A 24-year-old man presents to an outpatient clinic, reporting that 36 hours previously he had receptive anal intercourse without the use of a condom with an anonymous male partner who was known to have had sex with other men. The patient is known to the clinical practice and has had several negative tests for human immunodeficiency virus (HIV) infection, most recently 6 months previously. How should he be evaluated and treated?

THE CLINICAL PROBLEM

There are more than 50,000 new cases of HIV infection in the United States and 2.7 million new cases worldwide annually, and strategies for HIV prevention are a major focus of clinicians and researchers. Vaccines for the prevention of HIV infection have thus far yielded mixed results, and safe and effective microbicides to block HIV are not yet available. However, HIV infection is not an instantaneous consequence of exposure to HIV, so there may be a window of opportunity for preventing infection after an exposure.

STRATEGIES AND EVIDENCE

The use of postexposure prophylaxis against HIV infection dates back to the early 1990s, when only limited antiviral treatment for chronic infection was available. Prophylaxis was primarily used after occupational exposures — exposures of health care workers to HIV-infected blood and body fluids, usually through needlestick injuries or contact with splashed blood or body fluids. Enrollment was not completed in a randomized, placebo-controlled trial of zidovudine (also known as azidothymidine, or AZT) for prophylaxis after occupational exposure.\(^3\) A case–control study in 1997 showed that health care workers who received zidovudine after needlestick exposures were 81% less likely to undergo seroconversion to positivity for HIV.\(^4\) Despite the important limitations of the study (including the retrospective design, small numbers of case patients, geographic differences between cases and controls, and lack of a uniform protocol for postexposure prophylaxis), these data made it untenable to conduct a placebo-controlled trial of postexposure prophylaxis, and active controlled trials would be prohibitively expensive, given the low per-exposure seroconversion rates.

After exposure to HIV through sexual contact or injection-drug use, antiretroviral therapy may also be administered for prophylaxis against infection. No efficacy data are available for this strategy, but substantial safety and feasibility data have led to its widespread acceptance.

ASSESSING THE NEED FOR POSTEXPOSURE PROPHYLAXIS

The use of postexposure prophylaxis presupposes that the person who was exposed to HIV is HIV-negative; thus, a negative result of a baseline enzyme-linked immu-
nosorbent assay (ELISA) for antibodies to HIV should be documented concomitantly with the assessment for postexposure prophylaxis. Testing to assess the HIV viral load, in the absence of signs or symptoms that are consistent with primary HIV infection, is currently not routinely recommended because of concerns about false positive results and cost, although a qualitative nucleic acid amplification test has been approved by the Food and Drug Administration for this purpose. Characteristics of both the exposure and the source patient should guide the decision about whether to administer postexposure prophylaxis.

**TYPE OF EXPOSURE**

**Occupational Exposure**

The overall rate of HIV transmission through percutaneous inoculation (i.e., by means of a needle or other instrument that pierces the skin) is widely reported to be 0.3% (95% confidence interval [CI], 0.2 to 0.5); features of exposure that are associated with a higher rate of transmission include a needle that was used to cannulate a blood vessel in the source patient, advanced HIV disease in the source patient, a deep needlestick, and visible blood on the surface of the instrument. Theoretically, any exposure that involves piercing of the skin may transmit infection, but clinical judgment is required to assess the likelihood that the inoculum is sufficient to pose a credible threat of transmission; many clinicians use a puncture that draws blood as a general threshold. Splashes of infectious material to mucous membranes (e.g., conjunctivae or oral mucosa) or broken skin also may transmit HIV infection (estimated risk per exposure, 0.09% [95% CI, 0.006 to 0.5]).

