CLINICAL PRACTICE

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HIV Infection — Screening, Diagnosis, and Treatment

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 28-year-old woman is brought to the emergency department after a motor vehicle collision. She has no clinically significant injuries other than a fractured radius. A urine drug screen is positive for opioids and marijuana. As part of a universal screening program, she undergoes testing for human immunodeficiency virus (HIV) infection, and the results are positive. The patient is single and heterosexual, and she reports that she does not use injection drugs but occasionally trades sex for drugs. She has not been tested for HIV previously. Her other routine laboratory studies are normal except for mild lymphopenia. How would you further evaluate and treat this patient?

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THE CLINICAL PROBLEM

When the acquired immunodeficiency syndrome (AIDS) was first identified in the early 1980s, it was believed to be constrained to a small number of risk groups.[1] As more information became known about the epidemiologic picture of HIV transmission, it became clear that the infection was transmitted primarily through sexual contact and blood (including through injection-drug use), as well as perinatally.[2] In the United States, HIV type 1 (HIV-1) is the predominant virus, whereas HIV type 2 (HIV-2) is endemic in other areas of the world (e.g., West Africa).

In 2018, approximately 38,000 new cases of HIV infection were diagnosed in the United States and its territories.[3] Although perinatal transmission in the United States has decreased to very low levels owing to routine screening for HIV and initiation of antiretroviral therapy (ART) in HIV-infected women during pregnancy, cases in adolescents and adults decreased by just 7% between 2014 and 2018.[4] Since the 1980s, the populations most affected by HIV infection have changed, and HIV infection is now diagnosed disproportionately in persons who are poor, disenfranchised, and have high barriers to medical care. In 2018, 21% of new HIV infections were diagnosed in youths, 69% were diagnosed in men who have sex with men, 10% in injection-drug users, 42% in Blacks, and 27% in persons of Hispanic or Latino descent.[3] A quarter of all new cases occur in White persons, who make up 73% of the population.

An estimated 1 in 7 persons with HIV infection in the United States is unaware of the infection.[3] Many persons at risk — in particular, members of racial and ethnic minorities — do not have regular access to health care and, therefore, do

An audio version of this article is available at NEJM.org

KEY CLINICAL POINTS

HIV INFECTION — SCREENING, DIAGNOSIS, AND TREATMENT

- Despite extensive knowledge about human immunodeficiency virus (HIV), the number of cases of incident HIV infection decreased by only 7% between 2014 and 2018.
- One in seven persons with HIV infection in the United States is unaware of the infection, and transmission from these persons accounts for at least a third of new infections annually.
- Clinicians should test for HIV routinely in their practices, with repeat HIV testing in persons who inject drugs, have multiple sexual partners, exchange sex for money or drugs, or have incident sexually transmitted infections.
- Persons with a new diagnosis of HIV infection should be promptly referred to a clinical setting where a full HIV assessment can be performed and antiretroviral therapy can be initiated rapidly.
- Long-term retention in care and maintenance of successful antiretroviral therapy allow persons with HIV infection to have a near-normal life span and virtually eliminate transmission of HIV to others.

not receive a diagnosis until they present with advanced disease, when treatments may be less effective and the risk of death is highest.[5]

In 2019, the United States initiated the "Ending the HIV Epidemic" plan with a goal of reducing the number of new infections by 75% by 2025 and by 90% by 2030.[6] The plan includes four components: to identify all persons with HIV infection, preferably early; to successfully treat them with ART; to prevent new infections; and to respond quickly to outbreaks as they occur. The foundation for the first two components includes minimization of gaps in diagnoses, improvement in linkage to care, rapid initiation of therapy for HIV infection, and maintenance of viral suppression through successful retention in care.

STRATEGIES AND EVIDENCE

HIV SCREENING

U.S. guidelines recommend that all sexually active persons be tested at least once for HIV[7] and that those who have an ongoing high risk of infection be tested at least annually.[8] Persons with high risk are defined as those with an incident sexually transmitted infection; sexual partners of persons with sexually transmitted infections; persons who have had more than one sexual partner (or whose sexual partners have had more than one partner) since their most recent HIV test; injection-drug users; and persons who exchange sex for money or drugs. Testing is also recommended after the diagnosis of incident sexually transmitted infections and during pregnancy.

