19

Postexposure Prophylaxis

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Clinicians who care for children can be exposed to human immunodeficiency virus (HIV) while providing medical or nursing care. More rarely, they may be consulted about the management of children exposed to HIV in hospitals, homes, or elsewhere. Appropriate management of such exposures often requires quick judgment about the possible need for postexposure prophylaxis (PEP). PEP, also referred to as "postexposure treatment" (PET), is the timely administration of antiretroviral chemoprophylaxis to reduce the probability of becoming infected with HIV after an acute, well-defined exposure. PEP is currently categorized as "occupational" or "nonoccupational" in reference to whether or not an exposure occurs in the context of working in a health care setting. This chapter reviews current U.S. Public Health Service (USPHS) recommendations for PEP following occupational exposures to HIV. In addition, this chapter reviews the principles of PEP that can be considered when evaluating children who have had exposure to HIV.

Occupational PEP

For the purposes of this chapter, a health care worker (HCW) is defined as any person whose activities involve contact with patients, or with blood or other body fluids from patients, in a health care or laboratory setting. Exposures to blood, tissue, or other body fluids that could place a HCW at risk for HIV infection for which PEP could be beneficial include (a) a percutaneous injury (e.g., a needlestick or cut with a sharp object), (b) contact of mucous membranes or nonintact skin (e.g., when the exposed skin is chapped, abraded, or afflicted with dermatitis), or (c) contact of intact skin when the duration of contact is prolonged (i.e., several minutes or more) or when contact involves an extensive area. In addition, any direct contact (i.e., without barrier protection) to concentrated HIV in a research laboratory or production facility is considered an exposure. The category "other body fluids" includes (a) semen, vaginal secretions, or other body fluids contaminated with visible blood that have been implicated in the transmission of HIV infection (1,2); and (b) cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids, which have an undetermined risk of HIV transmission (1). Although one nonoccupational episode of HIV transmission has been attributed to contact with blood-contaminated saliva (3), this incident is not analogous to contact with saliva that may occur during the provision of health care services. Therefore, in the absence of visible blood in the saliva, exposure to saliva from a person infected with HIV is not considered to pose a risk for HIV transmission. Exposures to tears, sweat, or nonbloody urine or feces do not require postexposure follow-up. Contact with human breast milk has been implicated in perinatal transmission of HIV (4–6). Although

occupational exposure to human breast milk has not been implicated in HIV transmission to HCWs, the Centers for Disease Control and Prevention (CDC) state that "gloves may be worn by health care workers in situations where exposures to breast milk might be frequent, for example, in breast milk banking" (2). This latter recommendation suggests that frequent direct skin contact with breast milk in such situations should be avoided.

Nonoccupational PEP

A "nonoccupational exposure" has been defined as "an exposure to HIV that does not occur during the performance of a health care-related job or occupation". It typically refers to exposure through unprotected sex or sharing needles with HIV-infected persons, or to an infant's exposure to infected breast milk. While occupational exposures are primarily accidental, one-time events, nonoccupational exposures may occur repeatedly (7).

EPIDEMIOLOGY OF HIV EXPOSURES

Health Care Worker (HCW) Exposures

The average risk for HIV infection for HCWs exposed to HIV-infected blood has been estimated at 0.3% for percutaneous exposures (8) and 0.09% for mucous membrane exposures (9). The risk is unknown for skin exposures but is thought to be less than that for mucous membrane exposures (10). As of December 1997, the CDC has received reports of 54 U.S. HCWs with documented HIV seroconversion temporally associated with occupational HIV exposure and has been informed of an additional 132 HCWs who report occupationally acquired HIV infection without such documentation (11). The factors that may affect the risk of HIV transmission after an occupational exposure include characteristics of the exposure, such as those involving large quantities of blood, and of the source patient, such as a patient with terminal HIV-related illness (Table 19-1). Patients with a terminal HIV-related illness presumably have higher concentrations of virus in the

Table 19-1. Logistic regression analysis of risk factors for HIV transmission after percutaneous exposure to HIV-infected blood

