

CLINICAL PRACTICE

Occupational Exposure to HIV in Health Care Settings

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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.

While obtaining a peripheral venous blood sample from a patient with the acquired immunodeficiency syndrome (AIDS), a 35-year-old phlebotomist is injured by a bloody 18-gauge needle attached to a syringe. The patient has been taking didanosine and stavudine for more than six months, but her quantitative plasma human immunodeficiency virus (HIV) RNA titer and CD4 T-lymphocyte count have not been measured for many weeks. What is the appropriate postexposure treatment for the phlebotomist?

THE CLINICAL PROBLEM

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Health care personnel who have occupational exposure to blood are at risk for HIV infection. Prevention of blood exposure, through safer practices, barrier precautions, safer needle devices, and other innovations, is the best way to prevent infection with HIV and other bloodborne pathogens.^{1,2} Although these strategies have been successful in reducing the frequency of blood exposure and needle-stick injuries in the past decade, the hazard has not been eliminated.

As of December 2001, the Centers for Disease Control and Prevention (CDC) had received voluntary reports of 57 documented cases of HIV seroconversion temporally associated with occupational exposure to HIV among U.S. health care personnel.^{1,3} An additional 138 infections among health care personnel were considered possible cases of occupational HIV transmission. Occupational transmission of HIV has been reported in most countries, but the global surveillance data required to estimate the true frequency of this problem are not available. Because there is no cure or effective vaccine for AIDS, optimal postexposure care, including the administration of antiretroviral drugs to prevent HIV infection, remains a high priority for protecting health care personnel.

Percutaneous injury, usually inflicted by a hollow-bore needle, is the most common mechanism of occupational HIV transmission. The CDC estimates that more than 380,000 needle-stick injuries occur in U.S. hospitals each year; approximately 61 percent of these injuries are caused by hollow-bore devices.⁴ Although the number of needle-stick injuries that occur in nonhospital settings, where 60 percent of the health care labor force is employed, is not known, it is probably large. The proportion of injuries involving exposure to blood from HIV-infected sources is not known, but each exposure is an urgent health issue for the exposed person. Clinicians in emergency departments, acute care clinics, and many other primary care settings must be equipped to assess the potential for HIV transmission after occupational exposure to blood and must determine the need for treatment and testing. Such clinicians must also be able to administer immediate postexposure treatment when indicated and refer exposed persons for appropriate follow-up medical care and counseling.

STRATEGIES AND EVIDENCE

There are two main strategies for managing occupational exposure to blood. The first approach is to provide empirical treatment with two or more antiretroviral drugs unless additional information (e.g., the result of an HIV test in the source patient or a detailed description of the exposure) suggests that this treatment is not warranted. The second approach is to conduct a thorough assessment of the exposure (including an HIV test in the source patient if HIV infection has not already been diagnosed) and then initiate antiretroviral treatment only if the exposure poses a risk of HIV transmission. A single antiretroviral drug or two or more antiretroviral drugs in combination may be used. Factors that should be considered in the choice of treatment for an exposed health care worker include the risk of HIV infection associated with the exposure, the expected benefit of antiretroviral treatment, the risks associated with the proposed treatment, and the probability that the infecting strains will be susceptible to the antiretroviral regimen used.¹

RISK OF HIV TRANSMISSION

A patient whose blood or other potentially infectious body fluid is involved in an occupational exposure should be evaluated to determine the likelihood of HIV infection, in accordance with relevant state regulations and local policies. The interval between the onset of viremia and the detection of HIV antibody, with the use of current enzyme immunoassays for HIV, is a few days at most.⁵ Hence, if the result of a reliable HIV test in the source patient is negative, the risk of transmission is assumed to be zero, unless the patient has risk factors for infection and the clinical findings are compatible with acute HIV infection (e.g., fever, pharyngitis, rash, lymphadenopathy, and malaise).

