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The HIV-Positive Patient in the ED: HIV/AIDS Update for 2006: Part I

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Today, advanced treatment with highly active antiretroviral therapy (HAART) has pushed back the development of AIDS in many HIV-positive patients. Consequently, more people are living longer with HIV infection, increasing the likelihood that patients will present to the emergency department (ED) at some time during the course of their illness.

According to the Centers for Disease Control (CDC), roughly 40,000 people become infected with HIV in the United States every year.[1] The most recent CDC data from 2003 show that up to 1,100,000 people, or 1 in every 250 Americans, are living with HIV. Further, at least 400,000 of these people have AIDS. The worldwide data are even worse: there are more than 40 million people infected with HIV, two-thirds of whom (27 million) live in Africa. Most experts estimate that by the year 2010 there will be between 70 and 80 million cases of HIV in the world. Globally, there are 14,000 new cases of HIV infection daily and 3 million people die every year from complica-

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tions of HIV infection.[1] This makes HIV/AIDS the third leading cause of death worldwide. Overall, AIDS has killed more than 25 million people since 1981, making the HIV epidemic one of the most deadly infectious diseases in history.

Of the 1,100,000 people estimated to be HIV-positive in the United States, a dangerously high proportion have not been diagnosed; fully 250,000 individuals or 23% of those infected in the United States are not aware of their HIV status. While this is a high number, the percentage is in the same range as undiagnosed diabetics in the United States (28% or 5.2 million out of 18.2 million). However, diabetes is not contagious, and the undiagnosed people with HIV likely are responsible for the lion's share of new HIV cases each year. It is estimated that the 250,000 undiagnosed HIV-positive patients in the United States account for up to 66% of the 40,000 new cases of HIV each year.[2]

Until 1987, fully 50% of AIDS cases were found in only five large cities: New York, Newark, Miami, San Francisco, and Los Angeles.[3] No longer confined to big cities, HIV infection has touched all parts of the United States, and emergency physicians (EPs) in smaller towns also are treating patients with HIV and AIDS with increasing regularity. New drugs and new drug regimens are being used that can further complicate ED care. The ED also is the front-line for many health care workers who potentially become exposed to HIV (and other blood-borne diseases) through needle sticks and body fluid exposures. This article will give a brief overview of the virus, describe the presentation of HIV seroconversion (acute retroviral syndrome), and review the clinical effects of HIV/AIDS by organ system. Antiretroviral drugs and PEP recommendations also will be discussed. Lastly, recent advances in development of HIV vaccines will be described.

The Human Immunodeficiency Virus

Evolution of HIV. Most physicians know that HIV/AIDS first was recognized as a result of case reports of a few previously healthy homosexual men developing Kaposi's sarcoma (KS)[4] and *Pneumocystis carinii* pneumonia (PCP),[5] and that the virus was first isolated and identified in 1983.[6] Evidence from vertical transmission (mother to child) can trace HIV infection back to 1977.[7] Others have detected the virus in samples taken in the United States from individuals in the early 1970s, who are presumed to have become infected in the 1960s.[8] The earliest known detection of HIV was in a sample taken in Africa in 1959.[9] The evidence to date supports that HIV originated in Africa from a similar virus previously found in primates, simian immunodeficiency virus (SIV). SIV is thought to have crossed over into humans through hunters who repeatedly were exposed to infected blood when monkeys and chimpanzees were butchered and eaten, in a similar fashion to the way influenza viruses can cross over from birds to humans through close contact with infected animals.

Mutation is common in viruses, but the rate of mutation in HIV is particularly high. The two basic types are HIV-1 and HIV-2. HIV-1 is the primary virus affecting the United States and world. HIV-2 first was discovered in West Africa in 1986[10] and has spread throughout the world since, but is found in overall lower numbers than HIV-1. HIV-1 has continued to evolve into more than 17 different recognized types. This illustrates how difficult designing retroviral drugs and vaccines can be, as some forms of the virus may not be affected equally by all drugs/vaccines. Even if they are, the high rate of mutation makes resistance almost a certainty.

Life Cycle of HIV. HIV can enter the body via direct contact with the blood (e.g., injection drug abuse, accidental needle sticks, transfusion) or can enter through mucosal surfaces (sexual contact, breast milk). There, HIV specifically targets human CD4 T-lymphocytes and macrophages. HIV surface protein (gp120) binds to CD4 to initiate fusion with the host cell. Epidermal Langerhans (or dendritic) cells may be the entry point for mucosal surface infection of HIV. These cells have low levels of CD4 proteins on their surface, can take up the virus, and migrate to local lymph nodes where T-cells can become exposed and spread the infection. Thus, initial infection with the virus begins in the lymph nodes and explains the widespread lymphadenopathy seen with initial HIV infection.

HIV is a retrovirus (or RNA virus) and not a DNA virus. Rather than DNA, retroviruses contain strands of RNA that can be incorporated directly into the host cell's DNA. Retroviruses use reverse transcription, or make DNA from the RNA strand, and then can incorporate the viral DNA into the host cell's DNA. Unfortunately, viral reverse transcriptase found in HIV is particu-

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larly error-prone and is the basis for the high mutation rate of HIV and subsequent resistance to antiviral drugs.

Once infected, the host cell can remain dormant and permanently carry the viral DNA, or actively produce new virus. Dormant cells will pass on viral DNA anytime the cell divides, further complicating treatment attempting to eradicate HIV infections from the body. This also may explain how some individuals may continue to be HIV-positive but have very low levels of circulating virus detected even without drug therapy. When the infected host cell begins actively transcribing viral DNA, it makes new copies of the virus using the cell's proteins. The new viruses are released into the extracellular space or bloodstream, and the process repeats, ending in death of the CD4 lymphocyte and spread of the virus. Viral replication initially proceeds unabated, resulting in a high viral load early on in the illness until the immune system responds and dramatically lowers circulating HIV levels. This high viral load and subsequent immune response account for the acute HIV syndrome. (*See Clinical Effects in Part II.*) After the acute HIV syndrome resolves, the patient is in a latent phase of infection.

In the latent phase, the virus still is replicating slowly and depleting the body of CD4 cells, but the patient has no clinical effects. The median time for progression without treatment from initial HIV infection to the development of AIDS is about 8-10 years.[11] During the latent phase, the CD4 count steadily declines from the normal range (600-1500 cells/microL). Usually when the CD4 levels drop below a critical number (< 200 cells/microL), the immune system is no longer effective. Without the immune response to keep virus levels low, HIV levels in the blood once again begin to rise significantly. The patient becomes susceptible to opportunistic infections and neoplasms and at that point has developed AIDS. Low CD4 counts do not entirely explain the effects of HIV, though, as KS and some neurologic conditions in AIDS are independent of T-cell counts.

Current antiretroviral treatment can extend the time period before the critical drop in CD4 counts in many patients, but does not prevent it in the majority of cases. Thus, nearly all patients with HIV eventually will develop AIDS. The stage of the illness, and therefore the potential viral load in the patient's bloodstream, influences how infectious the patient's body fluids can be, and is important when assessing needle-stick injuries and other body fluid exposures. (*See section on Post-Exposure Prophylaxis.*) However, it is important to note that the patient always is potentially contagious at any stage of infection despite a lack of clinical signs of the illness.

Who Has HIV? Worldwide the ratio of males to females is roughly 1:1, with heterosexual contact as the primary mode of transmission. However, in the United States HIV affects men more often than women. Data from patients diagnosed with HIV in 2003 show that 70% of the new cases are men and 30% are women.[1] Of the infected men, 60% are from homosexual contact, 25% from injection drug use (IDU), and only 15% from heterosexual contact.[1] The newly diagnosed women are infected in 75% of cases from heterosexual contact and the other 25% from IDU.[12] Just over half of the new cases are in people younger than 25 years of age,[13] and minorities make up a higher proportion of HIV cases as well.

