CLINICAL PRACTICE

Management of Newly Diagnosed HIV Infection

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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.*

As part of a routine examination for insurance coverage, a 25-year-old previously healthy woman is found to have a positive test for human immunodeficiency virus type 1 (HIV-1) antibody. Heterosexual contact is her only risk factor for HIV acquisition. She is asymptomatic and has a normal physical examination. The results of hematologic and other routine laboratory tests are normal. Her CD4 cell count is 325 cells per cubic millimeter, and her plasma HIV-1 RNA level is 60,000 copies per milliliter (both confirmed on repeated testing). How should her case be managed?

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THE CLINICAL PROBLEM

In the United States, it is estimated that 900,000 to 1 million persons are infected with HIV-1. One quarter to one third of these persons do not know their infection status, thus jeopardizing their own care and putting others at risk through transmission that might be prevented with counseling, behavior modification, and potentially, antiretroviral therapy.[1] The number of new cases of acquired immunodeficiency syndrome (AIDS) reported each year in the United States has been stable, at approximately 40,000, but the incidence of HIV-1 infection and other sexually transmitted infections has increased in certain at-risk populations, such as men who have sex with men. Blacks, Hispanics, and women are disproportionately represented among persons with HIV-1 infection, AIDS, or both.[2]

The era of potent antiretroviral therapy, which began in 1996, has resulted in marked reductions in the rates of illness and death due to HIV-1 infection in the developed world and has led to the management of HIV-1 infection as a chronic disease, with life expectancies after diagnosis now measured in decades.[3]

STRATEGIES AND EVIDENCE

SCREENING FOR HIV INFECTION

When evaluating patients, physicians should routinely consider the possibility of HIV infection. Screening is relevant not only in patients with opportunistic infections or HIV-associated cancers but also in patients who have severe illnesses, such as pneumococcal bacteremia, that are seen with increased frequency in the setting of HIV infection; those who have illnesses that may indicate a risk of HIV acquisition (e.g., sexually transmitted infections, such as syphilis, gonorrhea, *Chlamydia trachomatis* infection, and genital herpes simplex virus infection) or subtle immunodeficiency (e.g., herpes zoster, oral candidiasis, and oral hairy leukoplakia); and those who report high-risk behavior (e.g., unprotected sex and the use of illicit drugs) when presenting for care for any reason. Recently, the Centers for Disease Control and Prevention (CDC) launched a pro-

gram to promote HIV antibody testing as a routine element of medical care.[4] The goals of routine screening are to better define the true prevalence of infection in the United States, to bring persons infected with HIV-1 into care, to offer opportunities for prevention of the secondary spread of infection, and in persons found to be HIV-seronegative, to provide the opportunity for counseling in order to reduce the risk of virus acquisition. Recent reports have suggested that screening for HIV in the general U.S. adult population, in which there is a low prevalence of HIV-1 infection (1 percent or less), could be cost-effective whether performed once or repeated every three to five years.[5,6]

TESTING AND COUNSELING

Making HIV testing more widely available requires having adequate services in place to ensure proper counseling before and after testing, with fully informed consent from patients. Approval by the Food and Drug Administration of rapid HIV antibody tests, which can provide results in as little as 20 minutes, has improved the efficiency of point-of-care testing. The sensitivity and specificity of the approved rapid HIV antibody kits are similar to those of standard serum enzyme-linked immunosorbent assay tests[7]; confirmation of the result by another test, such as a Western blot analysis, is still required. Rapid testing is useful in several circumstances, such as at the time of delivery for pregnant women who have not received prenatal care, at sexually transmitted disease clinics, and at emergency departments, urgent care centers, and in-hospital settings, where immediate knowledge of patient status will affect decisions regarding care and follow-up. Appropriate counseling is necessary for patients who test positive, to address issues such as stigma and the fear of disclosure of one's HIV status; the need to inform previous or current sexual partners who may have been put at risk; HIV testing of children who may have been conceived after the patient became infected with HIV; strict adherence to safe-sex practices; and avoidance of drugs such as methamphetamines that may disinhibit behavior.[8]

The use of condoms should be emphasized as an effective means to prevent sexual transmission of HIV-1 as well as to prevent the acquisition of other sexually transmitted infections, including superinfection with another strain of HIV-1.[9] The effectiveness of condoms in the reduction of HIV-1 transmission has been estimated at 87 percent (range, 60 to 96).[10] Counseling should underscore

the fact that, although it is a lifelong problem, HIV disease can be managed successfully in the vast majority of persons. Patients should be encouraged to reveal their HIV status to trusted and supportive family members and friends, and they should be offered professional counseling.