According to data from the National HIV Surveillance System of the Centers for Disease Control and Prevention (CDC), more than 75% of persons in high-risk categories who had seen a primary care provider within the previous year were not offered an HIV test,[5] and many patients with undiagnosed HIV infection had multiple health care visits before receiving an HIV test.[9] This lack of testing is a failure of the health care system, because each encounter is an opportunity to reduce the incidence of HIV transmission. Up to 38% of new HIV infections are transmitted by persons who are unaware of their HIV status.[10] Moreover, once HIV infection is identified and appropriately treated to maintain HIV RNA levels below 200 copies per milliliter, patients can have a near-normal life span and do not transmit the virus to others.[11,12]

Several studies have shown that in health care settings (including emergency departments and sexually transmitted disease and primary care clinics), more HIV infections are identified with the use of routine "opt-out" testing (i.e., all adult patients are informed that an HIV test could be performed, but they can opt out if they wish to)[13-16] than with physician-directed testing. Recommendations for opt-out testing have been in place since 2006.[7,17,18] Routine testing in the emergency department has been shown to be cost-effective.[19]

DIAGNOSTIC TESTS

Many tests are available to accurately diagnose HIV infection. The choice of the most appropriate test for a given clinical presentation depends on an understanding of the natural history of HIV infection (i.e., which marker is present at a given point after infection) (Fig. 1), the volume of the specimen, and the test-performance specifications.[20] During the "eclipse" period, before

establishment of viremia at day 5, infection cannot be detected. By days 6 to 8, virus can be detected by a nucleic acid amplification test (NAAT). Viral proteins (p24 antigen) can be detected between days 13 and 20. Antibodies, initially in the form of IgM, are detectable by day 20, and IgG is detectable by day 30. Most patients present long after the initial infection, when tests for antibodies and nucleic acid are both positive.

Owing to the high cost of NAAT, combination antigen–antibody tests, which use p24 antigen to identify patients in early stages of infection, are now the standard tests in hospital and commercial laboratories. Most of these tests can detect HIV-1 and HIV-2 infections. The CDC algorithm for testing is shown in Figure 2.

Several available point-of-care rapid tests use one of two techniques: lateral flow or flow-through. Once antibodies bind to antigens, they are detected by an indicator. Rapid tests can use either whole blood (<10 to 50 μl) collected by fingerstick or an oral swab as specimens; these tests are convenient and easy to administer. Although the sensitivity and specificity of these tests are typically greater than 98%, laboratory-based tests are more accurate, especially in early infection, and they are required to confirm any diagnosis made on the basis of a point-of-care rapid test.

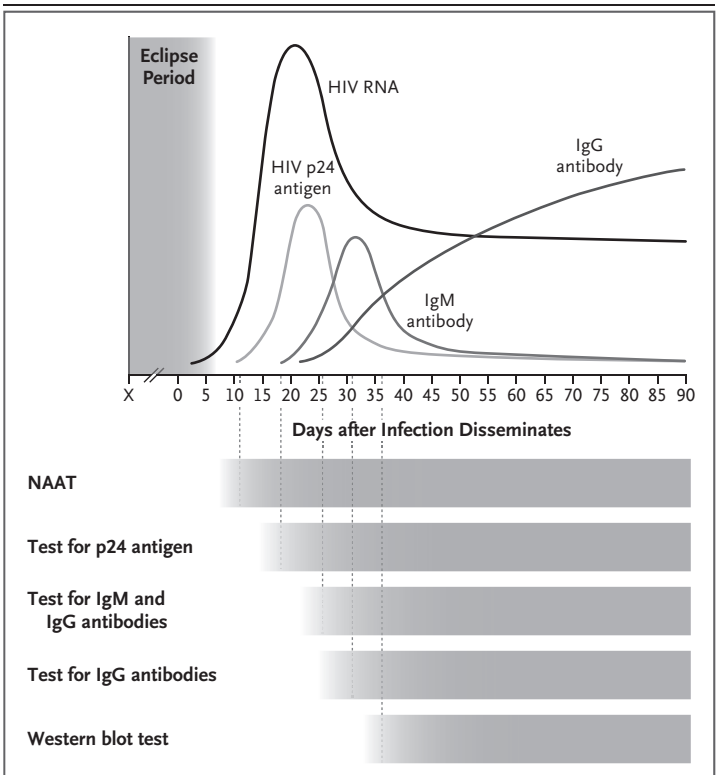

Figure 1. Progression of HIV Viremia and Immune Response after Initial Infection.