Risk factor	Adjusted Odds Ratio	(95% Confidence Interval)
Deep injury	15	(6.0–41)
Visible blood on device	6.2	(2.2–21)
Procedure involving needle in a vein or artery	4.3	(1.7–12)
Terminal illness in source patient	5.6	(2.0–16)
Postexposure use of zidovudine	0.19	(0.06–0.52)

Adapted from Ref. 43.

blood. The risk of HIV transmission from exposures that involve a larger volume of blood, especially when the source patient's virus load is probably high, is estimated to exceed the average risk of 0.3%.

There are very limited epidemiologic data on the most common exposures to blood for health care workers in pediatric health care settings. One study investigated the frequency, circumstances, and management of sharp-object injuries (SOIs) in pediatric facilities and found that 113 SOIs (six injuries per 100 employees every year) were reported (12). Although nurses and physicians experienced the greatest percentage of SOIs (46% and 23%, respectively), phlebotomists experienced the highest rate of SOIs (25.5 injuries per 100 full-time equivalent employees per year). These occurred most commonly in the patient's room (27%), operating room (25%), and intensive care units (17%). Injuries most often involved needles (71%) and procedural devices (22%). Although most injuries occurred before disposal, either during (48%) or immediately after (42%) use of the item, 7% occurred after disposal. Twenty percent were associated with loose sharp objects and 15% with inadvertent patient movement. Only 2% of injuries were associated with recapping. Eighty-eight percent of the objects were contaminated with blood or body fluid. Of 88 known source patients, one tested positive for hepatitis B virus surface antigen, two for hepatitis C virus, and none for HIV.

Pediatric Exposures in Health Care Settings

Children are present in hospitals either as patients or as visitors and are subject to situations that could place them at risk for HIV infection. For example, cases have been reported in which children were probably exposed inadvertently to blood from an HIV-infected person in hospitals or during health care in the home (13,14). The CDC received a case report of a child who bit through a glass blood sample tube filled with blood from an adult patient with a history of injecting drug use but unknown HIV infection status (15). The child suffered lacerations to the inside of the oral mucosa. The CDC also received a case report of an infant who was inadvertently fed the expressed breast milk of another infant's mother (16). In another situation, an infant was inadvertently taken to the wrong mother to be breast-fed while in the hospital (17). The frequency of such hospital-related potential HIV exposures in children is unknown.

Pediatric Exposures Outside of Health Care Settings

Similarly, children are subject to exposures to HIV outside of the hospital setting. Examples include exposures to HIV-containing breast milk; sexual abuse involving oral, anal, or vaginal penetration by an HIV-infected perpetrator; human bites that compromise the skin integrity and involve an exchange of HIV-infected blood; or needlesticks in the home or public areas with recently discarded syringes containing HIV-containing blood.

Breast Milk Exposures

Because breast milk from HIV-infected women may contain HIV and breast-feeding is known to transmit HIV (18), even a single episode of ingestion of breast milk from an HIV-infected woman

should be considered to carry some risk for transmission. However, in the United States, because the prevalence of HIV infection in childbearing women is less than two per 1000 (19) and because HIV testing is recommended for all pregnant women and HIV-infected women are recommended not to breast-feed their children (20), the likelihood that breast milk from an unknown source contains HIV is probably small. One study estimated that between 5% and 10% of HIV-uninfected infants born to HIV-infected mothers in the United States subsequently become HIV-infected through breast-feeding (21). This corresponds to an estimate of 21–42 infants infected with HIV through breast-feeding annually in the United States, assuming 7000 infants are born to HIV-infected women per year (21). HIV-infected women who knew their infection status were much less likely to breast-feed than women without such knowledge (2% versus 30%, respectively) (21). The study was not able to ascertain why HIV-infected mothers breast-fed their infants. Anecdotally, some hypotheses include lack of knowledge about the risk for transmission from breast milk due to communication barriers or lack of education, inadequate supply of formula (e.g., being unable to afford formula), or denial of their infection status. Other potential exposures to infected breast milk are the switching or mislabeling of bottles containing expressed breast milk (e.g., in day-care settings) and using the services of a wet nurse with unknown infection status. The risk of transmission in such situations is probably low, but each situation must be considered on a case-by-case basis. For example, factors that may affect the likelihood of transmission of HIV in breast-feeding mothers include the development of primary infection in the mother during the postpartum period (22,23), the number of breast milk exposures, the presence of cracked or bleeding nipples in the mother, and the status of the infant or child's oral mucosa (e.g., presence of inflamed gingiva secondary to teething or oral abscesses).