EVALUATION OF THE PATIENT

Patients with a new diagnosis of HIV-1 infection should provide a complete history and undergo physical examination to determine whether there are any clinical manifestations of infection. Given the projected long-term management of HIV disease, the evaluation should also include screening and counseling for health-maintenance issues not related to HIV and recognition of conditions that may interact with the management of HIV, particularly with respect to potential interactions of other drugs with antiretroviral agents and cardiovascular risks that may be increased by some antiretroviral drugs.[11] Recommended laboratory tests are summarized in Table 1. It is essential to determine CD4 cell counts and plasma HIV-1 RNA levels (i.e., the viral load), both to establish the prognosis and to inform the decision regarding whether to start antiretroviral therapy (Table 2). Testing for resistance to drugs used in the treatment of HIV infection should also be considered, since primary acquisition of drug-resistant HIV strains is a risk.[8,12,15-17] Once the diagnosis of HIV infection is confirmed, referral to a specialist in HIV care is appropriate.[19]

PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS

Manifestations of HIV-related opportunistic disease can occur at virtually any level of CD4 cell count, but the incidence of serious and potentially life-threatening infections increases dramatically as the CD4 cell count drops below 200 cells per cubic millimeter. CD4 thresholds of 200, 100, and 50 cells per cubic millimeter have been established as levels that demarcate the risks of *Pneumocystis jiroveci*, *Toxoplasma gondii*, and *Mycobacterium avium* complex infections, respectively, and are indications for prophylaxis[20-25] (Table 3). Randomized trials indicate that the risks of these infections can be reduced by 50 to 80 percent or more with appropriate prophylaxis.[22,23]

INITIATION OF ANTIRETROVIRAL THERAPY

Consensus guidelines support the strategy of offering antiretroviral therapy to anyone with HIV-

Table 1. General Laboratory Tests Recommended for Persons with Newly Diagnosed HIV Infection.*

Test	Comment
Complete blood count	Anemia may contraindicate use of zidovudine.
Electrolytes, blood urea nitrogen, creatinine, fasting blood sugar	Abnormal renal function may contraindicate use of tenofovir or indicate need for adjustment of renally excreted nucleoside or nucleotide analogues; baseline presence of diabetes may contraindicate use of protease inhibitors, which can cause insulin resistance.
Bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase	Indinavir and atazanavir can elevate indirect bilirubin levels. Abnormal liver-enzyme levels may indicate need for further workup, may influence choice of antiretroviral agents, which carry risk of hepatotoxicity, or both.
Creatine kinase	Elevated value may reflect, most commonly, exercise or underlying HIV myopathy; a baseline value is helpful, to monitor zidovudine therapy, which may cause drug-induced myopathy.
Amylase, lipase	Baseline values may be helpful for making decisions regarding use of drugs (e.g., didanosine) that carry risk of pancreatitis.
Fasting lipid profile	Abnormal baseline values may indicate need for dietary therapy, drug therapy, or both, or possible avoidance of therapy with certain protease inhibitors.
Serologic tests for syphilis (e.g., plasma reagin test)	Evidence of past or recent exposure requires treatment unless there is documentation of adequate course of treatment.
Serologic tests for hepatitis A, B, and C viruses	If negative, counseling to prevent acquisition of all three viruses and vaccination for hepatitis A and B viruses are indicated. If active infection with hepatitis B or C virus, or both, is present, decision should be made about specific treatment and its relation to antiretroviral therapy.
Toxoplasmosis titer	If negative, counseling to prevent acquisition of *Toxoplasma gondii* (including avoidance of undercooked meat and of cat feces) is indicated. If positive, and CD4 cell count is <100 per mm³, primary prophylaxis is indicated. (Patients with very advanced HIV infection may lose antibody to *T. gondii*.)
CMV titer	If negative, counseling is indicated to prevent acquisition of virus through intimate contact or blood transfusion. If blood products are needed, screening should be considered, to prevent CMV acquisition. Whether there is a routine need for this test is debatable, given the decreased incidence of CMV-associated disease with the use of potent antiretroviral therapy.
Cervical Papanicolaou smear	Important, given the prevalence of HPV infection and increased risk of cervical neoplasia.
Anal screening for HPV	No consensus recommendation exists, but consideration of Papanicolaou smear, HPV DNA test, or both, is reasonable, given associated risk of anal carcinoma.
Tuberculin skin test	If positive (induration ≥5 mm) and active tuberculosis is ruled out, isoniazid therapy for nine months should be considered.
Electrocardiography	Baseline tracing may be important, given potential for increased cardiovascular risk associated with antiretroviral therapy (especially some protease inhibitors). Atazanavir can prolong PR interval.
Chest radiography	Important to consider obtaining a baseline film, owing to numerous HIV-related complications that can manifest as pulmonary disease.

