means that permission for HIV testing is included in the general consent for medical care unless the patient explic- itly declines after being notiﬁed that testing will include an HIV test. Written consent and pretest and posttest coun- seling were eliminated by the 2006 rec- ommendations as required elements

primary care providers and subspecial- ists have an essential role in the EHE ini- tiative, starting with provision of uni- versal opt-out screening for HIV and effective linkage to treatment. Pre- vention and treatment advances have shifted HIV to a model of chronic care management, most of it well within the scope of primary care, except for per- sons with very advanced disease and antiretroviral drug resistance, who need care from an HIV specialist.

of HIV testing. Those at increased risk for HIV infection should be tested annually and more often as indicated, including men who have sex with men; men and women who are having unprotected sex with multiple partners, have a sexually transmitted infection, or have a partner with a sexually transmit- ted infection; people who currently inject drugs or have done so in the past; people who engage in transac- tional sex (trading sex for money, drugs, or other commodities); people with past or present sex partners who are living with HIV, are bisexual, or inject drugs; and people who engage in receptive anal sex, regardless of sex- ual orientation. Screening should also be a routine part of prenatal care. Persons who request an HIV test de- spite reporting no risk factors may also be considered at increased risk be- cause they may have risk factors that they are unable or unwilling to dis- close. Anyone who asks for an HIV test should receive one.

Also, because many adults continue sexual activity past age 64 years and 51% of HIV-infected persons are now aged 50 years or older, testing *all* sexu- ally active adults, regardless of age, is appropriate (6). These recommenda- tions are based partially on the fact that risk-based testing has not been effec- tive because providers seldom ade- quately assess risk, approximately 10% to 25% of persons with undiagnosed HIV are unaware of any risk factors or

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are uncomfortable disclosing them, and almost half of patients are identi- ﬁed late in the disease course, when they can no longer receive the maxi- mum beneﬁt from ART (7).

In addition, all persons in the following subgroups should be routinely scree- ned for HIV: those diagnosed with and initiating treatment for tuberculosis, hepatitis B, or hepatitis C; survivors of sexual assault; all women with un- known HIV serostatus who present in labor; and infants exposed to HIV in utero (8, 9). Persons whose blood or body ﬂuid is the source of an occupa- tional exposure should be informed of the incident, and a request should be made for HIV testing of the source patient. Assessment of potential occu- pational exposure to HIV should follow the U.S. Public Health Service guide- lines, including postexposure prophy- laxis if indicated (10, 11).

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

According to the 2019 Association of Public Health Laboratories revised HIV testing algorithm, screening for HIV

starts with the “fourth-generation” HIV- 1/2 combination antigen/antibody (HIV Ag/Ab) test (Figure 1) (12). The “eclipse period,” before viremia is de- tectable at day 5, means that HIV can- not be detected in the ﬁrst few days after exposure; by days 6 to 8, a nucleic acid ampliﬁcation test (NAAT), such as RNA polymerase chain reaction (PCR), can detect HIV viremia, and by days 13 to 20, viral p24 antigen can be detected (Figure 2). Although the “window period” before antibodies can be detected is typically 20 days for IgM and 30 days for IgG, the combined Ag/ Ab test can detect infection in as little as 10 days (13). A positive result is fol- lowed by a test to differentiate HIV-1 from HIV-2; HIV-2 is very unusual in the United States. The combined HIV Ag/ Ab test is the most accurate diagnostic test in medical use (>99.7% sensitivity and >99.3% speciﬁcity) and can iden- tify more than 80% of acute infections that would otherwise require NAAT conﬁrmation (13, 14). However, as with all screening tests, the predictive value of individual positive or negative results depends on local seropreva- lence (15, 16). Chronic HIV infection

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*Figure 1.* HIV testing algorithm.

**Fourth-generation HIV-1/2 Ag/Ab immunoassay**

**Reactive**

**HIV-1/2 either negative or indeterminate**

**HIV-1/2 antibody differentiation immunoassay**

**HIV-1 positive HIV-2 positive**

**Both HIV-1 and HIV-2 antibodies detected**

**HIV-1 negative HIV-2 positive**

**HIV-2 antibodies detected**

**HIV-1 positive HIV-2 negative**

**HIV-1 antibodies detected**

**HIV-1 NAAT**

**Undetected Negative for HIV-1**

**Detected Acute HIV-1 infection**

**Nonreactive**

**HIV-1 antigen and HIV-1/2 antibodies not detected**

**Occurs automatically**

Ag/Ab = antigen/antibody; NAAT = nucleic acid ampliﬁcation test.

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*Figure 2.* Timeline of HIV tests in acute infection.

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US and HIV-2 infected individuals from Ivory

**X 0 10 20 30 40 50 60 70 80 90**



**Eclipse period**

**RNA**

**IgG**

**p24**

**IgM**

**Days After Infection Disseminates**

**NAAT **

**p24/IgM/IgG sensitive**

**IgM/IgG sensitive ** **IgG sensitive ** **Western blot **

NAAT = nucleic acid ampliﬁcation test.

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12836626]

should not be diagnosed solely by an

HIV quantitative RNA PCR assay be- cause 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 set- ting of acute infection.