The time point X indicates the moment of initial exposure, and day 0 indicates the establishment of infection. In most persons, exposure to human immunodeficiency virus (HIV) does not result in infection or results in a transient infection that does not become established; however, in persons in whom long-term infection develops, the virus replicates in the exposed tissues, expressing antigen on the surface of the infected cell or cells. An immune response is mounted, with activated CD4 cells and macrophages migrating to the site of infection. Ironically, these activated cells are the primary targets of HIV, and once infected, they generate a stronger immune response, propagating further infection. This process takes 3 to 4 days after exposure (during the "eclipse" period, which is defined as the time between exposure and the ability to detect HIV RNA in plasma). Once a critical mass of immune-system cells is reached, viral replication expands exponentially, producing 10 to 100 billion virions per day. These viral particles (as measured by HIV RNA) can be detected as early as day 5 after establishment of infection and peak at day 20, at which time a more effective immune response begins to bring the infection under control. Viral antigen (p24 protein) can be detected at approximately day 14. Depending on the strength of the immune response, symptoms of acute seroconversion syndrome may manifest in the patient at approximately day 7 to day 12. Evidence of the immune response can be detected by day 20 as IgM antibody positivity, followed soon after by detectable serum IgG antibody. The time to reactivity for each diagnostic test is shown below the graph. Adapted from Hurt et al.[20] NAAT denotes nucleic acid amplification test.

LINKAGE TO CARE

All persons who receive a diagnosis of HIV infection should be referred for initiation of ART and long-term follow-up. According to 2018 CDC surveillance data, only 78% of patients are linked to care within 30 days after diagnosis, and sustained viral suppression is achieved in only 55 to 60% of persons (and a smaller percentage of infected adolescents and young adults) with diagnosed HIV.[21,22]

The sooner that an initial clinic visit is scheduled after diagnosis, the more likely it is that the patient will show up for the visit.[23] One trial in sub-Saharan Africa showed that "immediate" initiation of ART at the time of a positive home-based test increased follow-up with care.[24] Similar findings related to immediate initiation of therapy at the point of testing have been reported in resource-rich countries, although structural barriers often block implementation of immediate therapy, especially in hectic emergency departments.[25] In the United States, "rapid" initiation of ART, within 1 week after diagnosis, is the recommended practice.[11] Establishing an