* Because of potential past exposure to pathogens that may reactivate with immunosuppression, additional baseline laboratory screening tests to consider in persons with newly diagnosed HIV infection may include titers for *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*. If these tests are negative, counseling (e.g., regarding travel and recreation) to avoid acquisition should be considered. If positive, the awareness that risk increases as immunosuppression worsens may help in the management of HIV infection. In the United States, histoplasmosis is endemic in the Mississippi River Valley, Puerto Rico, and foci in other parts of the country; coccidioidomycosis is endemic in central California and the Southwest; and blastomycosis is endemic in the Southeast. Blastomycosis is relatively rare in patients with AIDS, so the role of testing for this infection is particularly uncertain. Stool examination for *Strongyloides stercoralis* also should be considered in patients with a history of travel to or residence in tropical or semitropical areas. If positive, treatment is indicated to avoid the potential for future development of hyperinfection syndrome with advanced immunosuppression. However, routine testing cannot be recommended on the basis of available data. CMV denotes cytomegalovirus, and HPV human papillomavirus. Data are from the Department of Health and Human Services[12] and Aberg et al.[13]

Table 2. HIV-Specific Baseline Tests for Persons with Newly Diagnosed HIV Infection.*	
Test	**Comment**
CD4 cell count	Critical for determining patient's disease stage and short-term and mid-term risk of opportunistic complication, and for assessing need to recommend prophylaxis against opportunistic infections and initiation of antiretroviral therapy. Two values, obtained one to four weeks apart, should be considered, to establish firm baseline value.
Plasma HIV-1 RNA	Critical for determining viral burden, assessing potential rate of loss of CD4 cells, and evaluating mid-term and long-term risk of opportunistic complication. Adjunctive to CD4 cell count in assessing need to recommend antiretroviral therapy. Two values, obtained one to four weeks apart, should be considered, to establish firm baseline value. Best quantitative laboratory marker to monitor success of antiretroviral therapy.
Genotype test for antiretroviral drug resistance	Helpful in choice of initial therapy in areas where prevalence of drug-resistant HIV is >5%, although uniform surveillance data are not available. Should definitely be considered for persons thought to have acquired infection relatively recently (i.e., within the previous three years) and increasingly should be considered for all patients with established infection as part of baseline evaluation. (Persistence of drug-resistant variants of HIV after primary acquisition is dependent on fitness of mutant virus and evolution of viral diversity after infection. Some mutations may persist for months to years [e.g., K103N], and others, which are less fit, may recede to a small fraction of the overall viral population, only to reemerge with therapy.)

* Data are from the Department of Health and Human Services,[12] Mellors et al.,[14] Hirsch et al.,[15] Little et al.,[16] Yeni et al.,[17] and Egger et al.[18]

related symptoms or signs.[12,17] Although data from randomized trials are not sufficient to guide the decision regarding when to initiate antiretroviral therapy in asymptomatic persons, several observational cohort studies have provided useful information.[18,26-33] The near-uniform finding that disease progression and mortality are significantly worse among patients whose treatment is delayed until the CD4 cell count is less than 200 per cubic millimeter[18,27-34] indicates that antiretroviral therapy should be initiated when the CD4 cell count is above this level. Persons who present initially with CD4 cell counts of less than 200 cells per cubic millimeter should be offered treatment as soon as the baseline evaluation and initial counseling regarding drug adherence are completed. Persons with CD4 cell counts of more than 350 per cubic millimeter generally can be observed without therapy, on the basis of data showing similar outcomes with and without therapy among patients with CD4 cell counts in this range[30]; exceptions are patients whose plasma HIV-1 RNA level is more than 100,000 copies per milliliter,[18] since this level is associated with an increased risk of progression to AIDS that is independent of the CD4 cell count. In persons who are being followed without therapy, a rapid decline in the CD4 cell count (i.e., a decline of more than 100 cells per cubic millimeter per year) may also be factored into the decision regarding when to initiate therapy.[17]