In the 1980s, HIV primarily was a disease of homosexual white men, but the majority of HIV cases now occur in racial and ethnic minorities (defined as black, Hispanic, Asian and Pacific Islander, Native-American, and Alaska Native).[14] In 1985 minorities accounted for 40% of those infected, but this has increased to 70% by 2002.[15] Of the AIDS cases diagnosed between 1985 and 2004, 48% were in black non-Hispanics who make up only 13% of the U.S. population. Hispanics account for 17% of AIDS cases but also make up only 13% of the population. White non-Hispanics account for 34% of the cases but make up 69% of the U.S. population.[1] These differences are blamed largely on a confluence of factors, including lower socioeconomic status,[15] IDU and substance abuse in general,[16] unprotected intercourse,[16] and disproportionate rates of other sexually transmitted diseases (STDs), especially gonorrhea and syphilis.[17]

For 2002, HIV ranked as the sixth cause of death for those between 25 and 34, killing 4.4% of this group. HIV was the fifth cause for those 35-44 and killed 6.3%, while it was the eighth cause for those 45-54, killing 2.6% of that group. For blacks aged 25-34, HIV is the third leading cause of death, killing 11%. Further, HIV is the number one cause of death for black females aged 25-34 and is responsible for 14.8% of deaths in that group for 2002. For Hispanics aged 35-44, HIV is the third leading cause of death with 10.4% of males killed by the disease.[18]

Modes of Transmission and Risk Factors. The virus is passed from person to person by exposure to another person's infected body fluids. HIV is found in high concentration in a variety of body fluids, such as blood, semen, vaginal fluid, and breast milk. HIV also has been found in low levels in almost every other kind of body fluid, including sweat, urine, cerebrospinal fluid (CSF), tears, bone marrow, alveolar fluid, synovial fluid, amniotic fluid, and saliva.[3] Fortunately, the virus does not survive well outside the body. Drying for only a few hours[19] or simple cleaning with bleach effectively eliminates HIV.[20]

It is important to realize that just because the virus is found in a certain body fluid it does not mean that this body fluid can transmit the virus. For example, HIV is found in low levels in saliva, but there have been no proven cases of transmission by exposure to saliva alone. In the one case of possible transmission through kissing, the HIV-positive partner had bleeding gums at the time.[21] Only exposure to semen, vaginal secretions, blood or blood products, breast milk, and transplacental transmission in utero has been proven to transmit HIV.[3] The viral load of the patient also plays an important role in the risk of transmission of the virus (See section on Post Exposure Prophylaxis). Transmission by insects, tears, and sweat does not occur. Table 1 summarizes the estimated risk for common modes of HIV infection based on a single encounter.

In general, any patient with CD4 count less than 200 cells/microL and/or viral loads greater than 50,000 is considered to be at greater risk of AIDS-defining illness, and can be considered higher risk for transmission of the virus. CD4 counts in healthy non-HIV infected people vary from 500 to 1500

Table 1. Estimates of Per-Contact Risk of HIV Infection[22-25]

TYPE OF CONTACT	RISK
Needle-sharing	6/1000 to 3/100
Occupational needle stick	1/300
Receptive anal	8/1000 to 3/100
Receptive vaginal	8/1000 to 2/1000
Insertive anal or vaginal	3/10,000 to 1/1000
Receptive oral	Case reports/no denominator
Transfusion of 1 unit of infected blood (current estimated range of infected blood in donated supply: 1/1,900,00)	1/1.05 to 1/1

cells/microL and are about 40-70% of the total lymphocyte count. In the ED CD4 counts often are unavailable, but one can use the total lymphocyte count to roughly estimate the CD4 count. Total lymphocyte counts less than 1000 cells/microL have been shown to strongly correlate with CD4 count less than 200 cells/microL.[26]

Sexual Contact. Sexual contact is by far the leading cause of HIV infections. More than 75 million people worldwide have become infected with HIV, the majority of which have been through sexual contact.[23] According to the CDC, fully 75% of the new HIV cases in 2002 in both men and women are due to sexual contact; 60% of these contacts in men are homosexual.[1] HIV transmission via sexual contact is not an efficient process. Receptive anal sex carries the highest risk, while insertive oral sex carries the lowest. It is clear that oral exposure to ejaculate can result in HIV transmission.[22]

Two predominant factors that increase HIV transmission are the viral load of the patient and presence of other sexually transmitted diseases (STDs), especially the presence of genital ulcers.[27] It is intuitive that a higher viral load of the source patient will result in exposure of greater viral numbers. One study found that seroconversion of HIV-negative partners was not observed if the infected partner had a plasma level of less than 1500 copies/mm HIV RNA.[28] Seroconversion was significantly less with plasma levels of 38,029 copies/mm compared to 90,254 copies/mm.[28]

Another recent study examined HIV transmission in heterosexual Ugandan monogamous partners where only one partner was HIV-positive. They found a transmission rate of 0.0082/coital act during the first 2.5 months of the infected partner's HIV course.[24] This shows that in the first few months of HIV infection, before the immune response lowers the viral load, the patient is most contagious.

Concurrent STD infection appears to increase transmission risk by several mechanisms.[23] Ulcerations as seen with syphilis and herpes simplex breach mechanical barriers to infection. Infection with HSV-2 (genital herpes) also greatly increases risk of HIV transmission[23] presumably via the same mechanism. Non-ulcerative inflammatory STDs chlamydia and *N. gonorrheae* increase white blood cell (WBC) levels (and therefore HIV) in genital fluids.[29] Uncircumcised males have an increased risk of infection as well,[30] as the inner surface of the foreskin contains a density of cellular HIV targets.

Injection Drug Use (IDU). Although AIDS incidence in IV drug users has declined since 1995,[31] estimates from the CDC show that as of the year 2000, IDU accounted for 25% of the HIV infections to date.[31] As seen in Table 1, the risk of HIV transmission for a single needle-sharing event can be as high as 3%. Many injection drug users erroneously believe that subcutaneous injection ("skin popping") or intramuscular injection ("muscling") is safe. At least one study supports the concern that injection drug users who are being treated for their HIV incorrectly believe that they are no longer contagious. Unfortunately, this false belief translates into increased rates of unprotected sex and needle-sharing.[32]

In some eastern European countries (i.e., Ukraine, Tajikistan), up to 50% of the economy is drug-related and up to 90% of the HIV cases are attributed to IDU.[33] Some European countries have opened safer-injection facilities (SIFs) where injection drug users are supplied with syringes that are clean. While these centers have been around for nearly 20 years, their use remains controversial.[34] Despite their long-standing use in Europe, little scientific evaluation of their effect on HIV or hepatitis B infection rates, or on reduction of drug-related deaths, exists.[34]

Transfusions. Exact data are hard to obtain, but the risk of HIV infection from a single incidence of transfusion or tissue transplantation from an HIV-infected donor is thought to be 95-100%. Not all blood products carry risk, though. While whole blood, packed red cells, platelets, leukocytes, and plasma all transmit the virus, transfusion of hyperimmune gamma-globulin, hepatitis B immune globulin, plasma-derived hepatitis B vaccine, and Rh immune globulin have not been shown to transmit HIV.[12]

At the peak of infectious risk in 1985, with no screening for HIV, the risk of a unit of blood being infected with HIV was nearly 1:100.[25] One estimate of the risk of HIV infection today is around 1:1,900,000[25] per unit of blood transfused. Another source cites that roughly 16 units of infected blood from the 12 to 14 million units (approximately 1:1,000,000) of blood donated every year in the United States make it past the screening processes and are available for use.[12] Up to 90% of people with HIV have evidence of past hepatitis B infection.[35] Serologic testing for syphilis also is employed to further screen the blood. Current technology cannot detect HIV RNA during the first 1-2 weeks of infection because of the low initial levels of viremia at this stage of infection. Thus sporadic cases of HIV infection from screened blood still will occur, as evidenced by a case in 2002 where two people became infected by blood from the same donor, who apparently had donated blood fewer than 10 days after he became infected with HIV.[12] In other countries, the risk is much greater. It is estimated that 6% of HIV infection in China results from people selling infected blood.[12]

The risk of HIV infection from tissue transplantation also still exists. Organ donors present further problems, as many die from trauma and may have received multiple transfusions of blood products during their treatment prior to donation. One estimate of HIV infection in tissue donors in 2004 found that 1 out of

Table 2. Factors Associated with High Risk of Occupational Exposures

SOURCE PATIENT
• Known high levels of viremia (Low defined as < 1500 RNA copies/mL)
• Known AIDS diagnosis
• Active opportunistic infection
• On multiple antiretroviral drugs
PERCUTANEOUS EXPOSURE
• Larger quantity of blood
• Visible blood on the sharp object
• Injury from device placed in vein or artery
• Hollow bore sharp
• Deeper injury
MUCUS MEMBRANE/NON-INTACT SKIN
• Larger quantity of blood
• Prolonged contact with body fluid
• Open wound on health care worker

Table 3. CDC 2005 PEP Recommendations: Percutaneous Exposure*

EXPOSURE TYPE	HIV CLASS 1 (LOW RISK)	HIV CLASS 2 (HIGH RISK)
Low Risk	2 drug regimen	> 3 drug regimen
Higher Risk	3 drug regimen	> 3 drug regimen

*** No PEP indicated for:**
- Known HIV-negative exposures

*** PEP not recommended but may consider 2-drug regimen for "high-risk source patients"**
- Source patient with unknown HIV status
- Unknown source patient

every 55,000 donors was HIV-positive.[36] This compares to 1 in 34,000 for hepatitis B and 1 in 42,000 for hepatitis C.[36]