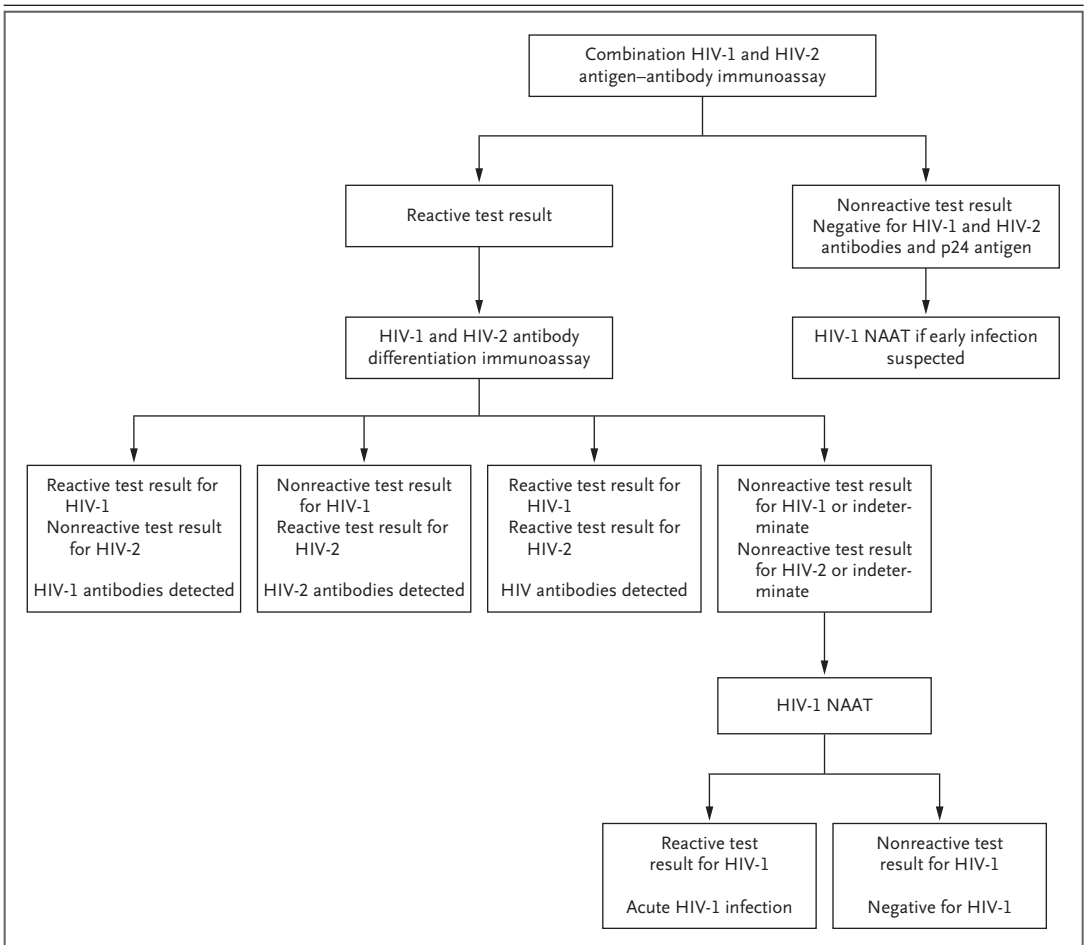

Figure 2. Recommended Laboratory Testing to Detect HIV in Serum or Plasma Specimens.

Initial testing for HIV should be performed with a Food and Drug Administration–approved antigen–antibody immunoassay that detects HIV type 1 (HIV-1) and HIV type 2 (HIV-2) antibodies and HIV-1 p24 antigen. If the test is nonreactive on the initial immunoassay, it is read as negative and no further testing is indicated unless there is clinical suspicion of very early infection (before p24 antigen can be detected); in that case, an HIV-1 NAAT to detect HIV RNA is performed. Specimens with a reactive antigen and antibody immunoassay result should be tested with a supplemental antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies; a reactive result on this test is interpreted as positive for HIV-1 antibodies or HIV-2 antibodies, respectively. Specimens that are reactive on the initial antigen and antibody assay but nonreactive (or indeterminate) with the HIV-1–specific and HIV-2–specific antibody assay should be tested with an HIV-1 NAAT. A positive NAAT in this case is diagnostic of acute HIV-1 infection. A negative HIV-1 NAAT result and a nonreactive or indeterminate HIV-1 antibody differentiation immunoassay result indicate an HIV-1 false positive result. Adapted from the Centers for Disease Control and Prevention (https://stacks.cdc.gov/view/cdc/50872).

active relationship with the patient, providing assistance in setting up the first appointment, maintaining contact with the patient until the first visit, and addressing any barriers to keeping the first appointment (e.g., transportation) are associated with an increased incidence of linkage to treatment.[26]

BASELINE ASSESSMENT AND INITIATION OF ART

A comprehensive intake evaluation should be performed at the initial visit. The items to be covered in the first visit are provided in Table 1. The history taking should focus on the risk to other persons associated with exposure to the patient as well as the patient's sexual health,

ongoing use of substances (including alcohol), and mental health disorders. A physical examination should be performed to evaluate for signs of advanced HIV infection such as thrush, vaginal candidiasis, herpes simplex virus infection, Kaposi's sarcoma, lymphadenopathy, retinopathy, mental status alterations, and wasting. Counseling should address the implications of an HIV diagnosis, the importance of disclosure of the patient's HIV status to a few trusted friends or relatives (for emotional support) and established sexual partners, and potential barriers to keeping future appointments (e.g., lack of transportation, food insecurity and lack of housing [which may cause a person to prioritize day-to-day survival over medical visits], and interpersonal violence). Specific topics of discussion regarding prevention of transmission to others should include the routine use of condoms during sexual activity and avoidance of sharing needles or other equipment during intravenous drug use.