For persons with CD4 cell counts between 200 and 350 per cubic millimeter, the recommendation to start therapy should be considered on an individual basis. In practical terms, initiating antiretroviral therapy when the CD4 cell count is at the upper end of this range is reasonable if the patient is willing and committed. This strategy provides a buffer by which to avoid a drop in the CD4 cell count to less than 200 cells per cubic millimeter and may also prevent symptomatic disease, which can occur above this cutoff. One study has suggested that a level within the range of 200 to 350 cells per cubic millimeter, and specifically of about 275 cells per cubic millimeter, may be a threshold below which progression to AIDS is more likely.[31]

TREATMENT REGIMEN

Combination antiretroviral therapy should suppress the plasma HIV-1 RNA titer to less than 50 copies per milliliter. This target correlates with durability of viral suppression, prevention of the emergence of drug resistance, and immunologic and clinical benefit. Viral evolution and genotypic changes in the virus over time due to errors in reverse transcription, selective drug or immune pressure, or both may still occur in HIV reservoirs at this level of suppression; however, when a change does occur, it typically involves the gene encoding the HIV envelope (not the reverse transcriptase and protease genes), thus preserving susceptibility to the major classes of HIV enzyme inhibitors.[35-40]

There are now 21 antiretroviral agents, repre-

Table 3. Primary Prophylaxis against Major Infectious Pathogens That Can Cause Complications in the Patient with Newly Diagnosed HIV Infection.*

Pathogen	CD4 Count (cells/mm³)	Agent	Major Side Effects	Alternative Agent
Pneumocystis jiroveci	<200	Trimethoprim–sulfamethoxazole, 160 mg and 800 mg, once daily	Rash, fever, abnormal liver-enzyme levels, hematologic toxicity, pancreatitis	Dapsone, 100 mg once daily (if G6PD level is normal)
Toxoplasma gondii	<100	Trimethoprim–sulfamethoxazole, 160 mg and 800 mg, once daily	Rash, fever, abnormal liver-enzyme levels, hematologic toxicity, pancreatitis	Dapsone, 200 mg, plus pyrimethamine, 75 mg, plus leucovorin, 25 mg, once weekly
Mycobacterium avium complex	<50	Azithromycin, 1200 mg, once weekly	Gastrointestinal symptoms	Clarithromycin, 500 mg, twice daily
M. tuberculosis	Any (tuberculin skin test, positive at induration of ≥5 mm, or history of significant exposure)	Isoniazid, 300 mg, once daily (with pyridoxine, 50 mg, once daily) for 9 months; Active tuberculosis should be ruled out before initiating treatment with isoniazid	Abnormal liver-enzyme levels, peripheral neuropathy	Risks and benefits of alternative prophylactic regimens should be carefully evaluated on an individual basis
Streptococcus pneumoniae	Any, but response to vaccine is better in persons with >200	23-valent pneumococcal polysaccharide vaccine; need for revaccination after 5 years has not been established	Local reaction at site of injection; transient systemic symptoms	
Influenza virus	Any	Inactivated influenza vaccine once yearly	Local reaction at site of injection; transient systemic symptoms	Oseltamivir, 75 mg, once daily during outbreak if not protected by vaccination
Hepatitis A virus	Any	Hepatitis A vaccine	Local reaction at site of injection	Combined hepatitis A and B vaccine now available
Hepatitis B virus	Any	Hepatitis B vaccine	Local reaction at site of injection; transient systemic symptoms	Combined hepatitis A and B vaccine now available

* G6PD denotes glucose-6-phosphate dehydrogenase. Data are from the CDC[24] and the U.S. Public Health Service.[25]

senting five drug classes, and five fixed-dose combinations approved in the United States for the treatment of HIV-1 infection. Randomized trials of triple-drug combination regimens in patients who have not previously received treatment have shown that regimens that include nonnucleoside reverse-transcriptase inhibitors and those based on ritonavir-boosted protease inhibitors result in viral suppression to a level of less than 50 copies per milliliter in more than 60 percent of patients and raise CD4 cell counts by approximately 175 to 200 per cubic millimeter after 48 weeks of treatment.[41] Intolerance of or an inadequate response to any one regimen frequently requires a change to an alternative regimen; assessment of drug adherence should always be the first step when considering why a response to therapy is suboptimal.