The use of a rapid HIV test can reduce the time needed to rule out HIV infection to a few hours or less. One test that is currently available, the Single Use Diagnostic System HIV-1 Test (Abbott-Murex Diagnostics), is highly sensitive, and a negative result is reliable evidence that infection is not present.⁶ A positive test is presumptive evidence of HIV infection, but confirmatory tests should be performed, since false positive results do occur. When properly performed by experienced laboratory personnel, rapid testing may not only decrease unnecessary antiretroviral treatment and save money but also allay the anxiety of the exposed person.⁷

Pooled data from several prospective studies of

health care personnel suggest that the average risk of HIV transmission is approximately 0.3 percent (95 percent confidence interval, 0.2 to 0.5) after a percutaneous exposure to HIV-infected blood and approximately 0.09 percent (95 percent confidence interval, 0.006 to 0.5) after a mucous-membrane exposure.¹ The average risk associated with exposure of nonintact skin and exposure to HIV-infected fluids and tissues other than blood or bloody fluids is too low to be estimated in prospective studies. In a retrospective study, the CDC found that the risk of transmission of HIV to health care workers was increased when the device causing the injury was visibly contaminated with blood, when the device had been used for insertion into a vein or artery, when the device caused a deep injury, or when the source patient died within two months after the exposure.⁸ These risk factors may be surrogate markers of the viral inoculum (the volume of the exposure and the viral titer), but this hypothesis has not been proved. A low plasma HIV RNA titer may indicate a lower inoculum but does not exclude the possibility of transmission, especially since this measurement does not account for cell-associated HIV. Transmission from source patients with undetectable HIV RNA has, in fact, been documented.¹

Suture needles have not been implicated as a source of infection in prospective studies, but occupational HIV infection has been reported among surgical personnel, and suture needles are one potential source of such infection. Exposure of intact skin to contaminated blood has not been identified as a risk for HIV transmission. The risk associated with bite injuries has not been quantified, but both the biter and the victim should be evaluated for the possibility of infection. The victim is usually at low risk unless the biter's saliva is contaminated with blood, as might happen during an altercation. If the bite results in a puncture wound or bleeding, then the biter may have had mucosal exposure to the victim's blood, which poses a risk of infection that is low but greater than zero if HIV is present.¹

BENEFITS OF CHEMOPROPHYLACTIC TREATMENT

A convergence of indirect evidence suggests that treatment with antiretroviral drugs soon after occupational exposure to HIV decreases the risk of infection. The pathogenesis of the initial infection provides suggestive evidence that there is a window of opportunity in which antiretroviral treatment can prevent infection or abort it before irreversible systemic infection and HIV seroconversion occur.

Early animal models provided conflicting infor-

mation about the probability of effective postexposure prophylaxis, but more recent and more appropriate models have consistently demonstrated the benefit of treatment.⁹⁻¹³ Several factors appear to affect the probability of transmission in animal models of postexposure treatment: the viral inoculum, the interval between viral inoculation and the initiation of treatment, the duration of treatment, and the choice of antiretroviral drugs.^{10,11,13}

In the CDC's retrospective case-control study of health care personnel, postexposure treatment with zidovudine was associated with an 81 percent reduction (95 percent confidence interval, 43 to 94) in the risk of HIV infection.⁵ However, there are no data from randomized, controlled trials to assess the efficacy and effectiveness of postexposure prophylaxis among health care personnel. Given the low risk of transmission, several thousand persons would have to be enrolled for such a trial to have enough power to show an effect. Data from clinical trials of prophylaxis against perinatal HIV transmission consistently demonstrate that antiretroviral treatment can prevent HIV infection after exposure, even among neonates who are not treated until after birth.¹⁴⁻¹⁹ The relevance of this clinical situation to occupational exposure is not known.

Although these data are encouraging, it is clear that, whatever benefit is afforded by postexposure treatment, the protection is not absolute. Twenty-one cases of HIV infection have been reported in health care personnel in the United States and elsewhere, despite postexposure antiretroviral treatment, which included two or more antiretroviral drugs in some cases.^{1,20-25} A variety of factors may have contributed to the treatment failure, including an intrinsic lack of efficacy of prophylactic antiretroviral treatment and resistance to antiretroviral drugs.