Patients should be reassured that they can expect a near-normal life span[27] and no risk of transmission to others once viral suppression is achieved and maintained with ART.[12] From 2011 to 2017, among patients receiving standard ART regimens, the incidence of death at 5 years after diagnosis differed by only 2.7 percentage points from that of age-matched controls.[28]

With rare exception, ART should be initiated at the first clinic visit. The primary reason for not initiating treatment is that the patient is identified as an "elite controller"[29,30] (i.e., a person who has no detectable HIV RNA on presentation) or is not ready to begin treatment for personal reasons. Retention in care is improved when ART is prescribed at the initial visit and not delayed.[31,32]

TREATMENT

USE OF ART

The choice of initial therapy has been streamlined over the past 5 years (Table 2). Guidelines suggest the use of an integrase strand-transfer inhibitor (INSTI)–based therapy with tenofovir (either tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide fumarate [TAF] formulations) and either lamivudine (3TC) or emtricitabine (FTC).[11,33] Often ART is prescribed before the availability of baseline laboratory results; therefore, on the first visit, initial therapy should be limited to either bictegravir–FTC–TAF or dolutegravir plus a fixed-dose combination (TDF–FTC, TDF–3TC, or TAF–FTC), owing to their effectiveness, acceptable side-effect profile, activity against hepatitis B virus (HBV), and higher barrier to development of resistance than other options. The regimens can be adjusted once the HIV RNA level, CD4 count, and renal, liver, HBV, hepatitis C virus (HCV), and HIV genotypic data are known. The data may indicate that the treatment may be simplified to a two-drug (dolutegravir–3TC) single tablet.[11] Recommended ART treatments have yielded greater than 90% sustained virologic suppression in clinical trials.[11]

The initiation of ART in patients with active opportunistic infections or underlying conditions and in pregnant women is beyond the scope of this review. In general, the use of a regimen that includes an INSTI that does not require pharmacologic boosting with cobicistat is typically the best choice in patients with these conditions owing to the potency, pharmacokinetic profiles, and reduced drug–drug interactions associated with these regimens. Prophylactic therapy for opportunistic infections is summarized in Table 3.[11,34]

FOLLOW-UP AND RETENTION IN CARE

Follow-up visits should occur 4 to 6 weeks after the initiation of ART and then every 3 to 4 months until virologic suppression is achieved. Once suppression is sustained for a year, follow-up visits should occur every 6 months.[11] At each visit, assessment of adherence to the ART regimen and any adverse effects is essential. Any difficulties with the regimen should be addressed during the visit and, if warranted, the regimen should be switched. Laboratory tests (Table 1) should be performed, and the patient should be evaluated for sexually transmitted infections, ongoing use of substances (including alcohol), mental health disorders, and barriers to maintaining health (including housing issues, food insecurity, domestic violence, and other social determinants of care). Medication changes or adjustments in dosages may be warranted if new renal, hepatic, or hematologic abnormalities are detected on laboratory tests. Counseling, ideally

Table 1. Evaluation and Screening in Persons with HIV Infection.*

Test or Screening Procedure	At Diagnosis	At First Clinic Visit	At Subsequent Visits	With Regimen Change
Clinical evaluation				
Clinical history taking	Yes	Yes	Yes	Yes
Physical examination	Yes	Yes	Yes	Yes
Screening test for HIV antibody and antigen	Yes			
Measurement of HIV RNA (viral load)	Yes, if ART initiated at time and place of diagnosis or if acute HIV seroconversion suspected	Yes, but not needed if ART initiated at time and place of diagnosis	Yes	Yes
CD4 count	Yes, if ART initiated at time and place of diagnosis or if acute HIV seroconversion suspected	Yes, but not needed if ART initiated at time and place of diagnosis	Yes, every 6 mo until HIV RNA sustained (<100 copies/ml) for 1 yr and CD4 >250 cells/mm^3; then no longer check CD4 count (unless HIV RNA is confirmed >200 copies/ml); CD4 count most valuable early in course of treatment and evaluation	Yes, at time of confirmed virologic failure (detectable viremia)
Assessment of HIV resistance genotype	Yes, if ART initiated at time and place of diagnosis; HIV RNA obtained if acute HIV seroconversion suspected	Yes, but not needed if ART initiated at time and place of diagnosis	No	Yes, at time of confirmed virologic failure (detectable viremia)
Assessment of resistance to INSTIs	No	Yes, if known sexual partner is receiving an INSTI	No	Yes, at time of confirmed virologic failure (detectable viremia); also if known sexual partner is receiving an INSTI or if patient is receiving an INSTI at time of virologic failure
Liver and kidney profile	Yes	Yes	Yes	Yes
Serum lipid profile	No	Yes	Yes, only once per yr	No
Complete blood count with differential	Yes	Yes	Yes	Yes
Urinalysis	No	Yes	Yes, only once per yr	No
HBV serologic test	No	Yes	Yes, perform again if any unexplained increase in serum AST or ALT level or annually in patients who remain at high risk for infection or reinfection (high-risk sexual exposure or ongoing injection drug use); in patients who were previously infected and successfully treated, perform HCV RNA screening tests	No