**Nonoccupational Exposure**

The per-contact risk of HIV transmission from sexual exposure varies according to the nature of the exposure. The estimated risks are 1 to 30% with receptive anal intercourse, 0.1 to 10.0% with insertive anal intercourse and receptive vaginal intercourse, and 0.1 to 1.0% with insertive vaginal intercourse. As compared with other forms of intercourse, oral intercourse is considered to pose a lower risk of HIV transmission, although good risk estimates are lacking, and there are case reports of HIV infections in persons in whom the only reported risk factor was oral intercourse. The risks of sexual transmission are difficult to quantify; the wide ranges reported for the risks of per-contact transmission derive from observational studies and are influenced by many factors, including the presence or absence of concomitant genital ulcer disease, other disease states, and cervical or anal dysplasia; circumcision status; the viral load in the genital compartment; and the degree of viral virulence. The estimated risk of transmission associated with sharing needles for injection-drug use is approximately 0.67% per needle-sharing contact.

**CHARACTERISTICS OF THE SOURCE PATIENT**

The question of whether postexposure prophylaxis is warranted after any potentially risky exposure hinges on the likelihood that the source patient is HIV-positive. In occupational settings, this question can often be resolved quickly with the use of a highly sensitive rapid ELISA, unless there is a known or suspected, recent high-risk behavior that would put the source patient at risk for occult seroconversion. Such exceptions aside, a negative result of a rapid ELISA in the source patient obviates the need for postexposure prophylaxis. If testing in the source patient must be delayed for any reason, it is prudent to administer a first dose of postexposure prophylaxis pending testing in the source patient.

The Centers for Disease Control and Prevention (CDC) categorizes source patients in occupational settings into the following subgroups: patients who are known to be HIV-positive with a high viral load (i.e., patients who are undergoing acute seroconversion and patients with chronic infection who have viral loads ≥1500 copies per milliliter), patients who are known to be HIV-positive with a low viral load (<1500 copies per milliliter), patients with an unknown HIV status, and patients who are known to be HIV-negative. A more useful threshold for risk stratification according to viral inoculum might be a detectable load (i.e., ≥50 copies per milliliter), although there is no viral level below which transmission cannot occur. It would be appropriate to consider the use of postexposure prophylaxis in a person who was exposed to HIV through contact with any of these source patients except those known to be HIV-negative (with caveats as previously noted); details are reviewed in guidelines from the CDC.

The source patient in nonoccupational settings is rarely available for testing, so a risk assessment based on other epidemiologic factors is required. Consensus guidelines recommend the consideration of prophylaxis in persons who have been exposed to known HIV-positive source patients...
and to selected high-risk populations with unknown HIV status among whom the seroprevalence of HIV infection is considered to be sufficient to justify the toxicity and cost of treatment.\textsuperscript{7,14-17} These populations include men who have sex with men, men who have sex with both men and women, commercial sex workers, injection-drug users, persons with a history of incarceration, persons from a country where the seroprevalence of HIV is 1% or greater, and persons who have a sexual partner belonging to one of these groups. Perpetrators of sexual assault are also considered to be at high risk for being HIV-positive; this risk is sufficient for the consideration of postexposure prophylaxis in the victim.

**Timing and Duration of Treatment**

Postexposure prophylaxis should be initiated as rapidly as possible after exposure to HIV. Data from macaques that were exposed to challenge with simian immunodeficiency virus suggest a greater benefit of postexposure prophylaxis when it is initiated within 36 hours after exposure as compared with 72 hours after exposure.\textsuperscript{18,19} One study indicated that postexposure prophylaxis was beneficial in infants born to untreated women with HIV infection when initiated within 48 hours after peripartum exposure.\textsuperscript{20} Postexposure prophylaxis should be continued for 28 days, on the basis of macaque models that showed incomplete protection conferred by shorter courses of postexposure prophylaxis after intravenous challenge.\textsuperscript{21}