Maternal-Fetal Transmission. An HIV-infected mother can transmit the virus to her child via three distinct mechanisms: exposure to the fetus before birth, during delivery, or by breast-feeding. The majority of infections occur during the birth process, accounting for 50-65% of cases;[37] 15-20% of children are infected through breast-feeding. Use of Cesarean section to reduce exposure of the fetus to maternal blood during delivery in combination with antiretroviral maternal treatment reduces the rate of transmission during birth in the United States to fewer than 1%.[38]

Occupational. Several thousand epidemiologic studies have traced thousands of patients treated by HIV-positive surgeons, obstetricians, dentists, and nurses, and only three health care workers world-wide have been identified as the source of their patients' HIV infection. The only U.S. case is the relatively well-known dentist in Florida who infected six of his patients in 1986. He apparently practiced for two years while HIV-positive, and while 10 of his 1100 patients became HIV-positive, only six were traced to the dentist.[39] The other two cases involve infection of a single patient in France (one by an orthopedic surgeon, the other by a surgical nurse).[12]

An estimated 600,000 to 800,000 needle sticks and other sharp injuries occur every year.[12] Besides HIV, other viruses (i.e., Hepatitis B, C), bacteria, protozoa (malaria), and even tumor cells have been transmitted via percutaneous exposure.[40] Data from non-immunized individuals show the risk of acquiring hepatitis B from a single percutaneous exposure is in the range of 40-60%,[41] higher than for any other infectious disease. Early estimates of hepatitis C risk were as high as 10%,[42] but more recent estimates put the risk at 0.5 to 2%.[43] One author calculated the risk of anesthesia personnel becoming infected with HIV or hepatitis C based on estimates of the number of needle sticks per year and the seroprevalence of both diseases.[40] They determined there would be 0.6 HIV infections and 5.2 hepatitis C infections per year in anesthesia personnel in the United States.[40]

The overall risk of HIV infection from a needle stick or other sharp object has been well studied and stands at about 0.3%.[44] Mucus membrane exposures are less risky, with about a 0.09% rate of HIV transmission.[45] Exposure through non-intact skin has occurred, but the risk has not been possible to calculate. It is thought to be much less than for mucus membrane exposure.[12] Exposure to larger quantities of infected blood (visible blood on the sharp object), higher viral levels of the source patient (end-stage AIDS), injury from a device placed in a vein or artery, hollow bore sharp objects, and deeper injury to the health care worker are all associated with higher risk of HIV transmission. (*See Table 2.*) Increased risk for mucus membrane exposures occurs with cases of prolonged contact with the infected blood, exposure to a large volume of blood, and presence of a visible potential entry portal (open wound on the health care worker).

Even with all of the sharp injuries each year, as of 2002 only 57 health care workers had become HIV-positive from a documented occupational exposure.[44] Of the 57, 33% were laboratory workers, 42% were nurses, and only 10% were physicians. Percutaneous exposures accounted for 84% of the cases, and only 9% were from mucus membrane exposure. An additional 137 other health care workers have HIV/AIDS, but the cause of their exposure was not documented. The following sections provide the current CDC recommendations for post-exposure prophylaxis for health care workers, followed by an overview of current antiretroviral drugs.

Post-Exposure Prophylaxis (PEP)

The most recent CDC update on PEP for HIV in 2005 (www.cdc.gov/mmwr/PDF/rr/rr5011.pdf) expands the list of antiretroviral drugs that can be used for PEP, and lists potential drug interactions between PEP medications and other drugs, both prescription and non-prescription. (*See section on Drug-Drug Interactions.*)[46] As before, PEP drug regimens are based on the severity of the exposure combined with the level of the source patient's viremia. Table 2 summarizes factors used to evaluate the severity of exposure and infectivity of the source patient. Examples of less severe exposures would be a superficial sharp injury or injury from a solid needle. More severe exposures

Table 4. CDC 2005 PEP Recommendations: Mucus Membrane or Non-intact Skin Exposure

EXPOSURE TYPE	HIV CLASS 1 (LOW RISK)	HIV CLASS 2 (HIGH RISK)
Small volume	Consider 2-drug regimen	2-drug regimen
Large volume	2-drug regimen	> 3-drug regimen

* No PEP indicated for:
- Known HIV negative exposures
- Small volume exposure from unknown source/unknown patient status

* PEP not recommended, but may consider 2-drug regimen for "high-risk source patients"
- Large volume exposure from unknown source/unknown patient status

include those with large-bore hollow needles, deep punctures, those with visible source blood on the device, or injury from a needle used in the patient's artery or vein. Lower-risk patients are asymptomatic HIV-positive patients or those with known low viral load (< 1500 RNA copies/mL). Higher-risk source patients are those with active opportunistic infections, history of AIDS, known acute seroconversion, or known high viral loads.

Table 3 summarizes the CDC 2005 PEP guidelines for percutaneous injuries and Table 4 summarizes the same for mucus membrane/non-intact skin exposures. Both percutaneous and mucus membrane/non-intact skin exposures are approached in the same fashion. Less severe exposures from low-risk source patients still are treated with a two-drug regimen. More severe exposures from low-risk source patients also are treated as before, with a three-drug regimen. Both less and more severe exposures from higher risk patients (as defined in Table 2) are now treated with three or more drugs. The drug regimens recommended in the 2005 CDC update are given in Table 5. (*See section on Antiretroviral Drugs for additional details on the drugs used in the various PEP regimens.*)

A web-based program designed to walk the user through the decision points from the 2005 CDC PEP updates also exits. This site is organized by UCLA, termed "Needlestick!", and it can be found at: www.needlestick.mednet.ucla.edu. Table 6 summarizes recommendations from the CDC on when to consult an infectious disease expert for advice on PEP. If local experts are unavailable, UCSF maintains a 24 hour National Clinicians' Post-Exposure Prophylaxis Hotline where physicians can consult for advice on individual cases: 1-888-448-4911. Table 7 summarizes a variety of other Internet and national telephone services where one can also seek expert advice. Many health care workers taking PEP do not complete the full 28-day course secondary to common side effects (i.e., nausea, headache, fatigue, and diarrhea). This issue, as well as cost of PEP (*see Table 8*), is discussed in the next section.

Non-Occupational PEP (nPEP)

In 2005, the CDC issued an update and for the first time gave recommendations on PEP for nonoccupational exposures. (*See Table 9A.*) Nonoccupational exposures are defined as: "exposure to blood, genital secretions, or other potentially infectious bodily fluids of a person known to be HIV infected."[47] A 28-day PEP course now is recommended for persons presenting within 72 hours of the nonoccupational exposure. These recommendations are not without controversy. At least one author doubts the effectiveness of nPEP, and suggests the major effect of nPEP may be just to increase the transmission of drug-resistant virus.[48]

Tables 9A and 9B summarize the newest CDC nPEP recommendations. The two most important points of the CDC nPEP recommendations are: No PEP is recommended for any exposure after 72 hours; and nPEP is advised only for exposure to high-risk fluids (i.e., blood, semen, vaginal fluid, rectal fluid, breast milk, or any visibly bloody fluid) from known HIV-infected sources. Treatment for exposure with these fluids from a source with unknown HIV status is to be decided on a case-by-case basis. Patients must be started on nPEP within 72 hours of the exposure, and patients exposed to fluids other than those listed above are not treated regardless of the source patient's HIV status. It is suggested that each ED may benefit from a policy on nPEP so that any patient presenting for nPEP is treated in a standardized fashion at that facility.

Challenges of nPEP for the ED. Several authors have argued that EPs are in a unique position to provide nPEP[49,50] as EDs already provide PEP for health care workers and provide the necessary 24/7 access. While EDs are likely a potential untapped resource for nPEP, there are many complicating issues with ED nPEP treatment outlined below.

The first issue complicating use of the ED for nPEP are those of follow-up counseling and testing for both complications of PEP and acute HIV seroconversion. The CDC recommends beginning with a 3- to 5-day starter package of prophylaxis medications. Most EDs would need to keep these stocked to give out at the time of the patient visit, as often is done for occupational PEP. The CDC recommends the following: possible additional HIV testing on the source patient to confirm HIV status, counseling/support to determine if the patient desires to complete the full nPEP course, and assessment of medical adherence to the PEP medications. These issues are best addressed by infectious disease (ID) specialists or by local health departments, but these services may not always be available. Further, the CDC also recommends testing of the nPEP recipient at 4-6 weeks, 3 months, and at 6 months for HIV, hepatitis B and C, and for other STDs as well as pregnancy "when appropriate." Obviously the ED is not the ideal location for these services to be rendered, but not all patients will have access to primary care physicians/ID specialists due to transportation/finances and other reasons. It is not clear how follow-up testing and counseling for ED patients treated with nPEP is to be accomplished.