RISKS ASSOCIATED WITH CHEMOPROPHYLACTIC TREATMENT

All antiretroviral agents are associated with adverse events, especially gastrointestinal symptoms. Data from the National Surveillance System for Health Care Workers and the HIV Postexposure Prophylaxis Registry indicate that nearly 50 percent of health care personnel report adverse events while taking antiretroviral drugs prophylactically, and about one third stop taking the drugs as a result.^{1,26} Most of these symptoms are not serious and can be managed. Prophylactic regimens that include three drugs are more likely to result in adverse events and early

discontinuation of treatment than are two-drug regimens.²⁶

A variety of adverse effects have been associated with postexposure prophylaxis (Table 1). Serious events are rare, but they do occur and can be life-threatening. Nephrolithiasis, impaired ocular muscle movement, hepatitis, hyperglycemia, and pancytopenia have been reported.^{1,26-31} From March 1997 through September 2000, the Food and Drug Administration received reports of 22 persons with one or more serious adverse events related to the use of nevirapine as prophylaxis against HIV infection.^{30,31} There were 12 cases of hepatotoxicity (1 of which led to liver transplantation), 14 cases of skin reactions (including 1 documented and 2 possible cases of the Stevens-Johnson syndrome), and 1 case of rhabdomyolysis. On the basis of these reports, nevirapine is not generally recommended for prophylaxis. Because teratogenic effects have been observed in primate studies, efavirenz is not recommended during pregnancy. Reports of fatal lactic acidosis in pregnant women treated with a combination of stavudine and didanosine have prompted warnings about the use of these drugs during pregnancy. Indinavir is not recommended for use at the end of pregnancy because of the risk of hyperbilirubinemia in newborns.^{1,32}

ANTIRETROVIRAL-DRUG RESISTANCE

Resistance to antiretroviral drugs is a growing problem for all patients, including those whose blood is implicated in an occupational exposure. A study of occupational exposure conducted at seven U.S. sites in 1998 and 1999 showed that 16 of 41 source persons whose HIV viral genome was sequenced (39 percent) had mutations associated with resistance to reverse-transcriptase inhibitors, and 4 (10 percent) had mutations associated with resistance to protease inhibitors.³³ Resistance to antiretroviral drugs is most likely in patients with clinical progression of disease, increasing quantitative plasma HIV RNA titers, a decline in the CD4 T-lymphocyte count, or a combination of these findings.³⁴ Unfortunately, clinical data alone are not reliable in detecting resistance, and data from genotyping or phenotyping assays are rarely available in time to guide decisions about empirical postexposure treatment. For this reason, two or more antiretroviral drugs are usually used for prophylaxis after occupational exposure.¹

Table 1. Basic and Expanded Regimens of Postexposure Prophylaxis against Human Immunodeficiency Virus Infection.*

Regimen	Doses	Primary Adverse Effects
Basic		
Zidovudine (Retrovir) plus lamivudine (Epivir)†	600 mg of zidovudine daily in two or three divided doses; 150 mg of lamivudine twice daily	Zidovudine: anemia, neutropenia, nausea, headache, insomnia, muscle pain, weakness; lamivudine: abdominal pain, nausea, diarrhea, rash, pancreatitis
Lamivudine plus stavudine (Zerit)	150 mg of lamivudine twice daily; 40 mg of stavudine (if body weight is <60 kg, 30 mg) twice daily	Lamivudine: as above; stavudine: peripheral neuropathy, headache, diarrhea, nausea, insomnia, anorexia, pancreatitis, elevated liver-function values, anemia, neutropenia
Didanosine, available as a chewable or dispersible buffered tablet (Videx) or as a delayed-release capsule (Videx EC), plus stavudine	400 mg of didanosine daily, taken on an empty stomach if a buffered tablet is used (if body weight is <60 kg, 125 mg twice daily if a buffered tablet is used), or 250 mg daily if a delayed-release capsule is used; 40 mg of stavudine twice daily	Didanosine: pancreatitis, lactic acidosis, neuropathy, diarrhea, abdominal pain, nausea; stavudine: as above
Expanded (basic regimen plus one of the following)		
Indinavir (Crixivan)	800 mg every 8 hr, taken on an empty stomach	Nausea, abdominal pain, nephrolithiasis, indirect hyperbilirubinemia
Nelfinavir (Viracept)	750 mg three times daily, with a meal or snack, or 1250 mg twice daily, with a meal or snack	Diarrhea, nausea, abdominal pain, weakness, rash
Efavirenz (Sustiva)	600 mg daily, at bedtime	Rash (including Stevens–Johnson syndrome), insomnia, somnolence, dizziness, trouble concentrating, abnormal dreaming
Abacavir (Ziagen)‡	300 mg twice daily	Nausea, diarrhea, anorexia, abdominal pain, fatigue, headache, insomnia, hypersensitivity reactions

* The information is adapted from the recommendations issued in 2001 by the Public Health Service.¹

† A combined formulation is also available (Combivir); the recommended dose is one tablet twice a day.