**Regimens for Postexposure Prophylaxis**

In chronic infection, multidrug therapy (three or more agents) has been shown to provide optimal virologic and clinical benefit.\textsuperscript{22-24} However, the goals of treatment of chronic infection are distinct from those of postexposure prophylaxis; thus, it is questionable whether similar regimens are warranted for postexposure prophylaxis. The inoculum of virus to be inhibited in a person after exposure to HIV is orders of magnitude smaller than the viral burden in a patient with chronic infection; this might provide support for the sufficiency of fewer drugs. However, data suggesting that a single clone or a very small founder population of virions initiates the sentinel infection responsible for durable HIV propagation, at least in heterosexual transmission,\textsuperscript{25} underscore the importance of effectively inhibiting that small population; a greater number of drugs would improve coverage if the clone or founder population were resistant to one of the agents. Still, incremental toxicity has been observed with the use of increasing numbers of antiretroviral agents;\textsuperscript{26} this may lead to increased rates of discontinuation, with higher failure rates. Moreover, the addition of a third drug increases the costs of therapy.

Mathematical modeling suggests that the optimal regimen, balancing side effects, efficacy, and cost, would be a dual nucleoside regimen such as the fixed-dose combination zidovudine–lamivudine, unless the background rate of viral resistance in the source population is greater than 15%, in which case a three-drug regimen including a protease inhibitor would be favored.\textsuperscript{27} Regimens consisting of newer dual nucleoside combinations such as tenofovir plus emtricitabine are associated with substantially less toxicity and improved adherence, as compared with older nucleoside combinations.\textsuperscript{28,29}

The optimal components of a postexposure prophylactic regimen remain uncertain. Nucleoside analogues are the cornerstone of two-drug regimens, largely for historical reasons. If a third drug is added, a protease inhibitor, often boosted with low-dose ritonavir (e.g., ritonavir-boosted atazanavir, lopinavir, or darunavir), is commonly used; the use of a ritonavir-boosted regimen serves to improve the pharmacokinetics (Table 1). Nevirapine is not recommended for use in regimens for postexposure prophylaxis, given its associated risks of toxicity, including fulminant hepatitis and serious cutaneous adverse events with its use in persons who are not infected with HIV\textsuperscript{31,32} and concern about a lack of activity in some cases of transmitted resistance.

Reported rates of adherence to postexposure prophylactic medication are generally in the range of 70 to 80%, even with the use of newer agents.\textsuperscript{29,33,34} The level of adherence required to obtain the maximum benefit from a course of postexposure prophylaxis is not clear; specifically, it is not known whether the level of adherence considered necessary for a maximum treatment benefit in patients with chronic HIV infection (>95%)\textsuperscript{35} is applicable. Regular contact with the patient, as frequently as weekly during the 4-week regimen, either in person or by telephone or e-mail, is recommended to improve adherence.\textsuperscript{33}

**Baseline and Follow-up Assessments**

*Testing of the Source Patient*

In the event that a source patient with unknown HIV status is available for testing, a rapid ELISA
Table 1. Regimens for 28-Day Postexposure Prophylaxis for HIV Infection.†

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Daily Pill Burden† Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Two-drug regimens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir–emtricitabine (Truvada)‡</td>
<td>One tablet (300 mg of tenofovir with 200 mg of emtricitabine) once daily</td>
<td>1</td>
<td>Well tolerated; once-daily dosing</td>
</tr>
<tr>
<td>Zidovudine–lamivudine (Combivir)§</td>
<td>One tablet (300 mg of zidovudine with 150 mg of lamivudine) twice daily</td>
<td>2</td>
<td>Preferred in pregnancy</td>
</tr>
<tr>
<td><strong>Three-drug regimens¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir–lopinavir (Kaletra) (plus either tenofovir–emtricitabine or zidovudine–lamivudine)</td>
<td>Two tablets (50 mg of ritonavir with 200 mg of lopinavir per tablet) twice daily, or four tablets once daily</td>
<td>5 or 6</td>
<td>Either once-daily or twice-daily dosing; one copayment; no refrigeration required; most experience in pregnancy; high genetic barrier to resistance</td>
</tr>
<tr>
<td>Ritonavir plus atazanavir (plus either tenofovir–emtricitabine or zidovudine–lamivudine)</td>
<td>100 mg of ritonavir plus 300 mg of atazanavir once daily</td>
<td>3 or 4</td>
<td>Once-daily dosing; well tolerated</td>
</tr>
<tr>
<td>Ritonavir plus darunavir (plus either tenofovir–emtricitabine or zidovudine–lamivudine)</td>
<td>100 mg of ritonavir plus two tablets, each containing 400 mg of darunavir, once daily</td>
<td>4 or 5</td>
<td>Once-daily dosing; high genetic barrier to resistance</td>
</tr>
</tbody>
</table>