Sexual Abuse

In the United States during 1995, 126,095 cases of various types of sexual abuse in children less than 18 years of age were reported (24); however, it is recognized that sexual abuse is underreported. It is unclear how many of these reported cases involved the type of abuse that might put these children at risk for HIV infection (e.g., penile penetration of children's vaginal, anal, or oral cavities, and mucosal contact with semen). Of the 9136 cumulative cases of children less than 13 years of age with AIDS reported to the CDC through December 1996, 26 were reported to be cases of sexual abuse (17 confirmed, nine suspected) (25). These 26 cases are also thought to represent an underestimate as a result of the underreporting of such abuse. Among adults, the probability of HIV transmission associated with a single act of unprotected receptive anal intercourse has been estimated to be between 0.008 and 0.032 (26), and that associated with vaginal intercourse has been estimated at between 0.0005 and 0.0015 (27–29). The medical literature suggests that child sexual abuse may be a more efficient means of transmitting HIV than adult sexual abuse. For example, pediatric anatomic differences such as the relative thinness of vaginal epithelia in premenarchal children may predispose to HIV transmission (30). Also, a child can be repeatedly molested

by the same molester, particularly if the molester is a parent (31), can be abused by multiple perpetrators (32), and can suffer long-term abuse (33). Any child who has been sexually assaulted should be evaluated in a timely fashion to determine whether the assault may have exposed him or her to HIV or other sexually transmitted diseases (STDs).

The CDC recommends that practitioners who opt to offer PEP to sexual abuse victims should "assess the nature of the assault, any available information about HIV-risk behaviors exhibited by persons who are sexual assailants (e.g., high-risk sexual practices and injecting-drug or crack cocaine use), and the local epidemiology of HIV/AIDS" (34). It delineates the following situations as "involving high risk for STDs and a strong indication for testing" (34):

(1) A suspected offender is known to have an STD or to be at high risk for STDs (e.g., has multiple sex partners or a history of STD). (2) The child has symptoms or signs of an STD or of an infection that can be sexually transmitted. (3) The prevalence of STDs in the community is high. (4) Other indications (for testing) recommended by experts, including: (a) evidence of genital (anal), or oral penetration or ejaculation or (b) STDs in siblings or other children or adults in the household.

Higher-risk sexual assaults might include those with traumatic mucosal injuries of the anus or vagina associated with bleeding and contact with the semen of a known HIV-infected assailant. An example of a lower-risk exposure might involve the sexual abuse of unknown type (e.g., not clear if intercourse was involved) of a toddler by a perpetrator with unknown HIV infection status in an area with low HIV seroprevalence. In cases where there is no physical evidence of the type of sexual assault which would put a child at risk for HIV infection, whatever evidence is available must be carefully weighed to make a determination regarding risk.

Discarded Needles or Syringes

The risk of HIV transmission from discarded needles in public places is thought to be low (35). However, data regarding the frequency of such injuries and the likelihood of HIV transmission with such injuries are lacking. It is estimated that the probability of HIV transmission associated with a puncture wound involving a known HIV-contaminated needle in a health care setting is 0.0032 (36). It is likely that discarded needles in outdoor public settings have a lower risk for transmission because of the effect of environmental factors and the built-in delay from time of injection drug use to accidental puncture. There are few studies on the incidence of such injuries in children. A study of childhood needlestick injuries in a large metropolitan area over a 16-month period revealed 52 cases (37). Most of these occurred in inner-city areas with a recognized high prevalence of injecting drug use. Among nine children with hepatitis B virus, hepatitis C virus, and HIV testing, none had been noted to become HIV seropositive. In a study of hepatitis B virus prevention and risk of HIV infection in 249 children injured by discarded needles and/or syringes, 101 completed HIV testing and no HIV infection was detected (38). A child who is witnessed to have been injured by picking up a freshly discarded syringe would be considered to be at higher risk for HIV transmission than someone who gets stuck with a syringe that has been laying on the ground for an undetermined period of time.