The regimens based on nonnucleoside reverse-transcriptase inhibitors that are currently being prescribed involve either efavirenz or nevirapine in combination with either two nucleoside analogue reverse-transcriptase inhibitors or a nucleoside analogue and a nucleotide analogue reverse-transcriptase inhibitor (Table 4). Of the nonnucleoside reverse-transcriptase inhibitors, efavirenz is generally favored because of its better toxicity profile and once-daily administration. Efavirenz should be avoided in pregnant women, however, because of its potential teratogenic effects. Nevirapine can cause serious hepatotoxicity and confers a higher risk of severe rash than does efavirenz.

The most commonly used dual nucleoside or nucleoside–nucleotide component is lamivudine or emtricitabine combined with either zidovudine or tenofovir disoproxil fumarate (Table 4). In a randomized trial, the combination of efavirenz and tenofovir–emtricitabine was superior to that of efavirenz and zidovudine–lamivudine; the proportions of patients with a plasma HIV-1 RNA level of less than 50 copies per milliliter were 77 percent and 69 percent, respectively, with increases in the CD4 cell count of 189 and 158 cells per cubic millimeter,

Table 4. Selected Initial Antiretroviral Regimens and Components for HIV-Infected Patients with Drug-Susceptible Virus.*

A Nonnucleoside Reverse-Transcriptase Inhibitor plus Two Nucleoside (or One Nucleoside and One Nucleotide) Reverse-Transcriptase Inhibitors†

	NNRTI Component	Alternative NNRTI Component	NRTI Components	Alternative NRTI Component
Examples	Efavirenz (Sustiva): 600 mg once daily	Nevirapine (Viramune): 200 mg once daily for 14 days, then 200 mg twice daily	Zidovudine–lamivudine (Combivir): 300 mg and 150 mg twice daily as fixed-dose combination; or tenofovir–emtricitabine (Truvada): 300 mg and 200 mg once daily as fixed-dose combination	Abacavir–lamivudine (Epzicom): 600 mg and 300 mg once daily as fixed-dose combination
Major side effects	Efavirenz: central nervous system symptoms (e.g., vivid dreams); rash; hepatotoxicity; teratogenic effects in first trimester‡	Nevirapine: rash, hepatotoxicity, hypersensitivity syndrome; should be used with caution in women and men with CD4 cell counts of >250/mm³ and >400/mm³, respectively, because of increased risk of hepatotoxicity	Zidovudine (Retrovir)§: headache, nausea, anemia, leukopenia; tenofovir (Viread)§: gastrointestinal symptoms, renal dysfunction; lamivudine (Epivir) and emtricitabine (Emtriva)§: generally well tolerated	Abacavir (Ziagen)§: 5% incidence of hypersensitivity syndrome (fever, rash, gastrointestinal symptoms, respiratory symptoms), which may be fatal, especially on rechallenge

A Protease Inhibitor plus Two Nucleoside (or One Nucleoside and One Nucleotide) Reverse-Transcriptase Inhibitors†

	PI Component	Alternative PI Component¶	NRTI Components	Alternative NRTI Component
Examples	Lopinavir–ritonavir (Kaletra): 400 mg and 100 mg twice daily or 800 mg and 200 mg once daily as fixed-dose combination	Atazanavir–ritonavir (Reyataz and Norvir): 300 mg and 100 mg once daily	Zidovudine–lamivudine: 300 mg and 150 mg twice daily as fixed-dose combination; or tenofovir–emtricitabine: 300 mg and 200 mg once daily as fixed-dose combination	Abacavir–lamivudine: 600 mg and 300 mg once daily as fixed-dose combination
Major side effects	Lopinavir–ritonavir: gastrointestinal symptoms; elevated liver-enzyme levels; hyperlipidemia; fat redistribution; insulin resistance	Atazanavir: increased indirect bilirubin levels; gastrointestinal symptoms; prolonged PR interval	Zidovudine§: headache, nausea, anemia, leukopenia; tenofovir§: gastrointestinal symptoms, renal dysfunction; can lower atazanavir levels unless latter is administered with low-dose ritonavir; lamivudine and emtricitabine§: generally well tolerated	Abacavir§: 5% incidence of hypersensitivity syndrome (fever, rash, gastrointestinal symptoms, respiratory symptoms), which may be fatal, especially on rechallenge