Several other important aspects of nPEP also need to be emphasized. It should be stressed to any patient being treated

Table 5. CDC 2005 Basic and Expanded Drug Regimen Recommendations for PEP[46]

PREFERRED BASIC (2 DRUG) REGIMEN	ADVANTAGES	DISADVANTAGES
Zidovudine (AZT, Retrovir) + Lamivudine (Epivir) as Combivir	OK in pregnancy	Resistance common
Zidovudine (AZT, Retrovir) + Emtricitabine (Emtriva)	Well tolerated	No long-term studies
Tenofovir (Viread) + Lamivudine (Epivir)	Well tolerated	Resistance
Tenofovir (Viread) + Emtricitabine (Emtriva) as Truvada		
ALTERNATIVE BASIC (2 DRUG) REGIMENS		
Lamivudine (Epivir) + Stavudine (Zerit)	Well tolerated	Source patient resistance
Emtricitabine (Emtriva) + Stavudine (Zerit)	Well tolerated	Source patient resistance
Emtricitabine (Emtriva) + Didanosine (Videx)	Once a day	Diarrhea, pancreatitis
Lamivudine (Epivir) + Didanosine (Videx)	Once a day	Diarrhea, pancreatitis
PREFERRED EXPANDED—BASIC REGIMEN PLUS		
Lopinavir + Ritonavir (Norvir) as Kaletra	Potent protease inhibitor	Diarrhea, high lipids
ALTERNATIVE EXPANDED REGIMENS—BASIC REGIMEN PLUS		
Atazanavir (Reyataz) + Ritonavir (Norvir)	Once a day, potent	Jaundice common
Fosamprenavir (Lexiva) +/- Ritonavir (Norvir)	Once a day	Rash, GI effects
Saquinavir (Invirase) + Ritonavir (Norvir)	Well tolerated	Serious drug interactions
Indinavir (Crixivan) +/- Ritonavir (Norvir)	Potent	Renal stones, jaundice
Nelfinavir (Viracept)	Well tolerated	Diarrhea, drug interactions
Efavirenz (Sustiva)	Once a day	Rash, CNS effects, teratogen
GENERALLY NOT TO BE USED FOR PEP	**SIDE EFFECTS**	
Nevirapine (Viramune)	Severe hepatotoxicity, Stevens-Johnson syndrome	
Delavirdine (Rescriptor)	Drug interactions, Stevens-Johnson syndrome	
Abacavir (Ziagen)	Severe hypersensitivity reactions in < 6 weeks	
Zalcitabine (Hivid)	Weak antiretroviral, not tolerated	
ONLY TO BE USED FOR PEP WITH EXPERT CONSULTATION	**DISADVANTAGES**	
Enfuvirtide (Fuzeon)	Subcutaneous injection only May lead to false positive ELISA tests in future	

with nPEP that they are not guaranteed to avoid HIV infection risk, only to reduce it. There is at least one study so far that documents suspected failure of nPEP to prevent HIV infection.[51] In that study of 702 patients receiving nPEP in San Francisco, 7 (1%) still seroconverted, but 4 of these had further exposure to HIV sources during their nPEP treatment. Thus 3 of the 7 likely represented true treatment failures, and this also underscores that some patients actually may increase risky behavior, falsely believing they are not able to get infected while taking nPEP.

One article did show that counseling in combination with nPEP was effective in reducing high-risk sexual behaviors among 73% of 397 adults followed for 12 months after treatment with nPEP.[52]

Two additional problems with nPEP (and PEP) are the cost and the compliance. Cost estimates can range from $600 to $2700. (*See Table 8.*)[47] Further, nPEP medication cost coverage under individual health insurance plans, Medicaid, Medicare, and other state agencies varies widely. The question also must arise on repeated use of nPEP. Is the ED obligated to provide repeated

Table 6. CDC 2005 PEP Recommendations: When to Consult for Expert Advice*

SITUATION	REASON
Delayed exposure (24-36 hours)	Benefit of PEP unclear
Unknown source (needle in sharp box)	PEP to be used on case-by-case basis
Exposed person pregnant (or suspected)	Pregnancy not a contraindication for PEP
Exposed person breastfeeding	Breastfeeding not a contraindication for PEP
Resistance of source virus	PEP drug selection should be modified to select drugs likely to be effective
Toxicity of initial PEP regimen	PEP likely to be finished with modification (i.e., modify dose interval, timing of food)

*** National Sources of Expert Advice:**
• Needlestick! site from UCLA: www.needlestick.mednet.ucla.edu.
• UCSF maintains a 24 hour National Clinicians' Post-Exposure Prophylaxis Hotline where physicians can consult for advice on individual cases: 1-888-448-4911.

Table 7. List of Contacts for Additional Information on HIV/AIDS

NATIONAL TELEPHONE HOTLINES	
CDC Info CDC hotline—source of statistics, referrals, answers to questions	800-CDC-INFO
AIDS "Warm" Line HIV telephone consult from Am. Academy of Family Physicians	800-933-3413
Project Inform Hotline Provides HIV treatment strategy information and resource guide	800-822-7422
INTERNET SITES	
AIDSinfo	http://aidsinfo.nih.gov
CDC	www.cdc.gov/hiv/
HIV InSite	http://hivinsite.ucsf.edu/
Medscape HIV/AIDS	www.medscape.com/hiv-home

courses of nPEP for individuals who continue high-risk behaviors?

Compliance with the entire 28-day course also can be problematic due to frequent unpleasant side effects, such as diarrhea, vomiting, rashes, and interaction with other medications. Although exact estimates vary, in one study of 492 health care workers prescribed PEP, fully 44% were not able to complete the full PEP course.[53] While 76% of people taking PEP in this study reported side effects (nausea, vomiting, fatigue, headache, and diarrhea) with a mean onset of only 3-4 days after beginning treatment, only 1% had "serious" side effects.[53]

Antiretroviral Drugs

Zidovudine originally was developed as an anti-cancer drug in the 1960s. It was not successful in this role, but was revived as the first antiretroviral approved for use in treating HIV. While trials found an initial benefit from zidovudine, this benefit was short-lived and zidovudine use alone did not increase survival time in HIV infection. In retrospect, this was the first evidence of how fast HIV mutates; virus strains rapidly (< 6 months) became resistant to zidovudine when used alone. Resistance to nevirapine has been found after only a few weeks in mothers who were only given a single dose during birth.[54]

It was not until 1996 that combination drug therapy for HIV was introduced. Also termed HAART, for highly active antiretroviral therapy, combination drug treatment has quickly become the mainstay of HIV treatment. Although antiretrovirals are not initiated by ED physicians, general knowledge of the principles of HIV drug therapy (HAART) and of the drugs currently used can be very useful when treating patients with HIV in the ED. HIV medications and their major side effects will be discussed briefly by class. (*See also Tables 5, 10A, and 10B.*)

General management principles are as follows. Most clinicians use CD4 levels and plasma RNA levels as markers for the magnitude of HIV replication and thus guidelines for treatment, but any patient with an opportunistic infection should be treated regardless of their CD4 counts or viral loads. Likewise, treatment should be started for any patient with acute HIV syndrome (acute seroconversion reaction). Otherwise, CD4 levels of 200-350 cells/microL or rapidly falling levels, and plasma HIV RNA levels greater than 50,000 to 100,000 copies per microliter are the thresholds most often used to begin treatment in the asymptomatic patient.[55,56] The patient's prognosis on HAART can be judged by the response to therapy after 6 months of treatment, and those with the lowest viral loads (< 500 copies/mL) have the best survival rates.[57] The goal of treatment is maximal suppression of HIV replication and preservation of immune system function.