* Tenofovir, emtricitabine, and lamivudine all have activity against hepatitis B. Patients with chronic active hepatitis B (i.e., patients who are positive for hepatitis B surface antigen) may have flares of hepatitis on withdrawal of these agents at the completion of postexposure prophylaxis treatment. Referral to a hepatitis specialist or serial monthly monitoring of liver-enzyme levels for up to 6 months after treatment should be considered.

† The daily pill burden in the three-drug regimens depends on which two-drug regimen is chosen.

‡ The dose of tenofovir–emtricitabine should be reduced to one tablet every 48 hours in patients with a creatinine clearance of 30 to 49 ml per minute. Tenofovir–emtricitabine is not recommended in patients with a creatinine clearance of less than 30 ml per minute or in patients who are undergoing hemodialysis; see the guidelines from the Department of Health and Human Services for considerations regarding doses of individual agents in patients with advanced renal dysfunction.

§ Zidovudine–lamivudine is not recommended in patients with a creatinine clearance of less than 50 ml per minute; see the guidelines from the Department of Health and Human Services for considerations regarding doses of individual agents in patients with renal dysfunction.

¶ The boosting agent ritonavir is not considered to be an active drug in tabulating the number of agents in the three-drug regimen.

for antibodies against HIV (in either oral transudate or whole blood) should be performed, as well as testing for the hepatitis B surface antigen (HBsAg) and an ELISA for antibodies against hepatitis C virus (HCV). If the source patient is at risk for recent HIV or HCV infection on the basis of recent exposure (e.g., in the previous 2 to 4 weeks), nucleic acid–based testing (e.g., HIV and HCV RNA viral-load testing) should be considered to rule out acute infection, which would confer an increased risk of transmission.

**Baseline Testing of the Exposed Patient**

In addition to baseline HIV testing in the patient who has been exposed to HIV, assessment for immunity to the hepatitis B virus (HBV) is warranted. Vaccination against HBV is recommended if hepatitis B surface antibody is not present and chronic HBV infection has been ruled out (on the basis of a negative test for HBsAg). In persons who have been exposed recently (within 1 week) to an HBsAg-positive source patient and who are negative for hepatitis B surface antibody, treatment with immune globulin for HBV infection should be considered. Evidence of the sexual transmission of HCV, especially among men who have sex with men, has prompted experts to recommend baseline and follow-up HCV-antibody and HCV RNA testing for sexual as well as percutaneous exposures (Table 2). Screening and treatment
(as needed) for syphilis, gonorrhea, and chlamydial infections are appropriate in patients who seek care after sexual contact.

A follow-up ELISA for antibodies against HIV should be performed at 4 to 6 weeks, 3 months, and 6 months after exposure. With the use of older assays, the majority of HIV seroconversions are detectable within 6 to 12 weeks, and virtually all are detectable by 6 months; newer assays may accelerate this timetable. However, rare cases of delayed seroconversion (>6 months) after the use of postexposure prophylaxis have been reported. Many experts recommend that persons who have been exposed to HIV use condoms during sexual contact and avoid sharing blood-contaminated fomites (e.g., razors and toothbrushes) until there is documentation of negative test results at 6 months. Table 2 lists comprehensive recommendations for laboratory testing during and after postexposure prophylaxis.