Human Bites

Because biting is common among young children, concern has been raised about the possibility of HIV transmission among children through biting. It has been estimated that 250,000 human bites occur annually in the United States (39); however, it is unclear how many of these involve a compromise in skin integrity and an exchange of blood-tinged saliva and how many such bites involve children. There is currently no evidence to support that human bites without the presence of blood-tinged saliva in the wound pose an HIV infection risk to the victim. Although biting has been cited as a possible mode of transmission in several case reports, in all of the well-documented reports, the bites were by adults and involved severe biting with blood exchange (40).

Vertical or Perinatal Transmission

Perinatal transmission accounts for 91% of pediatric AIDS cases reported in the United States through December 1997 (41). The epidemiology of vertical transmission and recommendations for antiretroviral therapy to reduce such transmission are discussed in further detail in Chapters 5 and 8.

PEP GUIDELINES FOR OCCUPATIONAL EXPOSURES IN HCWS

In 1990, the USPHS published its first statement on PEP (42). This statement was informational in nature and described PEP protocols using zidovudine (ZDV) in use at that time at institutions such as the National Institutes of Health and San Francisco General Hospital for managing occupational exposure to HIV. Because of lack of convincing data on the efficacy of PEP at the time, this statement did not make recommendations for or against PEP, but outlined considerations surrounding the possible use of ZDV for PEP.

In December 1995, the CDC published the results of a case-control study of HIV seroconversion in health care workers (HCW) in the United States, France, and the United Kingdom who had percutaneous exposure (i.e., needlestick or cut with a sharp object) to HIV-infected blood (43). An update of this study was published in 1997 (44). Case HCWs had "HIV seroconversion temporally associated with the exposure and no other concurrent exposure to HIV," whereas control HCWs had "a documented occupational percutaneous exposure to HIV-infected blood and were HIV seronegative at the time of exposure and at least 6 months later." PEP, generally consisting of 1000 mg/day of ZDV for 3–4 weeks, was used by nine of 33 (27%) case HCWs and by 247 of 679 (36%) control HCWs. As noted previously, the study suggested that risk factors for HIV transmission included characteristics of both the exposure, such as those involving large quantities of blood, and the source patient, such as having terminal HIV-related illness (see Table 19-1). It indicated that after controlling for other factors, the risk for HIV infection among HCWs who used ZDV for PEP was reduced by approximately 81%. However, this report acknowledged limitations of the study, including the fact that the retrospective case-control design is not the optimal study design for assessing ZDV efficacy. It has not been possible to conduct a prospective, placebo-controlled trial.

USPHS Recommendations for PEP for Occupational Exposures in HCWs

The USPHS updated recommendations on the use of PEP for occupational exposures to HIV in June 1996 (45) and in April 1998 (46). Consideration was given to several factors that influence the rationale and recommendations for PEP, including the biologic plausibility that infection can be prevented by using antiretroviral drugs and the risk/benefit of PEP to the exposed worker. Although studies that provide evidence to support the use of PEP generally used ZDV, the USPHS currently recommends the use of two or three drugs for PEP to optimize antiretroviral activity.

The USPHS recommendations for PEP are based on the principle that the decision to recommend PEP and the choice of PEP regimen must strive to balance the risk for infection against the potential toxicity of antiretroviral agents. Because PEP is potentially toxic and side effects are common, its use is not justified for exposures that pose a negligible risk for transmission. For exposures that represent an increased risk for transmission, aggressive treatment using a highly active "expanded" regimen that includes at least three antiretroviral drugs is recommended (see Table 19-2 and Fig. 19-1). However, most exposures do not represent an increased transmission risk, and for these exposures the CDC recommends a "basic" two-drug regimen.