Several rapid tests have been approved for detection of HIV antibodies that can be performed on serum, plasma, saliva, or dried blood spots and can return results in under 20 minutes. Rapid tests are reliable for established infection once an anti-HIV IgG antibody response has fully developed but are not reliable for detection of recent (past month) ac- quisition. There is 1 U.S. Food and Drug Administration (FDA)–approved com- bined Ag/Ab rapid test (Abbott Determine HIV-1 Ag/Ab Combo) that can be used by trained professionals in outreach settings for persons who may not have access to testing in traditional health care settings (17), but it cannot differentiate HIV-1 from HIV-2. It uses a whole-blood ﬁngerstick sample, which is not as sensitive as laboratory-based plasma samples. All rapid test results

must be conﬁrmed with an FDA-

approved Ag/Ab immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen (18). A specialist should be consulted when serologic results are inconsistent.

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

Acute HIV infection (also termed “acute seroconversion syndrome”) is a nonspe- ciﬁc viral syndrome similar to mononu- cleosis, inﬂuenza, and hepatitis and typically includes the common features of fever, fatigue, myalgia, arthralgia, lymphadenopathy, pharyngitis, and rash. However, the range of possible presentations is wide and encompasses neurologic syndromes (meningitis, en- cephalitis, radiculopathy), hepatitis, and gastrointestinal symptoms. If the CD4 cell count drops precipitously below 200 cells/mL, the person may present with an opportunistic infection that is the hallmark of AIDS.

Approximately 40% to 90% of persons who have seroconverted have symp-

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toms, but not all seek medical care

(19). Acute HIV infection is often not recognized by primary care and emer- gency physicians because the symp- toms mimic those of other common, typically self-limiting viral illnesses (20). Because the viral load in plasma and genital secretions is very high, those with acute HIV have a high rate of trans- mission to others and thus play a dis- proportionate role in maintaining the epidemic (21). Early detection is key to increasing rapid uptake of ART, decreasing both morbidity and the likelihood of transmission to others. Thus, there is signiﬁcant individual and public health beneﬁt to diagnosing and treating as soon as possible (22). Because the combined Ag/Ab test result may be negative or indetermi- nate early in infection, acute HIV is diagnosed by a quantitative RNA PCR assay, which should be done in all patients with a negative Monospot test result (23). Proof of seroconversion typ- ically occurs 2 to 6 weeks after expo- sure, and 99.9% of persons have a positive combination Ag/Ab test result by 12 weeks (18). Because the risk for transmission is directly related to viral load, which is typically high in acute infection, patients with negative results on the combined Ag/Ab test who may be acutely infected should avoid sex until they are retested. Pregnant women who develop acute HIV infec- tion should be rapidly referred to an HIV specialist and an obstetrician expe- rienced in HIV disease for immediate ART (24, 25).

What is HIV preexposure prophylaxis, and what regimens are currently available?

Preexposure prophylaxis (PrEP) involves use of ART to prevent acquisi- tion of HIV by those who engage in high-risk behaviors. Despite PrEP being available since 2012, there is an enor- mous gap in its use: In 2019–2020, only 23% of persons with an indication for PrEP were taking it (26). One goal set by the EHE initiative is that at least 50% of people with an indication for PrEP

will have been prescribed it by 2030. However, considerable disparities in uptake exist. Based on recent surveil- lance data, PrEP coverage was 8% for Black and African American persons, 13.7% in the Latinx community, and 61.1% among White persons (26). Inequalities also exist for women at risk for HIV, with PrEP coverage at 9% ver- sus 25.8% for men (27). Barriers due to systemic racism, inadequate access to health care, and limited knowledge of the beneﬁts and safety of PrEP interact to create these disparities. Surveillance data from 7 U.S. cities from 2019 to 2020 showed that 91.7% of transgen- der women are aware of PrEP but only 31.9% are actively prescribed it (28). Despite their signiﬁcant risk for HIV, transgender women experience many barriers to HIV testing, prevention, and care, including inadequate income, housing instability, lack of health insur- ance, stigma, transphobia, and sys- temic racism, making access to PrEP difﬁcult. Research has shown that PrEP awareness and knowledge in people who inject drugs is low. However, even when there is awareness of PrEP, uptake is low in this high-risk population. In a survey of people who inject drugs where knowledge of and willingness to accept PrEP was higher (59%) than in prior studies, only 2% (11 of 469) were actually taking PrEP (29). Barriers to uptake in this population are similar to those for transgender women and also include involvement in the criminal jus- tice system, but the issue is complicated by lack of perception of HIV risk. Reaching these marginalized popula- tions requires research that addresses the intersectional nature of the barriers they face in accessing health care in general and PrEP speciﬁcally.

PrEP consists of 1 or 2 antiretroviral agents but not a complete regimen used to treat HIV. The combination of emtricitabine/tenofovir disoproxil fu- marate (F/TDF) was the ﬁrst FDA- approved medication for PrEP (in 2012), followed by combined emtricita- bine/tenofovir alafenamide (F/TAF) in

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2019. Both are approved for adults and adolescents weighing at least 35 kg. When taken as directed, PrEP is approx- imately 99% effective in reducing sex- ual transmission and 74% to 84% effective in reducing transmission in people who use injection drugs (30– 34). The U.S. Public Health Service recently updated its PrEP guidelines

(35). In 2019, PrEP was given a grade A recommendation by the U.S. Preventive Services Task Force for all people at risk for HIV acquisition. Identifying risk involves taking a sexual and drug use history; however, when patients request PrEP, it is important to consider that they may minimize risk factors due to stigma, and this should not prevent the clinician from initiating PrEP. Provision of PrEP does not require specialist ex- perience and can be readily integrated into general medical practice.