HAART. Multiple drugs are available in three classes (see below): nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Most HAART regimens use one of the following: 2 NRTIs and 1 PI, 2 NRTIs and 2 PIs, or 2 NRTIs and 1 NNRTI. The treatment principle is similar to that for tuberculosis: use multiple effective medications in combination to reduce the likelihood of developing drug resistance. Note that pregnant patients are treated in similar fashion as other adults, but the side effects of certain antiretrovirals may compound those of

Table 8. CDC 2005 PEP and nPEP Estimated Costs*[47]

1. Occupational PEP (PEP)

ANTIRETROVIRAL DRUG	COST FOR 4-WEEK COURSE
A. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI) (Class side effects: lactic acidosis, hepatomegaly)	
Abacavir (Ziagen, ABC)	$400
Didanosine (Videx, ddI)	$260
Emtricitabine (Emtriva, FTC)	$280
Lamivudine (Epivir 3TC)	$300
Stavudine (Zerit, d4T)	$320
Tenofovir (Viread)	$400
Zidovudine (Retrovir, AZT)	$350
Zalcitabine (Hivid)	$260
B. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) (Class side effects: Stevens-Johnson syndrome)	
Efavirenz (Sustiva)	$420
Delavirdine (Rescriptor)	$292
Nevirapine (Viramune)	$275
C. Protease Inhibitors (PI) (Class side effects: GI intolerance, hyperlipidemia, diabetes)	
Atazanavir (Reyataz)	$760
Fosamprenavir (Lexiva)	$1260
Indinavir (Crixivan)	$500
Nelfinavir (Viracept)	$600
Ritonavir (Norvir)	$700-2800
Saquinavir (Invirase—hard-gel capsule) (Fortovase—oft-gel capsule)	$460
Tipranavir (Aptivus)	$1083
Amprenavir (Agenerase)	$666
D. Fusion Inhibitors	
Enfuvirtide (Fuzeon)	$1666
E. Combination Tablets (all NRTIs except Keletra)	
Lopinavir/ritonavir (Keletra) (PIs)	$650
Zidovudine/lamivudine (Combivir)	$640
Zidovudine/lamivudine/Abacavir (Trizivir)	$1020
Lamivudine/abacavir (Epizcom)	$760
Emtricitabine/tenofovir (Truvada)	$800
Total Cost for preferred 2 drug PEP regimen:	
Zidovudine + emtricitabine	$630
Zidovudine/lamivudine (Combivir)	$640
Tenofovir + lamivudine	$700
Emtricitabine/tenofovir (Truvada)	$800
Total Cost for preferred 3 drug PEP regimen: (Basic regimen ***PLUS*** Keletra)	$1280-$1450
Total Cost for > 3 drug PEP regimen:	up to $2760

2. Non-Occupational PEP (nPEP)

ANTIRETROVIRAL	COST FOR 4-WEEK COURSE
Total Cost for preferred 3 drug regimen: Efavirenz + Lamivudine or emtricitabine + Zidovudine or tenofovir	$1050-$1120
Total Cost for preferred > 3 drug regimen: Lopinavir/ritonavir (Keletra) + Lamivudine or emtricitabine + Zidovudine	$1280-$1300

*New drugs are continually being introduced, and thus this list may be incomplete at time of publication.

normal pregnancy. Lastly, HIV infection progresses to AIDS more rapidly in children, and although the same drugs can be used in children, HAART regimens are altered for pediatric patients.

Drug-Drug Interactions. Drug-drug interactions with HAART medications are relatively common and can be life-threatening in some cases.[58] (*See Tables 10A and 10B.*) The drug level alterations occur because HAART medications, especially PIs and NNRTIs, affect the cytochrome P450 system of the liver, which is a key component of drug metabolism for many medications.

Serum drug levels can be changed by inhibition or stimulation of the P450 system, and examples of this effect are already well known. For example phenytoin, carbamazepine, rifampin, and St. John's wort are known to induce P450 enzymes and thus can lower serum levels of other drugs. Other medications such as ketoconazole, fluconazole, macrolides, and selective serotonin re-uptake inhibitors (SSRIs) are know to inhibit the P450 system and can raise serum levels of other drugs. Medications used in HAART now also are known to have effects on the P450 system. PIs are inhibitors of the cytochrome P450 system, with ritonavir and lopinavir being the most potent inhibitors. These two drugs commonly are used together as the combination pill Kaletra. NNRTIs stimulate the P450 enzymes, and delavirdine (Rescriptor) and efavirenz (Sustiva) are the two most common ones cited.

Thus, the EP should be aware of two kinds of drug-drug interactions. The first involves patients who are on HAART who are prescribed outpatient drugs from the ED that can affect antiretro-

Table 9A. CDC 2005 nPEP (Nonoccupational) Recommendations[47]

EXPOSURE TYPE	< 72 HOURS SINCE EXPOSURE	> 72 HOURS SINCE EXPOSURE
Negligible risk*	nPEP ***not*** recommended	nPEP ***not*** recommended
Substantial risk*		
Source known HIV +	**nPEP recommended**	nPEP ***not*** recommended
Source unknown HIV status	Case-by-case use	nPEP ***not*** recommended

* **Negligible risk =** **exposure of:** vagina, rectum, eye, mouth, or other mucus membrane intact or non-intact skin, or percutaneous contact

with: urine, nasal secretions, saliva, sweat or tears if *not* visibly contaminated with blood

regardless: of the source patient's HIV status

* **Substantial risk =** **exposure of:** vagina, rectum, eye, mouth or other mucus membrane, intact or non-intact skin, or percutaneous contact

with: blood, semen, vaginal secretions, rectal secretions, breast milk, or *any* body fluid visibly contaminated with blood

when: the source is known to be HIV-infected

viral levels. The most common medications in this group that are likely to be prescribed by EPs are antifungals (ketoconazole, fluconazole) and anti-TB medications such as rifampin and rifabutin. (*See Table 10A and 10B.*) Unfortunately, it has been established that even short-term lowering of antiretroviral levels is associated with irreversible viral resistance and loss of clinical effectiveness for the HAART regimen.[59] Patients who are already on HAART and need to be given anti-TB or antifungals should have their case discussed with the physician in charge of their HAART regimen (usually an ID specialist).

The second kind of drug-drug interaction EPs need to be aware of is the type in which the HIV patient is given medications in the ED that will have their levels increased by the HAART drugs. Several medications commonly used in the ED can produce enhanced effects in these patients, including benzodiazepines, Ergot derivatives, calcium channel blockers, and antiarrhythmics. (*See Tables 10A and 10B.*) Midazolam (Versed) given in normal doses may produce more sedation and respiratory depression in patients on PIs.[60] Likewise, metabolism of ketamine is slowed by PIs and could produce unexpected respiratory depression during procedural sedation. Dihydropyridines, such as diltiazem (Cardizem), have been associated with hypotension and bradycardia.[61] Antiarrhythmics including amiodarone[62] and flecanide[63] also have been reported to have increased serum levels when given to patients on ritonavir.

Although few data are in the literature, fatalities have been reported as a result of patients taking both ritonavir and Ecstasy[64] or GHB.[65] (*See Table 10B.*) Likewise, it has been theorized that PIs should increase the effects of heroin, but no cases have been reported.[66] However, NNRTIs have an opposite effect and have been known to precipitate methadone withdrawal.[66]

HAART Limitations. It initially was hoped that HAART therapy actually could cure patients of HIV infection. Unfortunately, latent cells (like memory T cells) contain HIV and can cryptically harbor virus. True long-term data have yet to be obtained, but currently it is believed that HAART medications will not prevent the onset of AIDS and deaths from HIV—they will only delay it.[67]

Still, HAART has been successful in prolonging life, improving quality, and delaying onset of AIDS complications. Essentially, HAART prolongs the latent phase of the disease. (*See section on Clinical Effects of HIV in Part II.*) Many HAART medications have complications that make compliance an issue and necessitate changing to alternative drugs. Examples include mild side effects such as nausea, vomiting, diarrhea, headache, and fatigue. More serious side effects also occur, such as pancreatitis, Stevens-Johnson syndrome, and liver complications. Up to 25% of patients taking HAART discontinue the medications due to side effects.[68]

Another constellation of side effects arises from alteration of normal metabolism, specifically inhibition of mitochondria oxidative phosphorylation. This is seen most dramatically in PIs, but is a complication of all classes of antiretrovirals.[69] These include altered fat distribution, hyperinsulinemia, hyperglycemia, dyslipidemia, and increased blood pressure.[68] This list may sound familiar because it is the same as the list of major risk factors for coronary artery disease. As expected, one recent study found that low-density lipoprotein cholesterol levels were increased as much as 28% for patients using PIs.[70] Further, a full 70% of patients taking PIs developed dyslipidemia.[68] This translated to a 50% increase in

Table 9B. CDC 2005 nPEP Preferred Drug Regimens[47]

PREFERRED REGIMENS				
Efavirenz (Sustiva)	***PLUS***	Lamivudine (Epivir) ***OR*** Emtricitabine (Emtriva)	***PLUS***	Zidovudine (AZT, Retrovir) ***OR*** Tenofovir (Viread)
Lopinavir/Ritonavir (Kaletra)	***PLUS***	Lamivudine (Epivir) ***OR*** Emtricitabine (Emtriva)	***PLUS***	Zidovudine (AZT, Retrovir)

NOTE: There are numerous alternative regimens available. Consult CDC information or an infectious disease expert.
* Abacavir (Ziagen) is listed by the 2005 CDC update on PEP as an "antiretroviral generally not for use as PEP" due to "severe hypersensitivity reactions" that "can be confused with acute seroconversion."
** Triple NRTI regimen to be used only when NNRTI or PI-based regimen cannot or should not be used.