HCV serologic test	No	Yes	Yes, perform again if any unexplained increase in serum AST or ALT level or annually in patients who remain at high risk for infection or reinfection (high-risk sexual exposure or ongoing injection drug use); in patients who were previously infected and successfully treated, perform HCV RNA screening tests		No
Pregnancy test	No	Yes, in women of child-bearing potential	Yes, in women of child-bearing potential; evaluate as indicated		No
Initiation of prophylaxis against *Pneumocystis jiroveci* pneumonia	Yes, if ART initiated at time of diagnosis and if *P. jiroveci* pneumonia clinically suspected (lymphopenia, wasting, oral candidiasis)	Yes, according to guidelines when CD4 count is <200 cells/mm^3	No		Yes, in patients with virologic failure
Cryptococcal antigen screening	No	Yes, in all patients with CD4 counts <100 cells/mm^3 at diagnosis or first clinic visit	No		Yes, only once per yr
Urine test for histoplasmosis antigen	No	Yes, In patients with CD4 count <100 cells/mm^3 in areas where histoplasmosis endemic	No		No
Screening for sexually transmitted infection	Yes, if ART initiated at time of diagnosis; screen at diagnosis or first clinic visit and routinely thereafter (frequency of testing depends on level of at-risk sexual activity)	Yes	Yes, screen routinely (frequency of testing depends on level of at-risk sexual activity)		No
Evaluation for cervical cancer	No	No	Yes, annually (anal Pap smears, if available; digital rectal examination at a minimum)		No
Evaluation for anal cancer	No	No	Yes, annually (anal Pap smears, if available; digital rectal examination at a minimum)		No
Testing for HLA-B*5701	No	Yes, perform before prescribing abacavir	No		Yes, perform before prescribing abacavir
Tropism assay (CCR5)	No	Yes, perform before prescribing maraviroc	No		Yes, perform before prescribing maraviroc
General screening to assess psychosocial factors					
Medication adherence	No	No	Yes		Yes
Substance use	No	Yes	Yes		No
Alcohol use	No	Yes	Yes		No
Depression, anxiety, or both	No	Yes	Yes		No

Table 1. (Continued.)

Test or Screening Procedure	At Diagnosis	At First Clinic Visit	At Subsequent Visits	With Regimen Change
Suicidality	No	Yes, in patients with depression	Yes, in patients with depression	No
Sexual activity and exposure to sexually transmitted infection	No	Yes	Yes	No
Targeted screening				
Housing	No	Yes	Yes	No
Food insecurity	No	Yes	Yes	No
Domestic violence	No	Yes	Yes, only once per yr	No
Cognitive function	No	No	Yes, in patients >60 yr of age (or as indicated clinically), every 2 yr	No
Frailty	No	No	Yes, in patients >60 yr of age (or as indicated clinically), every 2 yr	No
Social isolation	No	No	Yes, only once per yr	No
Polypharmacy	No	No	Yes, only once per yr	No

* ALT denotes alanine aminotransferase, ART antiretroviral therapy, AST aspartate aminotransferase, HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus, INSTI integrase strand-transfer inhibitor, and Pap Papanicolaou.

in the same care facility, should be available if the patient has a new or recurring mental health disorder.

Not all patients reach "undetectable" levels of virus; some have a consistently maintained level of virus between 50 and 100 copies per milliliter owing to a large reservoir of latently infected cells. In such patients, new replication is stopped with ART and no further adjustment in treatment is necessary. In contrast, if a viral load is measured at more than 50 copies per milliliter after previous viral suppression to 50 copies per milliliter or less, the measurement should be quickly repeated, and medication adherence and the side-effect profile should be assessed.[11,33] A confirmed HIV RNA level above 200 copies per milliliter should prompt assessment of viral resistance, including evaluation of INSTI resistance if the patient is receiving an INSTI–based ART regimen.