F/TDF is the best-studied form of PrEP and the only medication evaluated in heterosexual women, while TDF alone is the sole approach that has been eval- uated among people who inject drugs. Because F/TAF has only been studied in men who have sex with men and transgender women who have sex with men, FDA approval excludes women who have vaginal intercourse. All approaches to PrEP require exclusion of preexisting HIV because administra- tion of an incomplete regimen for

established HIV may lead to resistance. Testing for pregnancy and for other sex- ually transmitted infections—syphilis and urine, rectal, and pharyngeal specimens for gonorrhea and chlamydia—is also part of the routine evaluation. Before F/ TDF or F/TAF is prescribed, evaluation also includes 1) ascertaining hepatitis B status, as PrEP cessation may result in a ﬂare because these agents are also active against hepatitis B, and 2) ensur- ing that the patient has adequate renal function (an estimated creatinine clear- ance [eCrCL] >60 mL/min for F/TDF and >30 mL/min for F/TAF) (Table 1). Men who have sex with men and peo- ple who inject drugs should also be screened for hepatitis C with an anti- body test that, if positive, is automati- cally followed by a NAAT to ascertain active infection. Prescription of a daily tablet with a limit of 90 tablets helps ensure that the patient returns for quar- terly follow-up clinic or telemedicine vis- its for HIV testing, possible sexually transmitted infection testing, and assessment of tolerability and adher- ence. Renal function is assessed every 6 months for persons aged 50 years or older or those with an eCrCL below 90 mL/min and every 12 months for per- sons younger than 50 years and those with an eCrCL of 90 mL/min or higher. Adherence is essential, and protection is correlated with the tenofovir level achieved by taking at least 4 tablets per week. Alternative, event-driven dosing for F/TDF has been evaluated for adult

*Table 1.* Oral PrEP Laboratory Tests\*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Test* | *Initial Visit* | *Every 3 Months* | *Every 6 Months* | *Yearly* | *When Stopping PrEP* |
| HIV Ag/Ab and/or HIV-1 RNA | ✓ | ✓ | — | — | ✓ |

eCrCL ✓ — If age ≥50 y or eCrCL <90 mL/min at initiation

If age <50 y and ✓

eCrCL ≥90 mL/min at initiation

Syphilis ✓ MSM, TGW ✓ — MSM, TGW

Gonorrhea/chlamydia NAAT

* + MSM, TGW ✓ — MSM, TGW

Lipid panel (F/TAF) ✓ — — ✓ —

Hepatitis B serologic testing

Hepatitis C serologic testing

* + — — — —
  + — — MSM, TGW, PWID —

*Ag/Ab = antigen/antibody; eCrCL = estimated creatinine clearance; F/TAF = emtricitabine/tenofovir alafenamide; MSM = men who have sex with men; NAAT = nucleic acid ampliﬁcation test; PrEP = preexposure prophylaxis; PWID = people who inject drugs; TGW = transgender women.*

*\* Adapted from reference 35.*

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*Table 2.* CAB PrEP Laboratory Tests\*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *Test* | *Initial Visit* | *1-Month Visit* | *Every 2 Months* | *Every 4 Months* | *Every 6 Months* | *Every 12 Months* | *When Stopping CAB* |
| HIV-1 RNA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Syphilis | ✓ | — | — | MSM and TGW only | Heterosexual women and | ✓ | MSM and TGW only |

men only

Gonorrhea/chlamydia NAAT

✓

—

—

MSM and TGW only

Heterosexual women and men only

✓

MSM and TGW only

Hepatitis B serologic testing†

Hepatitis C serologic testing

* + - — — — — — —
    - — — — — ✓ —

*CAB = cabotegravir; MSM = men who have sex with men; NAAT = nucleic acid ampliﬁcation test; PrEP = preexposure prophylaxis; TGW = transgender women.*

*\* Adapted from reference 35.*

*† Hepatitis B serologic testing is useful for vaccine administration, but CAB has no hepatitis B activity.*

men who have sex with men who do not have chronic hepatitis B: 2 tablets 2 to 24 hours before sex, followed by 1 tablet 24 and 48 hours after the initial dose. The most common adverse effects are mild headache and nausea; the most concerning are renal dysfunc- tion and decrease in bone mineral den- sity, both of which typically resolve after discontinuation.

The long-acting injectable integrase in- hibitor cabotegravir (CAB LA, 600 mg) was found to be superior to F/TDF in 2 studies, one in men who have sex with men and transgender women who have sex with men and the other in hetero- sexual women, with reductions of 63% and 89%, respectively, in HIV transmis- sion compared with F/TDF (36–38). In both studies, CAB LA was safe, with few differences in grade 2 events compared with F/TDF (36, 38). CAB LA is given ev- ery 2 months as a 3-mL gluteal injection and must therefore be administered in a health care setting. The same screen- ing for other sexually transmitted infec- tions should be performed when CAB LA is used for PrEP. Screening for hepa- titis B is useful for vaccine administra- tion, but because CAB LA has no anti– hepatitis B activity, there is no concern about ﬂare on PrEP discontinuation, and renal function does not need to be monitored (Table 2).