calculated risk of coronary disease over the next 10 years.[70] In 2003, one researcher estimated a 26% increased risk of myocardial infarction for each year the patient takes HAART.[71]

A potentially dangerous and initially unforeseen problem is that some patients misinterpret the successfulness of their HAART treatment. Numerous studies show that increased use of HAART directly correlates with increased incidence of STDs and decreased condom use in high-risk populations, including homosexual men[72] and IDUs.[73]

Complications aside, many fundamental questions on the basic use of HAART medications remain.[74] Data are unclear on exactly when to start HAART, whether to start with a two- or three-drug regimen, when to switch therapy based on poor results, resistance or side effects, and when (if ever) to stop therapy. More information on these issues can be found in the recent CDC update on guidelines for use of antiretrovirals.[75] Cost is another barrier, with one year of HAART medications ranging from $12,000 to $30,000.[76]

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs). NRTIs were the first drugs developed for antiretroviral treatment, and there are 12 of these currently approved by the FDA (4 as combinations in a single pill—See Table 8). Among the NRTIs are the first HIV antiretroviral zidovudine (AZT, Retrovir) and two of the most commonly prescribed drugs in CDC regimens (lamivudine and emtricitabine). They act by blocking the HIV reverse transcriptase enzyme, which halts the synthesis of viral DNA and stops viral replication. Unfortunately, this class of drugs is not very selective for HIV reverse transcriptase and also interferes with a variety of DNA polymerization reactions. Thus, serious side effects are more common with these drugs, including hepatic steatosis, lactic acidosis (via mitochondrial effects), peripheral neuropathy, and pancreatitis.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs). NNRTIs are similar in action to NRTIs in that they inhibit reverse transcriptase, but they are much more selective than the NRTIs. Consequently, side effects with NNRTIs are much less severe. Severe side effects still can occur, but they consist of rashes that can progress to Stevens-Johnson syndrome, and hepatic complications such as hepatic necrosis, cholestatic hepatitis, and fulminant liver failure. There currently are three drugs in this class approved by the FDA for use against HIV. (*See Table 8.*) However, they are only active against HIV-1 and have no activity against HIV-2 type viruses.

Protease Inhibitors (PIs). The number of patients dying from AIDS has fallen by 66% since PIs were introduced in 1996.[77] There currently are nine of these drugs approved by the FDA. (*See Table 8.*) Kaletra is the single pill combination of lopinavir/ritonavir and is one of the more common antiretrovirals prescribed. It is one of the drugs recommended in both preferred CDC regimens for PEP and nPEP. The protease enzyme they block is one used to complete the HIV virus replication cycle by activating HIV proteins after synthesis. Without this enzyme, new viruses released by infected cells are essentially not contagious and cannot infect additional cells. PIs commonly are used in combination with NRTIs and NNRTIs, and have been shown to be effective in individual patients for up to five years. As mentioned previously, though, PIs have significant side effects of altered lipid metabolism and can dramatically increase incidence of coronary artery disease.[70] Indinavir (Crixivan) also is known to produce renal colic from urinary crystals to the point of hydronephrosis, but will have no stones identified on CT scans.[78] These patients can be treated symptomatically.

Fusion Inhibitors. The newest class of antiretrovirals are fusion inhibitors.[79] Only one is currently FDA approved: enfuvirtide (Fuzeon). (*See Table 8.*) They act in a novel fashion by halting fusion of the HIV membrane with the CD4 cell membrane, thereby preventing insertion of the virus contents with the CD4 cell. As a new medication, currently no cross resistance exists between enfuvirtide and other antiretrovirals. Fusion inhibitors are also unique as they are peptides, and thus cannot be taken by mouth. They can only be given as daily subcutaneous injections. Early studies show the primary side effects are related to the injection site, but some other side effects have been noted (i.e., pancreatitis, myalgias, depression). Cost is likely to be another factor, as the estimated annual cost for one course of treatment with enfuvirtide is $20,000.

HIV Testing in the ED

HIV testing in the ED primarily is limited to treatment of health care workers occupationally exposed to HIV. Testing of

Table 10A. Drug-Drug Interactions with Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs)*: Drugs to Avoid[59,66,75,76]

DRUGS TO AVOID	SIDE EFFECTS
Benzodiazepines (Midazolam or Versed) (Triazolam or Halcion)	Enhanced effects, and respiratory depression
Antihistamines Terfenadine (Seldane) Astemizole (Hismanal) Cisapride**	QT prolongation, arrhythmias
Ergot derivatives (dihydroergotamine DHE)	Enhanced effects, vasospasm, ischemia
TB medications (Rifampin)	Lowers plasma PI / NNRTI levels by up to 90%
Statin drugs (Lovastatin or Mevacor) (Simvastatin or Zocor)	Rhabdomyolysis
Herbals—St John's wort	Lowers PI / NNRTI levels

* Protease inhibitors commonly cited for drug interactions: ritonavir (Norvir), Ritonavir/lopinavir (Kaletra), saquinavir (Fortovase, Invirase), indinavir (Crixivan), and nelfinavir (Viracept). NNRTIs commonly cited for drug interactions: delavirdine (Rescriptor) and efavirenz (Sustiva).

** Be aware that cisapride (Propulsid—taken off the U.S. market in 2000) is associated with potentially fatal arrhythmias when used with PIs and NNRTIs.

Table 10B. Known Drug Interactions Between Commonly Used Drugs and Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and/or Protease Inhibitors (PIs)*: Side Effects to Know[67,74,75,76]

USE THESE DRUGS WITH CAUTION	REASON
Benzodiazepines (Alprazolam or Ativan)	Enhanced effects, and respiratory depression
Calcium channel blockers (Dihydropyridines)	Enhanced effects, hypotension, bradycardia
Antiarrhythmics (Amiodarone, Flecainide. Lidocaine)	Enhanced effects, hypotension
Warfarin (Coumadin)	Increased PT with PIs, may increase or decrease with NNRTIs
Anticonvulsants (Phenobarb, phenytonin, or carbamazepine)	Decreased anticonvulsant levels (except Ritonavir may increase carbamazepine)
Ketamine	Enhanced effects, respiratory depression
Antifungals (Ketoconazole, fluconazole)	Increased serum PI levels
Antibiotics Clarithromycin	Increased antibiotic levels
Inhaled steroids (Fluticasone or Flonase)	Systemic corticosteriod side effects
Theoyphylline	Decreased serum levels taken with PIs
Drugs of abuse:	
Methadone	NNRTIs lower opiate levels, may precipitate withdrawal
Amphetamines, Ecstasy	Enhanced effects, hypertension, arrhythmias
GHB	Respiratory depression, bradycardia
Heroin	Enhanced effects from PIs, but no cases reported

*Protease inhibitors commonly cited for drug interactions: Ritonavir (Norvir), Ritonavir/Lopinavir (Kaletra), Saquinavir (Fortovase, Invirase), Indinavir (Crixivan), and Nelfinavir (Viracept). NNRTIs commonly cited for drug interactions: Delavirdine (Rescriptor) and Efavirenz (Sustiva).

others generally is not done due to constraints placed by CDC recommendations: obtaining informed consent, providing counseling, maintaining confidentiality, and ensuring appropriate follow-up.[80] Recent introduction of rapid HIV tests (with results in 20 minutes) may alter diagnosis of HIV in the ED in the future.

Most tests (ELISA, WB) screen for evidence of seroconversion, which may not have occurred yet. In other words, both tests screen for anti-HIV antibodies present in the serum. In the acute stage of HIV infection, anti-HIV antibodies have not yet been produced or may be at too low of a level for detection. This time period is referred to as the "window period," and is estimated to be only about two weeks in duration.[25]

ELISA. ELISA (enzyme-linked immunosorbent assay) tests for the presence of anti-HIV antibodies in the serum, but results take two days to obtain. ELISA results are scored as positive (highly reactive), indeterminate (partially reactive), and negative (non-reactive). It is very accurate for both HIV-1 and HIV-2, with specificity of 99%. However specificity of ELISA tests varies with the population tested. The specificity approaches 98.5% in

HIV-positive populations, but falls dramatically in low-risk populations. In voluntary blood donors, only 10% of ELISA positive results are later confirmed as true positives.[12] Multiple factors have been associated with false-positive results, including autoantibodies, hepatic disease, recent influenza vaccination, and acute non-HIV viral infections.[12] As a result of the varied specificity, anyone with positive or indeterminate results must have an additional confirmatory test. The most common confirmatory test is the Western blot (WB).

Western Blot (WB). Western blots use electrophoresis to separate anti-HIV antibodies from the subject's serum. If performed properly, it is nearly 100% sensitive and specific. WBs can be indeterminate, possibly due to very early seroconversion (i.e., low levels of antibodies) or to cross-reaction with other unrelated antibodies found in the patient's serum. The test then is repeated and, if still unclear, the ELISA/WB sequence is started over again in 3-6 months.