More than 85% of patients who consistently receive care have sustained virologic suppression indefinitely.[35] After a year of stable viral suppression, clinical care typically transitions to primary care, and HIV becomes secondary in focus during routine visits. Patients can receive care from both an HIV clinic and a primary care provider, or primary care can be provided in the HIV clinic. Weight gain is common, especially among patients who begin to receive an INSTI-based regimen combined with TAF, although the mechanism of weight gain remains incompletely understood.[36,37] Patients should be followed for coexisting conditions, including obesity, diabetes mellitus and other metabolic disorders, cancer, and cardiovascular, renal, and hepatic disease. These disorders occur more frequently and at a younger age in patients with successfully treated HIV infection than in age-matched controls.[38]

AREAS OF UNCERTAINTY

More than 42% of new HIV infections are transmitted by persons who are known to be infected with HIV but who are no longer receiving care[10]; this fact underscores the need for effective strategies for retention in care. Best practices to achieve this goal are still being developed. Centralized care,[39] the use of bilingual, bicultural teams,[40] clinic-based buprenorphine treatment for patients with concomitant opioid use disorder,[41] specialized services for the transition from jail to

Table 2. Current Recommended Initial Oral ART for Most Persons with HIV Infection.*

Regimen and Dose	Frequency	Adverse Effects	Comments
Bictegravir– FTC–TAF (50 mg/200 mg/25 mg)	Once daily as single-tablet regimen	Gastrointestinal symptoms (nausea, diarrhea), headache, IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class C liver function; contraindicated with dofetilide or rifampin; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Dolutegravir (50 mg)	Once daily	Gastrointestinal symptoms (nausea, diarrhea), headache, IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Plus TAF–FTC (25 mg/200 mg)	Once daily as single-tablet regimen	Gastrointestinal symptoms (nausea, diarrhea), IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Plus TDF–FTC (300 mg/200 mg)	Once daily as single-tablet regimen	Gastrointestinal symptoms (nausea, diarrhea), IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Plus TDF–3TC (300 mg/300 mg)	Individual tablets each once daily	Gastrointestinal symptoms (nausea, diarrhea), IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Dolutegravir–3TC (50 mg/300 mg)†	Once daily as single-tablet regimen (typically used after 12-wk lead-in period with other three-drug antiretroviral regimen)	Gastrointestinal symptoms (nausea, diarrhea), IRIS, lactic acidosis, hepatomegaly steatosis	Do not use with lamivudine resistance (M184V or M184I mutation) or HBV infection; not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Raltegravir (600 mg)‡	Two tablets once daily	Gastrointestinal symptoms (nausea, diarrhea), headache, IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Plus TAF–FTC (25 mg/200 mg)	Once daily as single-tablet regimen	Gastrointestinal symptoms (nausea, diarrhea), headache, IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Plus TDF–FTC (300 mg/200 mg)	Once daily as single-tablet regimen	Gastrointestinal symptoms (nausea, diarrhea), headache, IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin
Plus TDF–3TC (300 mg/300 mg)	Individual tablets each once daily	Gastrointestinal symptoms (nausea, diarrhea), headache, IRIS, lactic acidosis, hepatomegaly steatosis	Not recommended in patients with creatinine clearance <30 ml/min or Child–Pugh class B or C liver function; contraindicated with dofetilide; avoid divalent cations (Ca^{++}, Mg^{++}, Fe^{++}), phenytoin, carbamazepine, and rifapentine; use with caution with metformin

* The Child–Pugh liver function scale is a three-category scale (A, B, or C), with C indicating the most severe compromise of liver function. Data are from the International Antiviral Society–USA guidelines reported by Saag et al.[11] FTC denotes emtricitabine, IRIS immune reconstitution inflammatory syndrome, TAF tenofovir alafenamide fumarate, TDF tenofovir disoproxil fumarate, and 3TC lamivudine.

† Dolutegravir–3TC is not recommended for patients with rapid start of ART or for patients with chronic HBV infection, HIV RNA greater than 500,000 copies per milliliter, or a CD4 cell count of less than 200 cells per cubic millimeter. Therapy is often initiated with one of the other regimens listed and then simplified to dolutegravir–3TC.