It is important to note that ART used as PrEP when a person has early HIV

infection may alter the dynamics of vire- mia and the immune response in ways that can affect how traditional HIV screen- ing algorithms perform, as highlighted by a statement from the Association of Public Health Laboratories (39). Because long-acting agents for PrEP extend the period during which a person who acquires HIV is vulnerable to the develop- ment of resistance, the updated CDC guidelines recommend screening for inci- dent HIV with a nucleic acid–based assay instead of the combined Ag/Ab test to identify breakthrough infections as quickly as possible (Table 2).

What are potential tools for PrEP that are currently in development?

A potential tool for PrEP is a ﬂexible silicone vaginal ring that contains the nonnucleoside reverse transcriptase in- hibitor dapivirine and is inserted monthly. Dapivirine is released slowly to protect against HIV at the site of potential infection. The phase 3 Ring and Aspire studies achieved HIV risk reduction of 35% and 27%, respec-

tively (40, 41). Islatravir, a nucleoside reverse transcriptase translocation in- hibitor with an extremely long half-life (42), is being studied as a single monthly oral dose in ongoing phase 3 trials, and subdermal implants are in the early stages of development (43). Broadly neutralizing HIV-1 monoclonal antibodies are another potential tool for future PrEP (44).

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## Initial Evaluation

**CLINICAL BOTTOM LINE**

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 at least annually and as indicated. Sexually active men who have sex with men can be retested as frequently as every 3 to 6 months, and persons receiving PrEP should be tested every 3 months. All pregnant people should be offered opt-out HIV testing and receive immediate treatment if results are positive to prevent vertical trans- mission. Careful evaluation with a detailed sexual and drug use history must be done before screening to identify which HIV tests should be performed.

What laboratory tests and evaluations are indicated in a patient with newly diagnosed HIV?

Once HIV is conﬁrmed by the combined Ag/Ab assay, the next step is to obtain a baseline HIV viral load (quantitative RNA PCR), a CD4 (helper T-cell) count and percentage, and an HIV resistance test (see the Box: Recommended Laboratory Tests for Newly Diagnosed HIV Infection). The viral load indicates

Recommended Laboratory Tests for Newly Diagnosed HIV Infection\*

*HIV tests*: HIV combined Ag/Ab testing (automatically distinguishes HIV-1 from HIV-2); CD4 cell percentage and absolute number (requires concomitant complete blood count and differential); plasma HIV RNA level; HIV genotype for resistance

*Possible additional HIV tests*: HLA-B\*5701 if considering abacavir; coreceptor tropism assay if considering CCR5 entry inhibitor; genotype for integrase resistance depending on exposure

*Other key tests*: serum chemistries to include measurement of electrolytes, renal and hepatic function, fasting blood glucose or hemoglobin A1c level, fasting lipids, and vitamin D level; complete urinalysis

*Co-infection and comorbidity tests*: Screening for tuberculosis by puriﬁed protein derivative or interferon-c–release assays (QuantiFERON [QIAGEN] or T-SPOT.*TB* [Oxford Immunotec]) and, if positive, chest radiography; screening for syphilis, chlamydia, and gonorrhea; screen- ing for viral hepatitis (hepatitis B surface antigen and antibody, hepatitis B core antibody, hepatitis A IgG, hepatitis C antibody with reﬂex to quantitative RNA); cervical Papanicolaou (Pap) test; anal Pap test if indicated

*Possible additional co-infection and comorbidity tests*: Pregnancy test in women of child- bearing potential before starting or changing ART; 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 with no history of chickenpox or shingles; dual-energy x-ray absorptiometry for bone mineral density as indicated

*\* Adapted from reference 24.*

the activity of the infection, and the CD4 testing reﬂects immune system damage. Both are used not only to stage a patient's disease but also as key indicators of response to treat- ment. An HIV genotype detects muta- tions in the viral reverse transcriptase and protease enzymes associated with antiretroviral resistance; a sepa- rate test for integrase mutations can be done as indicated.

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Which immunizations are indicated? Persons with HIV should receive vacci- nation for pneumococcal disease when they are diagnosed. They should also receive the routine vaccinations recommended for all adults; however,

**CLINICAL BOTTOM LINE**

Initial Evaluation... Before ART is started, initial laboratory tests must be performed and immunization status must be assessed in all newly diagnosed persons. These results are used to stage HIV disease, evaluate potential ART toxicity, and ensure all needed vaccinations are given.