### RISKS ASSOCIATED WITH POSTEXPOSURE PROPHYLAXIS

Pharmacologic prevention strategies such as postexposure prophylaxis may foster increased high-risk behavior. One strategy currently being studied in clinical trials is preexposure prophylaxis — the use of antiretroviral agents on an ongoing basis before or in anticipation of an exposure to HIV. Mathematical models suggest that changes in sexual behavior associated with this intervention may counteract protective efficacy, resulting in an increased incidence of HIV at the population level. Available data do not suggest associations between the use of postexposure prophylaxis and increased risk-taking behavior. However, these concerns underscore the need for the incorporation of strategies to reduce behavioral risks and counseling as part of HIV prevention.

Factors associated with seroconversion despite the use of postexposure prophylaxis include de-

### Table 2. Laboratory Tests Generally Recommended for Persons after Exposure to HIV.*

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommended during Treatment</th>
<th>Recommended at Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA for HIV antibodies</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Creatinine, liver function, and complete blood count with differential count</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HIV viral load</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Anti-HBs antibodies</td>
<td>Yes§</td>
<td>No</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Yes§§</td>
<td>No</td>
</tr>
<tr>
<td>HCV antibodies</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HCV RNA¶</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Screening, including rapid plasma reagin test, for other sexually transmitted infections‖</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Patients who receive zidovudine plus lamivudine–based regimens should have a complete blood count and measurement of liver-enzyme levels at 2 weeks of treatment, irrespective of the presence or absence of clinical symptoms. Tenoforv plus emtricitabine–based regimens generally involve few side effects, and symptom-directed assessment of serum creatinine or liver-enzyme levels should be considered. The addition of a ritonavir-boosted protease inhibitor should be followed by symptom-directed assessment of liver-enzyme levels, serum glucose levels, or both. Anti-HBs antibodies denotes hepatitis B virus surface antibodies, ELISA enzyme-linked immunosorbent assay, HBsAg hepatitis B surface antigen, and HCV hepatitis C virus.

† Symptom-directed tests are for signs or symptoms of toxic effects (rash, nausea, vomiting, or abdominal pain) or HIV seroconversion (fever, fatigue, lymphadenopathy, rash, or oral or genital ulcers).

§ If tests for anti-HBs antibodies and HBsAg are both negative, a vaccination series against HBV infection should be initiated and completed.

‖ Rapid plasma reagin testing and testing of urethral-swab and rectal-swab specimens for gonorrhea and chlamydia and of pharyngeal-swab specimens for gonorrhea should be performed as appropriate, according to the patient’s sexual risk-taking behaviors and the type of exposure to HIV.
layed administration of medication (>45 hours after exposure), receptive anal intercourse, nonadherence to treatment, and repeated exposures.\textsuperscript{49} Despite concerns that seroconversion in patients receiving postexposure prophylaxis might preferentially select resistant strains, limited case reports of seroconversion have shown the presence of wild-type virus, even when the virus is examined by sensitive sequencing methods. Paradoxically, seroconversion in patients receiving postexposure prophylaxis may be associated with a lower viral set point and attenuated disease progression.\textsuperscript{50} Data are needed from large prospective cohorts to establish the prevalence of sensitive and resistant infections when seroconversion occurs despite the use of postexposure prophylaxis. Nonadherence to treatment, subsequent exposures, or both may confound estimates of the efficacy of postexposure prophylaxis to provide protection against HIV infection.

The use of antiretroviral agents for postexposure prophylaxis that have activity against hepatitis B (including tenofovir, lamivudine, and emtricitabine) requires special consideration in persons with circulating HBsAg and a positive polymerase-chain-reaction test for HBV DNA, since flares of hepatitis B may occur on withdrawal of such agents.\textsuperscript{51} Follow-up with liver-function testing, consultation with a hepatologist, or both should be considered in such cases.