Other HIV Tests. Several other HIV tests have been designed specifically for early detection of acute seroconversion. These other tests look for the presence of DNA (polymerase chain reaction), RNA, or HIV antigens (p24 antigen), and are not more accurate than ELISA or WB tests but should be considered for use when a patient is suspected of having an acute retroviral syndrome. For example, polymerase chain reactions become positive in only 11 days after infection.[83]

Rapid HIV Tests. In November 2002, the FDA approved a rapid HIV test (OraQuick) that can be used on both oral fluid and serum. These tests detect both HIV-1 and HIV-2 variants. These single-use diagnostic system (SUDS) tests can provide results in fewer than 20 minutes. OraQuick is reported to be 99% specific and 99% sensitive, but positive results still require confirmation with ELISA or WB. Since then, several other companies (Reveal HIV-1) also have released rapid HIV tests, including a test designed for home use (Home Access HIV Test Kit).

Some authors have suggested that rapid HIV tests should be used in EDs for general HIV screening,[84,85] as ED populations can have a high incidence of undiagnosed HIV infection. When screened in previous studies, the baseline rate of HIV infection in selected ED populations was shown to be as high as 2-17% depending on the location of the ED.[86] This is a much higher incidence than the general population (0.3%, or 1 of every 297 people). Further, it has been shown that a disappointingly high number of people (18-41%) do not return to obtain their HIV test results in traditional clinic settings.[87] Although new cases of HIV would undoubtedly be diagnosed with ED screening, problems of counseling, referral, and follow-up would need to be addressed in each ED before initiating such a program.[88]

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Physician CME Questions

71. Which of the following is true?
    A. There are currently about 1,100,000 cases of HIV in the United States.
    B. There are 40,000 new cases of HIV in the United States every year.
    C. At least 23% of people with HIV in the United States are not aware of their status.
    D. Undiagnosed people in the United States cause 66% of the new cases of HIV every year.
    E. All of the above.

72. Which of the following is true concerning the life cycle of HIV?
    A. HIV is an RNA virus.
    B. HIV targets cells with CD4 proteins on their surface.
    C. CD4 can be found on lymphocytes and epidermal Langerhans (or dendritic) cells.
    D. All of the above.

73. Regarding HIV infection in the United States, which of the following is true?
    A. HIV affects women more often than men in the United States.
    B. More than half of infected men have been infected through homosexual contact.
    C. Over half of new cases are in people older than 25.
    D. More than half of infected women have been infected through IDU.

74. Fluids with known high concentrations of HIV include all of the following *except*:
    A. blood.
    B. semen.
    C. breast milk.
    D. CSF.

75. HIV in the United States is most often transmitted by:
    A. occupational needle sticks.
    B. injection drug use.
    C. maternal-fetal transmission.
    D. sexual contact.

76. The risk of infection from a single needle stick in general is:
    A. 0.5-2% for hepatitis C.

B. 40-60% for hepatitis B.
C. 0.3% for HIV infection.
D. All of the above are true.

77. Factors associated with higher risk needle-stick injuries include all of the following *except*:
A. active opportunistic infection in the source patient.
B. hollow bore sharp.
C. shallow injury.
D. visible source patient blood on the sharp object.

78. Non-occupational postexposure prophylaxis is recommended only for:
A. known HIV-positive source exposure in < 72 hours with exposure to blood, semen, vaginal fluid, or rectal fluid.
B. known HIV-positive source exposure in < 72 hours with exposure to urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood
C. known HIV-positive source exposure in > 72 hours with exposure to blood, semen, vaginal fluid, or rectal fluid.
D. known HIV-positive source exposure in > 72 hours with exposure to urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood

79. Concerning antiretroviral drugs and treatment for HIV infection, which of the following is true?
A. HAART stands for highly active antiretroviral therapy.
B. Treatment has dramatically reduced the incidence of many complications of HIV.
C. HIV cannot be cleared from the body with current therapy.
D. Drugs commonly used in the ED, such as benzodiazepines and antiarrhythmics, can have enhanced effects in patients on protease inhibitors.
E. All of the above.

80. All of the following statements about HAART are true *except*:
A. Lipodystrophy and increased coronary artery disease risks are side effects.
B. Frequent minor side effects such as diarrhea and fatigue are common reasons for patient non-compliance.
C. Some patients may believe they are no longer contagious when viral loads are low.
D. Antiretroviral therapy can prevent the development of AIDS.

CME Answer Key

71. E; 72. D; 73. B; 74. D; 75. D; 76. D; 77. C; 78. A; 79. E; 80. D

In Future Issues: **HIV Part II**

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

HIV Part I

CDC 2005 Basic and Expanded Drug Regimen Recommendations for PEP

PREFERRED BASIC (2 DRUG) REGIMEN	ADVANTAGES	DISADVANTAGES
Zidovudine (AZT, Retrovir) + Lamivudine (Epivir) as Combivir	OK in pregnancy	Resistance common
Zidovudine (AZT, Retrovir) + Emtricitabine (Emtriva)	Well tolerated	No long-term studies
Tenofovir (Viread) + Lamivudine (Epivir)	Well tolerated	Resistance
Tenofovir (Viread) + Emtricitabine (Emtriva) as Truvada		
ALTERNATIVE BASIC (2 DRUG) REGIMENS		
Lamivudine (Epivir) + Stavudine (Zerit)	Well tolerated	Source patient resistance
Emtricitabine (Emtriva) + Stavudine (Zerit)	Well tolerated	Source patient resistance
Emtricitabine (Emtriva) + Didanosine (Videx)	Once a day	Diarrhea, pancreatitis
Lamivudine (Epivir) + Didanosine (Videx)	Once a day	Diarrhea, pancreatitis
PREFERRED EXPANDED—BASIC REGIMEN PLUS		
Lopinavir + Ritonavir (Norvir) as Kaletra	Potent protease inhibitor	Diarrhea, high lipids
ALTERNATIVE EXPANDED REGIMENS—BASIC REGIMEN PLUS		
Atazanavir (Reyataz) + Ritonavir (Norvir)	Once a day, potent	Jaundice common
Fosamprenavir (Lexiva) +/- Ritonavir (Norvir)	Once a day	Rash, GI effects
Saquinavir (Invirase) + Ritonavir (Norvir)	Well tolerated	Serious drug interactions
Indinavir (Crixivan) +/- Ritonavir (Norvir)	Potent	Renal stones, jaundice
Nelfinavir (Viracept)	Well tolerated	Diarrhea, drug interactions
Efavirenz (Sustiva)	Once a day	Rash, CNS effects, teratogen

GENERALLY NOT TO BE USED FOR PEP	SIDE EFFECTS
Nevirapine (Viramune)	Severe hepatotoxicity, Stevens-Johnson syndrome
Delavirdine (Rescriptor)	Drug interactions, Stevens-Johnson syndrome
Abacavir (Ziagen)	Severe hypersensitivity reactions in < 6 weeks
Zalcitabine (Hivid)	Weak antiretroviral, not tolerated

ONLY TO BE USED FOR PEP WITH EXPERT CONSULTATION	DISADVANTAGES
Enfuvirtide (Fuzeon)	Subcutaneous injection only May lead to false positive ELISA tests in future

Drug-Drug Interactions with NNRTIs and Protease Inhibitors: Drugs to Avoid

DRUGS TO AVOID	SIDE EFFECTS
Benzodiazepines (Midazolam or Versed) (Triazolam or Halcion)	Enhanced effects, and respiratory depression
Antihistamines Terfenadine (Seldane) Astemizole (Hismanal) Cisapride**	QT prolongation, arrhythmias
Ergot derivatives (dihydroergotamine DHE)	Enhanced effects, vasospasm, ischemia
TB medications (Rifampin)	Lowers plasma PI / NNRTI levels by up to 90%
Statin drugs (Lovastatin or Mevacor) (Simvastatin or Zocor)	Rhabdomyolysis
Herbals—St John's wort	Lowers PI / NNRTI levels

* Protease inhibitors commonly cited for drug interactions: ritonavir (Norvir), Ritonavir/lopinavir (Kaletra), saquinavir (Fortovase, Invirase), indinavir (Crixivan), and nelfinavir (Viracept). NNRTIs commonly cited for drug interactions: delavirdine (Rescriptor) and efavirenz (Sustiva).

** Be aware that cisapride (Propulsid—taken off the U.S. market in 2000) is associated with potentially fatal arrhythmias when used with PIs and NNRTIs.