Recommended Immunizations for Adults With HIV\*

*Streptococcus pneumoniae*: Three vaccine options: 1) 13-valent conjugate (PCV13) *or*

15-valent conjugate (PCV15) for all patients at entry into care; 2) when CD4 count >200 cells/mL, 23-valent polysaccharide (PPSV23) ≥8 weeks after receiving PCV13 or PCV15, then single PPSV23 dose in 5 years and again at age 65 years, not to exceed 3 lifetime doses; or 3) single dose of 20-valent conjugate (PCV20)

*Inﬂuenza vaccine (inactivated)*: All patients, annually

*COVID-19*: All patients

*Hepatitis A*: All men who have sex with men; patients with or at risk for chronic hepatitis B and/ or C infection, such as those who inject drugs; patients with chronic liver disease; patients with no housing or unstable housing

*Hepatitis B*: All susceptible patients; for 2-dose adjuvanted regimen, check hepatitis B surface antibody 6 months after second dose and revaccinate as needed

*Human papillomavirus*: All patients through age 26 years

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

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

*Meningococcus*: All men who have sex with men; if never vaccinated, use 2-dose primary series of MenACWY conjugate vaccine at an interval of ≥2 months, and revaccinate every

5 years

*Herpes zoster*: 2 doses in all patients; consider delaying until CD4 count >200 cells/mL

*Other vaccines*: Administer 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.*

*\* The most up-to-date information can be found at the ACIP website* [*(www.cdc.gov/*](http://www.cdc.gov/) *vaccines/hcp/acip-recs/vacc-speciﬁc/index.html).*

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

Because HIV cannot yet be cured, the primary goal of therapy is to reduce morbidity, prolong survival, and increase the quality of life. This is accom- plished by maximally and durably sup- pressing the HIV load below the limit of

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 Adults with HIV) (45).

## Antiretroviral Therapy

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 even to treatment-experienced patients with drug resistance. Increasingly convenient

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and better-tolerated drugs that are highly active against multidrug-resistant HIV are available, and several complete well-tolerated regimens are now avail- able as a single daily tablet. As a result, treating a patient with newly diagnosed HIV is well within the scope of practice for a general internist.

Treatments for Adults and Pregnant People\* Recommended for nonpregnant adults

Integrase strand transfer inhibitor–based:

* Bictegravir/tenofovir alafenamide/emtricitabine
* Dolutegravir/abacavir/lamivudine (must conﬁrm HLA-B\*5701 negative and without chronic hepatitis B co-infection)
* Dolutegravir plus either emtricitabine or lamivudine plus either tenofovir alafenamide or teno- fovir disoproxil fumarate
* Dolutegravir/lamivudine (except in those with baseline HIV RNA >500 000 copies/mL or hepati- tis B virus co-infection; not ideal as a rapid-start regimen)

Preferred for pregnant people

* Dolutegravir plus tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate
* Dolutegravir/abacavir/lamivudine (must conﬁrm HLA-B\*5701 negative and without chronic hepatitis B co-infection)
* Darunavir/ritonavir plus tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/ emtricitabine

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

Achieving these goals requires indi- vidualization of therapy and encour- agement of adherence; it also has the public health beneﬁt of preventing transmission to sex partners and neo- nates (46, 47). Many providers and clin- ics offer same-day or rapid start (within a week) of ART as the standard of care for newly diagnosed persons.

*The START (Strategic Timing of Anti- retroviral Treatment) study was the ﬁrst large, international, randomized clinical trial showing that earlier treatment can decrease serious AIDS events (tubercu- losis, Pneumocystis pneumonia, AIDS- related cancer) as well as serious non– AIDS-deﬁning events (unrelated cancers; cardiovascular, renal, and liver disease) and death (48)*.

The cornerstone of treatment is the use of multiple agents directed at different steps in the HIV life cycle to increase the effectiveness of treatment and pre- vent the emergence of resistance

mutations. Typically, this involves a combination of 2 or 3 drugs from at least 2 of 7 classes. Maximum suppres- sion of virus replication to undetectable levels (“virologic success”) in a treat- ment-naive patient usually occurs in the ﬁrst 4 to 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, adherence to therapy, and absence of an opportunistic infection (24). The vast majority of patients can achieve this goal, although success rates in clin- ical practice tend to be lower than the 85% to 90% rate seen in clinical tri- als. “Virologic failure” is deﬁned as repeated viral loads 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 patients may then resuppress without any clinical consequences, resistance de- velopment, or change in ART. Most blips are small (50 to 500 copies/mL), and studies have reported that they are rela- tively common, occurring in 20% to 60% of patients (49, 50).

Drug–drug interactions are a common clinical issue but are often underrecog- nized. As infected persons age and

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those with well-suppressed dis- ease visit HIV specialists less fre- quently, they may begin to receive drugs that are contrain- dicated or that interact signiﬁcantly with ART. The most common and critical of these involve interactions affecting drug absorption or he- patic metabolism, such as use of statins or all forms of steroids with regimens that contain a protease inhibitor.

Treatment is lifelong, and inter- ruptions should be assiduously avoided. 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 (51). This morbidity may be due in part to inﬂammation that results from chronic, low-level 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

(52). This is often referred to as “treatment as prevention (TasP)” and “undetectable = untransmit- table (U = U)” and should be rein- forced at each visit. Treatment as prevention is critical to contain- ing the HIV epidemic because an effective vaccine remains elusive after more than 30 years of investigation.

*The HPTN 052 trial showed a 93% reduction in HIV transmis- sion among serodiscordant cou- ples when the HIV-infected partner received ART and was virologically suppressed (47). This study established the con- cept of “treatment as preven- tion”—the goal of as many HIV- infected persons as possible achieving virologic suppression*

*to greatly reduce the likelihood of infecting others.*

What should guide the selection of ART?