‡ Abacavir is available as a combined formulation with zidovudine and lamivudine (Trizivir).

AREAS OF UNCERTAINTY

It is unclear why 99.7 percent of occupational injuries involving percutaneous exposure to HIV do not transmit infection, and an assessment of the risk of transmission therefore remains imprecise. Potentially relevant factors, such as the role of the host's immunologic response and characteristics of the viral strain that affect infectivity, have not been iden-

tified.^{35,36} Neither the window of opportunity during which postexposure antiretroviral treatment is beneficial nor the optimal duration of treatment for the prevention of infection is known.

The most effective and safest antiretroviral regimen for exposed persons also remains uncertain. A combination of three or more antiretroviral agents is usually advised for the treatment of HIV infection, but there is no clinical evidence that such combina-

tions are more effective in preventing infection after occupational exposure than is treatment with a single drug. In fact, of the five health care workers who are known to have acquired HIV infection despite prophylactic treatment with more than one antiretroviral drug, three received three or more drugs.³³

Finally, the efficacy and safety of prophylactic treatment in pregnant and breast-feeding women are not fully established, and there are few data on the effect of treatment on fertility, spermatogenesis, teratogenesis, and oncogenesis in otherwise healthy people.

GUIDELINES

Current Public Health Service guidelines (available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm>) recommend that a basic four-week regimen of two drugs (zidovudine and lamivudine, lamivudine and stavudine, or stavudine and didanosine) be started as soon as possible after most cases of HIV exposure through percutaneous or mu-

cosal routes (Table 1).¹ If the source person is determined to be HIV-negative, treatment should be discontinued. Antiretroviral treatment is not indicated for contact between intact skin and blood or other body fluids contaminated by HIV.

The Public Health Service guidelines specify that when the injury involves an increased risk of infection (e.g., an injury caused by a large-bore needle, associated with a deep puncture, or caused by a device visibly contaminated with blood or a device in a patient's artery or vein), the regimen should be expanded to include a third drug (Table 2). Indinavir or nelfinavir is recommended as a good option when a third drug is indicated. Efavirenz, a nonnucleoside analogue, and abacavir are also considered potentially useful drugs when an expanded regimen is indicated. Routine use of three drugs is not recommended for all exposed persons, because adding a third drug increases the probability that adverse events will occur and that the four-week course of treatment will not be completed.^{1,26}

HIV testing of exposed persons is recommend-

Table 2. Recommendations for Prophylaxis against Human Immunodeficiency Virus (HIV) Infection after Percutaneous Injury, According to the Infection Status of the Source Person.*

Risk Posed by Exposure†	Infection Status of Source Person‡				
	HIV-Positive, Class 1	HIV-Positive, Class 2	Unknown Status	Unknown Source Person	HIV-Negative
Lower	Basic 2-drug prophylaxis recommended	Expanded (3-drug) prophylaxis recommended	Generally, prophylaxis not warranted, but basic 2-drug prophylaxis can be considered if source person has risk factors for infection§	Generally, prophylaxis not warranted, but basic 2-drug prophylaxis can be considered in settings where exposure to HIV-infected persons is likely	Prophylaxis not warranted
Higher	Expanded (3-drug) prophylaxis recommended	Expanded (3-drug) prophylaxis recommended	Generally, prophylaxis not warranted, but basic 2-drug prophylaxis can be considered if source person has risk factors for infection§	Generally, prophylaxis not warranted, but basic 2-drug prophylaxis can be considered in settings where exposure to HIV-infected persons is likely	Prophylaxis not warranted

* The information is adapted from the recommendations issued in 2001 by the Public Health Service.¹

† Injuries caused by solid needles and superficial injuries pose a lower risk of infection, and those involving a large-bore hollow needle, a deep puncture, a device visibly contaminated with blood, or a needle used in a patient's artery or vein pose a higher risk of infection.

‡ A class 1 positive status is defined by asymptomatic HIV infection or a low viral load (e.g., <1500 RNA copies per milliliter); a class 2 positive status is defined by symptomatic HIV infection, the acquired immunodeficiency syndrome, acute seroconversion, or a high viral load. If drug resistance is a concern, an expert should be consulted. Initiation of prophylaxis should not be delayed pending such consultation. Resources should be available to provide immediate evaluation and follow-up care for all exposed persons.