CDC 2005 PEP Recommendations: When to Consult for Expert Advice

SITUATION	REASON
Delayed exposure (24-36 hours)	Benefit of PEP unclear
Unknown source (needle in sharp box)	PEP to be used on case-by-case basis
Exposed person pregnant (or suspected)	Pregnancy not a contraindication for PEP
Exposed person breastfeeding	Breastfeeding not a contraindication for PEP
Resistance of source virus	PEP drug selection should be modified to select drugs likely to be effective
Toxicity of initial PEP regimen	PEP likely to be finished with modification (i.e., modify dose interval, timing of food)

*** National Sources of Expert Advice:**

- Needlestick! site from UCLA: www.needlestick.mednet.ucla.edu.
- UCSF maintains a 24 hour National Clinicians' Post-Exposure Prophylaxis Hotline where physicians can consult for advice on individual cases: 1-888-448-4911.

Known Drug Interactions Between Commonly Used Drugs and NNRTIs and/or PIs: Side Effects to Know

USE THESE DRUGS WITH CAUTION	REASON
Benzodiazepines (Alprazolam or Ativan)	Enhanced effects, and respiratory depression
Calcium channel blockers (Dihydropyridines)	Enhanced effects, hypotension, bradycardia
Antiarrhythmics (Amiodarone, Flecainide. Lidocaine)	Enhanced effects, hypotension
Warfarin (Coumadin)	Increased PT with PIs, may increase or decrease with NNRTIs
Anticonvulsants (Phenobarb, phenytonin, or carbamazepine)	Decreased anticonvulsant levels (except Ritonavir may increase carbamazepine)
Ketamine	Enhanced effects, respiratory depression
Antifungals (Ketoconazole, fluconazole)	Increased serum PI levels
Antibiotics Clarithromycin	Increased antibiotic levels
Inhaled steroids (Fluticasone or Flonase)	Systemic corticosteriod side effects
Theoyphylline	Decreased serum levels taken with PIs
Drugs of abuse:	
Methadone	NNRTIs lower opiate levels, may precipitate withdrawal
Amphetamines, Ecstasy	Enhanced effects, hypertension, arrhythmias
GHB	Respiratory depression, bradycardia
Heroin	Enhanced effects from PIs, but no cases reported

*Protease inhibitors commonly cited for drug interactions: Ritonavir (Norvir), Ritonavir/Lopinavir (Kaletra), Saquinavir (Fortovase, Invirase), Indinavir (Crixivan), and Nelfinavir (Viracept). NNRTIs commonly cited for drug interactions: Delavirdine (Rescriptor) and Efavirenz (Sustiva).

CDC 2005 PEP and nPEP Estimated Costs

1. Occupational PEP (PEP)

ANTIRETROVIRAL DRUG	COST FOR 4-WEEK COURSE
A. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI) (Class side effects: lactic acidosis, hepatomegaly)	
Abacavir (Ziagen, ABC)	$400
Didanosine (Videx, ddI)	$260
Emtricitabine (Emtriva, FTC)	$280
Lamivudine (Epivir 3TC)	$300
Stavudine (Zerit, d4T)	$320
Tenofovir (Viread)	$400
Zidovudine (Retrovir, AZT)	$350
Zalcitabine (Hivid)	$260
B. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) (Class side effects: Stevens-Johnson syndrome)	
Efavirenz (Sustiva)	$420
Delavirdine (Rescriptor)	$292
Nevirapine (Viramune)	$275
C. Protease Inhibitors (PI) (Class side effects: GI intolerance, hyperlipidemia, diabetes)	
Atazanavir (Reyataz)	$760
Fosamprenavir (Lexiva)	$1260
Indinavir (Crixivan)	$500
Nelfinavir (Viracept)	$600
Ritonavir (Norvir)	$700-2800
Saquinavir (Invirase—hard-gel capsule) (Fortovase—oft-gel capsule)	$460
Tipranavir (Aptivus)	$1083
Amprenavir (Agenerase)	$666
D. Fusion Inhibitors	
Enfuvirtide (Fuzeon)	$1666
E. Combination Tablets (all NRTIs except Keletra)	
Lopinavir/ritonavir (Keletra) (PIs)	$650
Zidovudine/lamivudine (Combivir)	$640
Zidovudine/lamivudine/Abacavir (Trizivir)	$1020
Lamivudine/abacavir (Epizcom)	$760
Emtricitabine/tenofovir (Truvada)	$800
Total Cost for preferred 2 drug PEP regimen:	
Zidovudine + emtricitabine	$630
Zidovudine/lamivudine (Combivir)	$640
Tenofovir + lamivudine	$700
Emtricitabine/tenofovir (Truvada)	$800
Total Cost for preferred 3 drug PEP regimen: (Basic regimen ***PLUS*** Keletra)	$1280-$1450
Total Cost for > 3 drug PEP regimen:	up to $2760

2. NON-Occupational PEP (nPEP)

ANTIRETROVIRAL	COST FOR 4-WEEK COURSE
Total Cost for preferred 3 drug regimen: Efavirenz + Lamivudine or emtricitabine + Zidovudine or tenofovir	$1050-$1120
Total Cost for preferred > 3 drug regimen: Lopinavir/ritonavir (Keletra) + Lamivudine or emtricitabine + Zidovudine	$1280-$1300

*New drugs are continually being introduced, and thus this list may be incomplete at time of publication.

CDC 2005 nPEP (Nonoccupational) Recommendations

EXPOSURE TYPE	< 72 HOURS SINCE EXPOSURE	> 72 HOURS SINCE EXPOSURE
Negligible risk*	nPEP ***not*** recommended	nPEP ***not*** recommended
Substantial risk*		
Source known HIV +	**nPEP recommended**	nPEP ***not*** recommended
Source unknown HIV status	Case-by-case use	nPEP ***not*** recommended

* **Negligible risk =** **exposure of:** vagina, rectum, eye, mouth, or other mucus membrane intact or non-intact skin, or percutaneous contact

with: urine, nasal secretions, saliva, sweat or tears if *not* visibly contaminated with blood

regardless: of the source patient's HIV status

* **Substantial risk =** **exposure of:** vagina, rectum, eye, mouth or other mucus membrane, intact or non-intact skin, or percutaneous contact

with: blood, semen, vaginal secretions, rectal secretions, breast milk, or *any* body fluid visibly contaminated with blood

when: the source is known to be HIV-infected

CDC 2005 nPEP Preferred Drug Regimens

PREFERRED REGIMENS				
Efavirenz (Sustiva)	***PLUS***	Lamivudine (Epivir) ***OR*** Emtricitabine (Emtriva)	***PLUS***	Zidovudine (AZT, Retrovir) ***OR*** Tenofovir (Viread)
Lopinavir/Ritonavir (Kaletra)	***PLUS***	Lamivudine (Epivir) ***OR*** Emtricitabine (Emtriva)	***PLUS***	Zidovudine (AZT, Retrovir)

NOTE: There are numerous alternative regimens available. Consult CDC information or an infectious disease expert.
* Abacavir (Ziagen) is listed by the 2005 CDC update on PEP as an "antiretroviral generally not for use as PEP" due to "severe hypersensitivity reactions" that "can be confused with acute seroconversion."
** Triple NRTI regimen to be used only when NNRTI or PI-based regimen cannot or should not be used.

Estimates of Per-Contact Risk of HIV Infection

TYPE OF CONTACT	RISK
Needle-sharing	6/1000 to 3/100
Occupational needle stick	1/300
Receptive anal	8/1000 to 3/100
Receptive vaginal	8/1000 to 2/1000
Insertive anal or vaginal	3/10,000 to 1/1000
Receptive oral	Case reports/no denominator
Transfusion of 1 unit of infected blood (current estimated range of infected blood in donated supply: 1/1,900,00)	1/1.05 to 1/1

CDC 2005 PEP Recommendations: Percutaneous Exposure*

EXPOSURE TYPE	HIV CLASS 1 (LOW RISK)	HIV CLASS 2 (HIGH RISK)
Low Risk	2 drug regimen	> 3 drug regimen
Higher Risk	3 drug regimen	> 3 drug regimen

* **No PEP indicated for:**
- Known HIV-negative exposures

* **PEP not recommended but may consider 2-drug regimen for "high-risk source patients"**
- Source patient with unknown HIV status
- Unknown source patient

CDC 2005 PEP Recommendations: Mucus Membrane or Non-intact Skin Exposure

EXPOSURE TYPE	HIV CLASS 1 (LOW RISK)	HIV CLASS 2 (HIGH RISK)
Small volume	Consider 2-drug regimen	2-drug regimen
Large volume	2-drug regimen	> 3-drug regimen

* No PEP indicated for:
- Known HIV negative exposures
- Small volume exposure from unknown source/unknown patient status

* PEP not recommended, but may consider 2-drug regimen for "high-risk source patients"
- Large volume exposure from unknown source/unknown patient status

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