The U.S. Public Health Service treatment guidelines classify combination regimens for non- pregnant adolescents and adults as “recommended initial regi- mens for most people with HIV” and “recommended initial regi- men in certain clinical situa- tions,” and familiarity with regimens in these categories is key (25). Regimens in the “pre- ferred” and “alternative” catego- ries may be useful in speciﬁc situations. Choosing among them involves balancing poten- tial adverse effects, drug interac- tions, adherence potential, convenience (pill burden, dos- ing frequency, food require- ments), resistance test results, and patient desire (see the Box: Treatments for Adults and Pregnant People). Other factors to consider include pregnancy or potential pregnancy, various comorbid conditions (cardiovas- cular, liver, or renal disease; sub- stance use disorder; psychiatric condition; hepatitis B and/or C co-infection; tuberculosis), and concerns about weight gain.

All antiretrovirals have the poten- tial for short- and long-term adverse effects; the ﬁrst few weeks are generally the most dif- ﬁcult, and adverse effects usually improve with time and occasion- ally supportive care, such as medication for nausea. With cur- rent 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. Viral load should be measured 2

to 8 weeks after therapy is initi- ated to reassure the physician and the patient that the infection is responding and the patient is adherent. Viral load and CD4+ cell counts are important prognos- tic indicators and key means of monitoring treatment response. They reﬂect different aspects of the patient's health status and thus have complementary value. The vi- ral load measures how well HIV replication is being suppressed, but it is important for patients to understand that although “unde- tectable” (viral load below the assay's limit of detection) can mean “untransmittable,” it 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 meas- ured routinely. Although the CD4 percentage is a better tool to mon- itor 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, the total CD4 cell count has customarily been the more familiar measure.

In general, asymptomatic per- sons should have interval testing of markers (CD4 cell count, viral load) every 3 to 6 months (24). However, after 2 years of ther- apy with consistently sup- pressed viral loads and clinical stability, viral load testing can be done annually, and monitoring is optional at a CD4 cell count above 500 cells/mL. A complete metabolic panel and complete blood count with differential should be repeated at the same time points (entry into care,

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before ART initiation or modiﬁ- cation, 2 to 8 weeks after ART initiation or modiﬁcation) and then every 6 months or as clini- cally indicated. Urinalysis, ran- dom or fasting lipid proﬁle, and glucose measurement should

be performed at diagnosis, before ART initiation, and then annually or as clinically indi- cated. A urinalysis should be done every 6 months for those using TDF. In patients who are symptomatic at entry into care,

monitoring certain clinical varia- bles is useful to reassure the patient and the physician. These include weight gain, increased energy level, resolution of minor skin problems and thrush (oral, vaginal), and improvement in other signs and symptoms.

**CLINICAL BOTTOM LINE**

Antiretroviral Therapy... ART is the cornerstone of HIV care and should be initiated at or close to diagnosis, as soon as the patient understands what is involved and indicates readiness. There are 4 initial combination regimens for antiretroviral-naive patients and several others that can be used in certain clinical scenarios, which allows indi- vidualization of treatment. HIV-infected women should be reassured that with ART, healthy pregnancies and pre- vention of vertical transmission are possible. Short- and long-term adverse effects and drug–drug interactions should be anticipated and managed proactively. With increased life expectancy, health care maintenance and pre- vention of common age-associated illnesses, such as cardiovascular disease, have become increasingly important.

## Other Management Strategies

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

With prolonged survival now the expectation, all routine preven- tive and health maintenance strategies for adults and adoles- cents are warranted (53, 54). These include appropriate immunizations (with special limi- tations on live vaccines based on CD4 cell count), smoking cessa- tion, control of hypertension and hyperlipidemia, minimizing car- diovascular risk factors by exer- cising regularly and adhering to a nutritious diet, preventing obe- sity, evaluating at-risk patients for decreased bone mineral density, and screening for can- cer (cervical, anal, breast, colon, prostate, lung) and for intercur- rent infectious diseases, espe- cially tuberculosis and hepatitis B and C.

There are no formal recommen- dations for yearly anal Pap screening; however, the CDC and the HIV Medicine Asso-

ciation state that anal cytologic screening in HIV-infected men who have sex with men may become a useful preventive measure and anal Pap tests should be considered (55). The AIDS Institute of the New York State Department of Health has published guidelines for yearly digital anal rectal examination and Pap screening of men who have sex with men, transgender women and men, and cisgender women.

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

200 cells/mL (approximately

<14%). As the CD4 count de- creases below 50 cells/mL, the risk extends to include oppor- tunistic infections associated with end-stage AIDS, such as disseminated *Mycobacterium avium* complex and cyto-

megalovirus retinitis. Conver- sely, once a patient's CD4 count is sustained above 200 cells/mL for at least 3 months or is 100 to 200 cells/mL if HIV RNA remains below limits of detection for at least 3 to 6 months, opportunis- tic infection prophylaxis can be safely discontinued (45). The U.

S. Public Health Service regularly updates guidelines on the pre- vention and treatment of oppor- tunistic infections (45).

What are the special gynecologic and obstetric considerations for people assigned female at birth with HIV?