* The regimens listed in this table were chosen to illustrate the selection of components of drug combinations that are based on nonnucleoside reverse-transcriptase inhibitors (NNRTI) and protease inhibitors (PI). Efficacy, toxicity, and simplicity of the regimens as demonstrated in clinical trials formed the basis of selection. This table is not intended to be comprehensive with respect to all possible initial combinations or to be a substitute for consensus guidelines; however, the regimens listed are concordant with these guidelines. NRTI denotes nucleoside or nucleotide reverse-transcriptase inhibitor. Data are from the Department of Health and Human Services[12] and Yeni et al.[17]

† Multiple drug interactions occur with nonnucleoside reverse-transcriptase inhibitors and protease inhibitors because of their metabolism by, and influence on, the CYP3A4 hepatic-enzyme system. All HIV and non-HIV medications prescribed for patients who take these drugs should be checked for possible interactions. Decreased bone mineral density in women and men may occur as a side effect of protease inhibitors or tenofovir, as a manifestation of underlying HIV disease, or both.

‡ Because of the potential for teratogenic effects, efavirenz is contraindicated during the first trimester of pregnancy and in women with childbearing potential who are not using effective contraception.

§ All nucleoside or nucleotide reverse-transcriptase inhibitors carry a warning label concerning the risk of mitochondrial dysfunction, steatohepatitis, and lactic acidosis, which can be fatal. The risk varies among the drugs in this class; tenofovir, lamivudine, emtricitabine, and abacavir have a lower risk, in relative terms, than does stavudine (Zerit). The former also confer a lower risk of lipoatrophy than does stavudine.

¶ Other alternative protease inhibitor components include saquinavir (Invirase)–ritonavir, 1000 mg and 100 mg, twice daily and fosamprenavir (Lexiva)–ritonavir, 700 mg and 100 mg, twice daily or 1400 mg and 200 mg once daily.

respectively, at 48 weeks.[42] Tolerance was a factor in these results, since there were more treatment discontinuations in the zidovudine–lamivudine group than in the tenofovir–emtricitabine group.

The basic alternative regimen is the combination of a ritonavir-boosted protease inhibitor (e.g., lopinavir, atazanavir, saquinavir, or fosamprenavir) and a dual nucleoside or nucleoside–nucleotide component, as described above (Table 4). At a dose of 100 to 200 mg once or twice daily, ritonavir does not have in vivo anti-HIV activity, but it acts to enhance the activity of the drug with which it is paired by inhibiting the hepatic CYP3A4-mediated metabolism of the latter.[43,44] The pharmacokinetic profile of the protease inhibitor nelfinavir is not appreciably enhanced by ritonavir, and this drug has been shown to be less potent than the combination of lopinavir and ritonavir.[45]

Protease inhibitors have been associated with a range of metabolic side effects, including the metabolic syndrome (hyperlipidemia, central fat accumulation, and insulin resistance), but the frequency with which they cause these abnormalities is variable. These metabolic derangements, along with those such as lipoatrophy and mitochondrial toxicity that are related to nucleoside analogues, have contributed to the rationale that the start of antiretroviral therapy should be deferred until it is clearly necessary. Cardiovascular risk is a concern. In a large, multicohort study, combination antiretroviral therapy was associated with a 26 percent increase in the risk of myocardial infarction per year of regimen exposure.[11] Atazanavir has the advantage of not inducing lipid-level elevations, but further study is needed to assess whether this advantage translates into reduced cardiovascular risk with this drug as compared with other protease inhibitors.