\textbf{Areas of Uncertainty}

The decision to initiate postexposure prophylaxis is a complicated one that is often predicated on the levels of risk-aversiveness and preferences of both the clinician and the patient. At a public health level, the costs of such treatment must be balanced against the risk of transmission associated with a given exposure. For both occupational and nonoccupational exposures, the interval after which postexposure prophylaxis will have no benefit is not known, but data are lacking to indicate a clear benefit when prophylaxis is initiated more than 48 hours after exposure. Data from randomized trials comparing various regimens for postexposure prophylaxis are lacking, and the optimal number and composition of antiretroviral agents to be used in a regimen remain uncertain.

The role in postexposure prophylaxis of agents that have recently been approved for the treatment of HIV infection remains unknown. Because of their mechanisms of action, raltegravir, the first HIV strand-transfer integrase inhibitor, and maraviroc, the first C-C chemokine receptor 5 receptor antagonist, are both attractive options for prevention. Experience with these agents for prophylaxis is limited to isolated case reports and small case series,\textsuperscript{52-54} in which their use appeared to be safe.

Postexposure prophylaxis has become the standard of care for occupational exposures, but it remains controversial as a public health intervention for nonoccupational exposures. Coverage for postexposure prophylaxis, which is associated with out-of-pocket costs of $1,000 or more for the requisite 28-day course of treatment, is not consistently provided by state Medicaid plans; thus, this strategy is inaccessible for patients who are reliant on such programs.

\textbf{Guidelines}

Guidelines for prophylaxis after occupational exposure are available from the CDC and the Department of Health and Human Services (DHHS).\textsuperscript{13,55} They are also available from the New York State Department of Health (2008)\textsuperscript{56} and the World Health Organization (WHO, 2007).\textsuperscript{17} Unlike the other guidelines, which recommend a 72-hour window for eligibility for postexposure prophylaxis, New York State’s guidelines recommend a 36-hour window and one specific first-line regimen (zidovudine, lamivudine, and tenofovir). The Occupational Safety and Health Administration refers to the CDC and DHHS guidelines as workplace standards.\textsuperscript{57} Guidelines for prophylaxis after nonoccupational exposure are also available from the CDC and the DHHS,\textsuperscript{7} the WHO,\textsuperscript{17} and some states. Clinicians may seek expert consultative services regarding occupational or nonoccupational exposures to HIV from the National Clinicians’ Post-Exposure Prophylaxis Hotline of the National HIV/AIDS Clinicians’ Consultation Center, available 24 hours a day (1-888-448-4911). The recommendations in this article are generally concordant with the CDC and WHO guidelines.

\textbf{Conclusions and Recommendations}

Prophylaxis is recommended after both occupational and nonoccupational exposure to HIV. Observational data suggest that such interventions
are approximately 80% effective in averting subsequent HIV seroconversion, but they are not a guarantee of protection. Prophylaxis should be reserved for exposures that are associated with a credible possibility of HIV transmission, usually considered to be at least a 0.1% risk of transmission from a source patient who is known to be HIV-positive or a source patient whose serologic status is unknown but who is at high risk for HIV infection. The man described in the vignette, who presented within 72 hours after receptive anal intercourse with a man who had an unknown serologic status and who was from a high-risk group (a man who had sex with men), should be offered postexposure prophylaxis. The regimen should be initiated as rapidly as possible after exposure and continued for 28 days. Testing for other sexually transmitted infections, including HBV and HCV infections, is also warranted. Vaccination against HBV and prophylactic therapy with immune globulin for HBV infection should be administered if indicated. Although data comparing different regimens for prophylaxis are lacking, we would recommend a 28-day course of tenofovir plus emtricitabine with or without a boosted protease inhibitor such as ritonavir–lopinavir; however, other combinations of two or three drugs would also be reasonable. Efforts to promote adherence to postexposure prophylaxis and referrals for counseling regarding risk reduction, as well as mental health, substance abuse, and domestic violence services, as appropriate, should be considered to be an integral part of programs for patients who receive postexposure prophylaxis.

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