Because gynecologic problems are common and cervical carci- noma is an AIDS-deﬁning condi- tion, a complete gynecologic and obstetric history, compre- hensive gynecologic assessment at entry into care, interval exami- nations, and Pap smears are indicated, but no earlier than age 21 years. Persons aged 26 years or younger should receive the human papillomavirus (HPV) vaccine series. For people

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assigned female at birth who are aged 21 to 29 years, cervical cytologic testing should be per- formed every 12 months for 3 years. If 3 consecutive results are normal, follow-up testing can be done every 3 years. For people assigned female at birth who are aged 30 years or older, cervical cytologic testing and HPV co- testing should be done at base- line, and if results of both are negative, follow-up cytologic testing and HPV co-testing can be done every 3 years. However, if the cytologic test result is nor- mal but the HPV result is posi- tive, follow-up with cytologic testing and HPV co-testing should be done in 1 year. If the 1-year follow-up cytologic test result is abnormal or the HPV result is positive, referral for col- poscopy is recommended (56, 57).

Pregnancy does not accelerate the course of HIV disease, and vertical transmission can be pre- vented. All pregnant people 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, as cesarean delivery is preferred for those with viral loads above 1000 copies/mL close to delivery (25). The U.S. Public Health Service regularly updates guidelines on the man- agement of pregnancy and pre- vention of vertical transmission (25).

How should clinicians counsel patients to decrease risk for vertical transmission?

At the initial visit and subse- quent intervals, plans for con- ception must be discussed. People with HIV who plan to have children should be coun- seled about safe conception and

prevention of vertical transmis- sion. Seronegative partners should be routinely tested for HIV every 6 to 12 months and counseled to seek immediate care if they develop symptoms of acute seroconversion, such as a mononucleosis- or ﬂu-like ill- ness (23). PrEP should be dis- cussed, which can be parti- cularly efﬁcacious while the part- ner with HIV is initiating ART and has not yet achieved durable vi- ral suppression.

Pregnant people with HIV should be given combination ART at the time of diagnosis, and treatment should be continued during pregnancy; some people may need intravenous zidovudine administration during labor and delivery, and prophylactic medi- cation is universally given to the neonate for the ﬁrst 4 to 6 weeks of life. Currently recommended ART during pregnancy is sum- marized in the Box “Treatments for Adults and Pregnant People.” In the United States, breastfeed- ing is discouraged because for- mula is readily available and breast milk can transmit HIV. Vaginal delivery is safe for those with a prenatal viral load below 1000 copies/mL, whereas those 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 people with HIV in the United States (25, 58). The rate of congenital malforma- tions as captured by the Anti- retroviral Pregnancy Registry does not differ from the back- ground population rate.

At every visit, the physician should ask about symptoms of sexually transmitted infections and discuss risk reduction behaviors and strategies. People who inject drugs should be counseled to never reuse or

share syringes, needles, cottons, or water used for drug prepara- tion and should be referred to syringe services programs if available. Syringes and “cook- ers” that are nonetheless shared should be cleaned with 10% bleach solution; cottons cannot be sterilized and should not be shared. Use of sterile water or water from a reliable source is preferred for drug preparation. People who inject drugs should clean the injection site with a new alcohol swab and not lick the needle.

When should an HIVspecialist be consulted?

An HIV specialist should be con- sulted for persons who 1) are diagnosed with advanced dis- ease and will need indicated prevention, diagnostic, and management services for oppor- tunistic infections or tumors; 2) have a baseline genotype indi- cating drug-resistant HIV; 3) have persistently elevated viral loads indicating virologic failure;

4) experience clinical deteriora- tion regardless of virologic response; 5) have the potential for antiretroviral toxicity that affects health, quality of life, and functioning and/or adherence;

6) have potential drug–drug interactions necessitating a change in therapy; and 7) have ART begun during treatment of an acute opportunistic infection or other illness requiring hospi- talization. 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 start- ing ART during therapy for most acute opportunistic infections, experience managing multiple potential drug interactions and toxicities is required in this set- ting as well as determining the

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optimal timing of ART initiation to avoid immune reconstitution inﬂammatory syndrome, indi-

cated by acute symptoms or frank illness due to the rapid return of immune competence

in the presence of opportunistic infection (45, 53).

**CLINICAL BOTTOM LINE**

Other Management Strategies... Prophylaxis and treatment of the opportunistic diseases (infections and tumors) that are the hallmark of advanced HIV disease (AIDS) are determined by the absolute CD4 cell count. With increased life expectancy, health care maintenance and prevention of common age-related illnesses, such as car- diovascular disease, have become increasingly important.

## 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 per- sons who become infected, 2) to increase access to care and opti- mize health outcomes for per- sons living with HIV, and 3) to reduce HIV-related health dis- parities (39). The Health Re- sources and Services Admini- stration has developed the

HIVQUAL-US program to facili- tate quality improvement through measurement of key quality indicators described for the entire range of HIV care (59).

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

There is a wealth of resources from professional organizations; these include evidence-based primary care guidelines for HIV- infected persons from the HIV

Medicine Association of the Infectious Diseases Society of America (last updated in 2021)

(53) and the American Aca- demy of HIV Medicine's *Funda- mentals of HIV Medicine*, which is periodically updated (60). 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.