A third alternative regimen, involving triple nucleoside–nucleotide combinations, is no longer considered optimal for initial therapy. The combination of zidovudine, lamivudine, and abacavir confers reasonable viral suppression but is inferior to a regimen containing efavirenz.[46] A regimen of zidovudine, lamivudine, and tenofovir holds promise,[47] but data from randomized, controlled clinical trials are needed before it can be recommended unequivocally. Other triple nucleoside–nucleotide regimens (e.g., didanosine, lamivudine, and tenofovir and abacavir, lamivudine, and tenofovir) are associated with unacceptably high virologic failure rates and should not be used.[12,17]

Once an antiretroviral regimen is begun, close support of the patient is mandatory, to help ensure maximum drug adherence, manage low-grade drug-related symptoms, watch for toxic effects of the drugs (including life-threatening hepatotoxicity and hypersensitivity reactions), and monitor virologic and immunologic responses. Clinical outcomes also have been directly linked to the level of adherence to antiretroviral therapy.[48] In the long term, continued support and close monitoring for metabolic toxic effects (including cardiovascular risks) are crucial.

AREAS OF UNCERTAINTY

Several questions remain unanswered with regard to antiretroviral therapy for established HIV infection. These include whether it is possible to improve potency or whether there is an irreducible reservoir of low-level viral replication that cannot be affected by current agents[37]; what clinical role recently developed laboratory techniques, such as monitoring drug levels and viral replicative capacity during therapy,[49] have; how best to manage or prevent the metabolic toxic effects — hyperlipidemia, lipodystrophic syndromes, insulin resistance, lactic acidosis, and osteopenia — that are associated with antiretroviral therapy, underlying HIV infection, or both[50,51]; and the optimal management of infection in patients who are also infected with hepatitis B virus, hepatitis C virus, or both.[52,53] In addition, the role of new classes of antiretroviral drugs (such as chemokine-receptor blockers and integrase inhibitors) in initial therapy for HIV infection will need to be determined in clinical trials.

GUIDELINES FROM PROFESSIONAL SOCIETIES

Two major U.S. guidelines for the use of antiretroviral therapy have been developed and are routinely updated by the Department of Health and Human Services and the International AIDS Society–USA (IAS-USA).[12,17] Primary care guidelines for the management of HIV infection have been published by the Infectious Diseases Society of America (IDSA)[13] and the U.S. Public Health Service–IDSA has issued recommendations for the prevention of opportunistic infections.[25] The recommendations in this article are consistent with these guidelines. Other useful documents include guidelines developed by the IAS-USA for testing for HIV

drug resistance[15]; guidelines for treating opportunistic infections, recently updated by the CDC, the National Institutes of Health, the HIV Medicine Association, and the IDSA[24]; guidelines developed by the Department of Health and Human Services for the treatment of pregnant women infected with HIV[54]; and recommendations developed by the IAS-USA and the AIDS Clinical Trials Group for the management of metabolic complications.[51,55]

CONCLUSIONS AND RECOMMENDATIONS

In patients with newly diagnosed HIV infection, the initial emphasis should be on counseling with regard to the disease process, limiting the risk of secondary transmission, ensuring that there is proper support for the patient, and building a trusting relationship between the patient and the caregiver. An otherwise healthy person with asymptomatic HIV infection and no coexisting illnesses, such as the woman described in the vignette, should be advised that decades of productive life, which can include intentional pregnancies if desired,[56] are possible with proper care. The woman in the vignette is at a disease stage (a CD4 cell count of 325 cells per cubic millimeter and a plasma HIV-1 RNA level of 60,000 copies per milliliter) at which routine vaccinations are indicated but at which prophylaxis against *P. jiroveci, T. gondii,* and *M. avium* complex infections is not. Performing a genotypic HIV drug-resistance test is prudent, to be sure the patient is not infected with a drug-resistant virus. Given her CD4 cell count, initiating antiretroviral therapy should be discussed. If the patient were committed to therapy, I would recommend treatment at this point, as would most physicians. If there was doubt on the part of the patient or clinician about starting therapy, three to six months or more of observation, with serial measurement of CD4 cell counts and plasma HIV-1 RNA levels, would further inform the decision of when to start antiretroviral therapy. A regimen based on a nonnucleoside reverse-transcriptase inhibitor would be a reasonable first choice; I would start with efavirenz combined with the fixed-dose combination of tenofovir and emtricitabine. (Nevirapine is contraindicated, given this patient's CD4 cell count.) This combination would provide a potent, once-daily, and probably well-tolerated regimen involving a total of two pills. Effective contraception is needed, given the potential for teratogenic side effects with efavirenz. Close follow-up, to watch for side effects of therapy, provide ongoing support of drug adherence, and monitor plasma HIV-1 RNA levels and CD4 cell counts, is warranted, to optimize outcomes.

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