§ If the source person has risk factors for HIV infection, prophylaxis is optional and should be based on an individualized decision made jointly by the exposed person and the treating clinician. If prophylaxis is administered and the source person is subsequently determined to be HIV-negative, prophylaxis should be discontinued.

ed as soon as possible after exposure (to establish that the infection was not already present) and periodically during the first six months after the exposure (to detect occupational transmission). Testing after six months is not usually indicated, but if the exposure posed an especially high risk or if the exposed worker needs further reassurance, additional testing may be helpful. An enzyme immunoassay for HIV antibody is the appropriate test for detecting new infections. The routine use of tests to detect plasma HIV RNA is not recommended. Since these tests are optimized to measure very low levels of HIV RNA, they have a relatively high rate of false positive results and a low positive predictive value when used to detect occupational infection — factors that can lead to unnecessary anxiety, unnecessary use of antiretroviral treatment, or both.^{36,37}

Laboratory monitoring, including a complete blood count and tests of renal and hepatic function, is recommended at base line and at two weeks. The use of additional tests depends on the specific regimen used (Table 1) and the medical condition of the source patient. The guidelines also recommend that persons who have acquired hepatitis C virus infection from the exposure be followed for 12 months, because anecdotal evidence indicates that they may be at risk for delayed HIV seroconversion.¹ All exposed persons, regardless of the postexposure treatment regimen, are advised to return for immediate evaluation if symptoms or signs that might be attributable to acute HIV infection appear.

Postexposure care must also address the risks of infection with hepatitis B virus and hepatitis C virus. The Public Health Service recommendations for management of occupational exposure to blood include strategies that target these viruses.¹

CONCLUSIONS AND RECOMMENDATIONS

In a case such as that described in the vignette, I would prescribe an antiviral regimen that included at least two drugs. I would choose drugs that were not part of the source patient's current treatment regimen, even though there is no evidence that this strategy reduces the risk of infection. Since the source patient was being treated with a stable regimen of didanosine plus stavudine, treatment of the exposed health care worker with zidovudine plus lamivudine would be reasonable. If the puncture was deep, the needle was visibly bloody before the injury, or the source patient had very advanced HIV infec-

Resource	Contact Information
National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline), University of California, San Francisco—San Francisco General Hospital†	Telephone: 888-448-4911 http://www.ucsf.edu/hivcntr
Needlestick! (online decision-making support for clinicians), Emergency Medicine Center, UCLA School of Medicine‡	http://www.needlestick.mednet.ucla.edu
CDC Hepatitis information line	Telephone: 888-443-7232 http://www.cdc.gov/hepatitis
To report occupational HIV infection and failure of prophylaxis	Telephone: 800-893-0485
Antiretroviral Pregnancy Registry	Telephone: 800-258-4263 Fax: 800-800-1052 http://apregistry.com
Food and Drug Administration To report severe or unusual toxic effects of antiretroviral drugs	Telephone: 800-332-1088 http://www.fda.gov/medwatch
AIDS treatment info	http://www.hivatis.org

* The information is adapted from the recommendations issued in 2001 by the Public Health Service.¹ AIDS denotes the acquired immunodeficiency syndrome.

† The hot line is supported by the Ryan White CARE Act, the HIV/AIDS Bureau, the Health Resources and Services Administration, and the Centers for Disease Control and Prevention (CDC).

‡ The Web site is supported by the Agency for Healthcare Research and Quality and the CDC.

tion or a high viral load when last tested, or if other factors suggested an increased risk of HIV transmission, I would discuss with the health care worker the rationale for my recommendation that a third drug, such as a protease inhibitor (e.g., indinavir), be added to the regimen. If I worked in a community where the incidence of primary resistance to zidovudine and lamivudine was known to be high, I would also encourage the use of a third drug. If information from recent tests of resistance to antiretroviral drugs was available or became available during treatment, I might adjust the regimen to include at least two drugs to which the virus was susceptible. To do so, I would rely on the strategies that form the basis for selecting empirical "salvage therapy" in persons with HIV infection, even though there is no evidence that this approach is effective.^{34,38} The U.S. National Clinicians' Post-Exposure Prophylax-

is Hotline (PEpline, 888-448-4911) is a useful resource for discussing treatment options and obtaining advice about the management of adverse effects of drugs. Table 3 lists additional resources for clinicians who are treating patients with occupational exposure to blood.

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