‡ Raltegravir is included in the recommended regimen according to the Department of Health and Human Services guidelines reported by Scheer et al.[32]

Table 3. Primary Prophylaxis against Opportunistic Infections in Persons with HIV Infection.

Indication and Regimen	Dose, Route of Administration, and Frequency	Adverse Effects	Comments
Prophylaxis against *P. jiroveki* (CD4 count <200 cells/mm^3 or thrush)			
Trimethoprim–sulfamethoxazole	One double-strength tablet (160 mg of trimethoprim and 800 mg of sulfamethoxazole) daily or 3 times/wk	Allergy, rash and erythroderma, rare Stevens–Johnson syndrome, nausea, diarrhea, anemia, neutropenia, hyperkalemia, drug-induced hepatitis	
Dapsone	100 mg, orally once daily	Rash, fever, methemoglobinemia, hemolysis	Used as alternative therapy
Pentamidine	300 mg, aerosolized through nebulizer monthly	Bronchospasm, pancreatitis (rare)	Used as third-line therapy; failure occurs as upper-lobe *P. jiroveci* pneumonia
Atovaquone	1500 mg, orally (liquid suspension) daily	Rash, gastrointestinal symptoms, headache, insomnia	Used as third-line therapy; must be given with food
Prophylaxis against cryptococcus (CD4 count <100 cells/mm^3 and positive serum cryptococcal antigen): fluconazole	200 mg, orally once daily	Rash, gastrointestinal symptoms, headache, alopecia, drug-induced hepatitis (rare)	Serum cryptococcal antigen test recommended for all persons with newly diagnosed HIV infection and, if positive, lumbar puncture should be performed; in absence of meningitis, initiate fluconazole
Prophylaxis against histoplasmosis (CD4 count <150 cells/mm^3 in areas where histoplasmosis is endemic only): itraconazole	200 mg, orally once daily	Gastrointestinal symptoms, rash, elevated liver-enzyme levels, edema	Capsules administered with food or acidic drink (e.g., cola)
Prophylaxis against *Mycobacterium avium* complex: no longer recommended in persons with rapid initiation of ART			

clinic,[42] behavioral interventions,[43] and enhanced patient contact through navigator programs[44] have been successful. Calling patients on the telephone if they do not show up for scheduled appointments is one of the most effective means of retaining patients in care.[44,45] An intervention that involved brochures, posters, and short verbal messages conveying the importance of continued health care visits was associated with a higher incidence of return for subsequent appointments than no such intervention.[46]

With the success of ART over the past 2.5 decades, the population of persons with HIV infection is aging. In the United States, more than 50% of the patients receiving care for HIV infection are older than 50 years of age; 18% are older than 60 years, and older persons with HIV infection are at higher risk for poor health outcomes than persons of similar age without HIV infection.[27] Incident cardiovascular, kidney, neurocognitive, and mental health disorders occur at younger ages in persons with HIV infection than in aged-matched controls. Older patients with HIV infection tend to have worse outcomes than younger patients because of the increased likelihood of polypharmacy,[47] frailty,[48] social isolation,[49] and stigma.[50] More data are needed to guide the care of patients as they age.

GUIDELINES

Professional guidelines regarding screening,[51-53] the selection of an ART regimen for individual patients,[11,33] and primary care for patients with HIV infection[54] are available. The recommendations presented here are concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette was at risk for HIV infection owing to an opioid use disorder and her engagement in sex in exchange for drugs. The diagnosis through routine opt-out screening in the emergency department underscores the benefit of this approach, because otherwise the diagnosis would probably have been made much later. An appointment at an HIV clinic should be scheduled within 1 week after diagnosis for a baseline evaluation (a detailed social history taking and laboratory testing, including testing for other sexually transmitted infections, and assessment of the CD4 count and viral load) and prompt initiation of ART, and she should be referred for management of substance abuse. She should be counseled regarding disclosure of her HIV status to trusted persons and sexual partners, the importance of using condoms and avoiding needle sharing to reduce disease transmission, the need to continue to receive ART as prescribed and to return for follow-up, and the expectation of a near normal life span if viral suppression is achieved and maintained. In subsequent appointments, adherence to and any adverse effects of ART, as well as substance use and other social factors that might interfere with adherence to ongoing treatment, should be routinely assessed.

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