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# In the Clinic

**Tool Kit**

Prevention and Initial Management of HIV Infection

*Patient Information*

*https://medlineplus.gov/hivaids.html* Information and handouts on HIV/AIDS from the National Institutes of Health's MedlinePlus.

*https://medlineplus.gov/hivprepandpep. html*

Information on HIV preexposure and post- exposure prophylaxis from the National Institutes of Health's MedlinePlus.

[*www.cdc.gov/hiv/default.html*](http://www.cdc.gov/hiv/default.html)[*www.cdc.gov/hiv/spanish/index.html*](http://www.cdc.gov/hiv/spanish/index.html)Information and resources on HIV in English and Spanish from the Centers for Disease Control and Prevention.

[*www.cdc.gov/hiv/risk/index.html*](http://www.cdc.gov/hiv/risk/index.html)[*www.cdc.gov/hiv/spanish/basics/*](http://www.cdc.gov/hiv/spanish/basics/) *prevention.html*

HIV risk and prevention information in

English and Spanish from the Centers for Disease Control and Prevention.

*Information for Health Professionals*

*https://clinicalinfo.hiv.gov/en/guidelines* HIV clinical guidelines from the National Institutes of Health's Ofﬁce of AIDS Research.

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*https://clinicalinfo.hiv.gov/en/guidelines/ perinatal/whats-new-guidelines* Recommendations for the use of antiretro-

viral drugs during pregnancy and inter- ventions to reduce perinatal HIV transmission in the United States from the Department of Health and Human Services Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission.

[*www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-*](http://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-) *prep-guidelines-2021.pdf*

2021 update of the clinical practice guideline on preexposure prophylaxis for the pre- vention of HIV infection in the United States from the Centers for Disease Control and Prevention.

*https://npin.cdc.gov/publication/updated- us-public-health-service-guidelines- management-occupational-exposures- human*

2013 updated guidelines for the manage-

ment of occupational exposures to HIV and recommendations for postexposure prophylaxis from the U.S. Public Health Service.

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## WHAT YOU SHOULD KNOW ABOUT HIV INFECTION

### What Is HIV?

HIV is an infection that damages your immune sys- tem when undiagnosed and untreated. When the immune system is badly damaged, HIV develops into AIDS. There is no cure for HIV or AIDS, but safe and effective lifelong treatment is available. These medications, when taken regu- larly, can reverse damage to the immune system and allow patients to live a normal lifespan.

HIV is passed through body ﬂuids, like blood, semen, and breast milk, in the following ways:

* By having anal and/or vaginal sex with an HIV- infected person, especially without a condom

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

### What Are the Symptoms?

Acute HIV usually occurs 2 to 6 weeks after infec- tion. Symptoms include fever; tiredness; sore throat; swollen glands in the neck, armpits, and groin; and rash. Chronic HIV infection is the sec- ond stage. Symptoms may not appear again for many years but may include swollen glands in the neck, armpits, and groin; shingles; anemia; and chronic vaginal yeast infections. These symptoms are similar to those of other illnesses, like the ﬂu or mono, making it difﬁcult to diag- nose HIV without testing.

### Who Should Be Tested?

All sexually active persons aged 13 years or older should be tested at least once.

Anyone who requests HIV testing should be tested.

All pregnant women should be offered testing at least once during pregnancy and treated if posi- tive to prevent transmission to the baby.

People who are at high risk for HIV may require more frequent testing, including:

* Men who have sex with men
* Men and women having unprotected sex with multiple partners, or those with a sexually trans- mitted infection or a partner with a sexually trans- mitted infection
* People who currently inject drugs or have in the past
* People who have sex for money, drugs, or other commodities
* People with past or current sex partners who have HIV, are bisexual, or inject drugs
* People who engage in receptive anal sex, regard- less of sexual orientation

Routine testing should also be done in people diagnosed with tuberculosis or hepatitis B or C and survivors of sexual assault.

### Can It Be Prevented?

Avoiding exposure to HIV-infected body ﬂuids is essential for preventing infection. Regular con- dom use, clean needles, and general precautions in medical settings can prevent HIV infection.

If you are not infected but are at high risk, talk to your doctor about preexposure prophylaxis (PrEP), which involves taking HIV medicines every day and can prevent infection. If you are taking PrEP, you should be tested for HIV every 3 months.

### How Is It diagnosed?

HIV infection is diagnosed with simple blood tests. Talk to your doctor about which tests are right for you.

### How Is It Treated?

You should start treatment with medications as soon as possible after diagnosis. Treatment involves a combination of medications known as antiretroviral therapy (ART). Before starting ART, you will need tests to check the health of your immune system and your risk for medication side effects. You must take ART for the rest of your life to prevent and reverse damage to your immune system. If your immune system has been signiﬁcantly damaged, you may need addi- tional medications to prevent other infections.

Patient Information

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

### Questions for My Doctor

* + What are the best strategies to prevent HIV infection?
  + 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 often should I see my doctor?
  + Can I have sex if I have HIV?
  + If I think I have been exposed to HIV, what should I do?

## For More Information

MedlinePlus



https://medlineplus.gov/hivaids.html

Centers for Disease Control and Prevention

[www.cdc.gov/hiv/basics/index.html](http://www.cdc.gov/hiv/basics/index.html)



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