Considerations for Determining the Level of Risk in Occupational Exposures and the Appropriateness of Offering PEP

For the purposes of PEP, how does one determine whether the exposed person should be given PEP, and if so, whether the basic

Table 19-2. "Basic" and "expanded" PEP regimens for occupational exposures

Regimen category	Application	Drug regimen
Basic	Occupational HIV exposures for which there is a recognized transmission risk (see Fig. 19-1).	Four weeks (28 days) of both zidovudine (ZDV) 600 mg qd in divided doses (i.e., 300 mg bid, 200 mg tid or 100 mg q4h) and lamivudine (3TC) 150 mg bid.
Expanded	Occupational HIV exposures that pose an increased risk for transmission (e.g., larger volume of blood and/or higher virus titer).	Basic regimen plus either indinavir 800 mg q8h or nelfinavir 750 mg tid.[a]

[a] Indinavir should be taken on an empty stomach (i.e., without food or with a light meal) and with increased fluid consumption (i.e., drinking six 8-oz. glasses of water throughout the day); nelfinavir should be taken with meals.
Reprinted from Ref. 46.

or expanded regimen should be given? (See Fig. 19-1.) The first step is collecting the relevant details (46) regarding the following:

1. Date and time of exposure.
2. The procedure being performed (how, where, involvement and type of sharp device).
3. The exposure (type and amount of fluid, severity of exposure, depth of wound, duration of contact, condition of skin). Potentially infectious fluids include semen, vaginal secretions, and cerebrospinal, pleural, peritoneal, pericardial, and amniotic fluids.
4. The source of exposure: infection status of person (HIV or other infectious disease) or presence of HIV in source material, stage of disease, history of antiretroviral therapy, viral load, and risk for HIV infection.

Figure 19-1 (Steps 1–3) is an algorithm that takes into account the details of the exposure and the HIV status of the exposure source to determine the appropriate level of risk and recommendations for follow-up (46). In Step 1, the details of the exposure regarding the source material, body areas affected, and degree of exposure are taken into account to determine the "exposure code" (EC). In Step 2, the HIV status and HIV titer of the exposure source are used to assign an "HIV status code" (HIV SC). In Step 3, the EC and the HIV SC are incorporated into a scale in order to make a PEP recommendation.

HIV Treatment Principles Used in Developing PEP Recommendations

The selection of the regimens recommended for PEP reflects the consideration of efficacy data, site of activity in the HIV replication cycle, and drug side effects. The USPHS emphasizes, however, that "determining which agents and how many agents to use or when to alter a PEP regimen is largely empiric" (46). Selected drugs from three classes of antiretroviral agents can be used for PEP: nucleoside analog reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Because the only data on PEP efficacy are with ZDV, an NRTI, it is recommended that ZDV be included in all PEP regimens. Dual and triple combination regimens have been shown to be superior to monotherapy in reducing HIV viral load. Therefore current HIV treatment principles recommend that three drugs be used for the treatment of early HIV infection, including two NRTIs and a PI. Although there are no studies to support the idea that using other antiretroviral agents in addition to ZDV will enhance the effectiveness of PEP, it is felt that the same factors that improve effectiveness of HIV treatment might similarly improve PEP effectiveness.

PEP for Occupational Exposures Among HCWs: "Basic" and "Expanded" Regimens

Because it is uncertain whether the potential additional toxicity of a third drug is warranted for PEP in lower-risk exposures, the USPHS has developed guidelines for dual- and triple-drug PEP regimens, known as "basic" and "expanded" regimens, respectively, based on the level of HIV transmission risk. For lower-risk exposures, the USPHS has recommended that a "basic" or dual NRTI regimen composed of ZDV and lamivudine (3TC) be used, based on

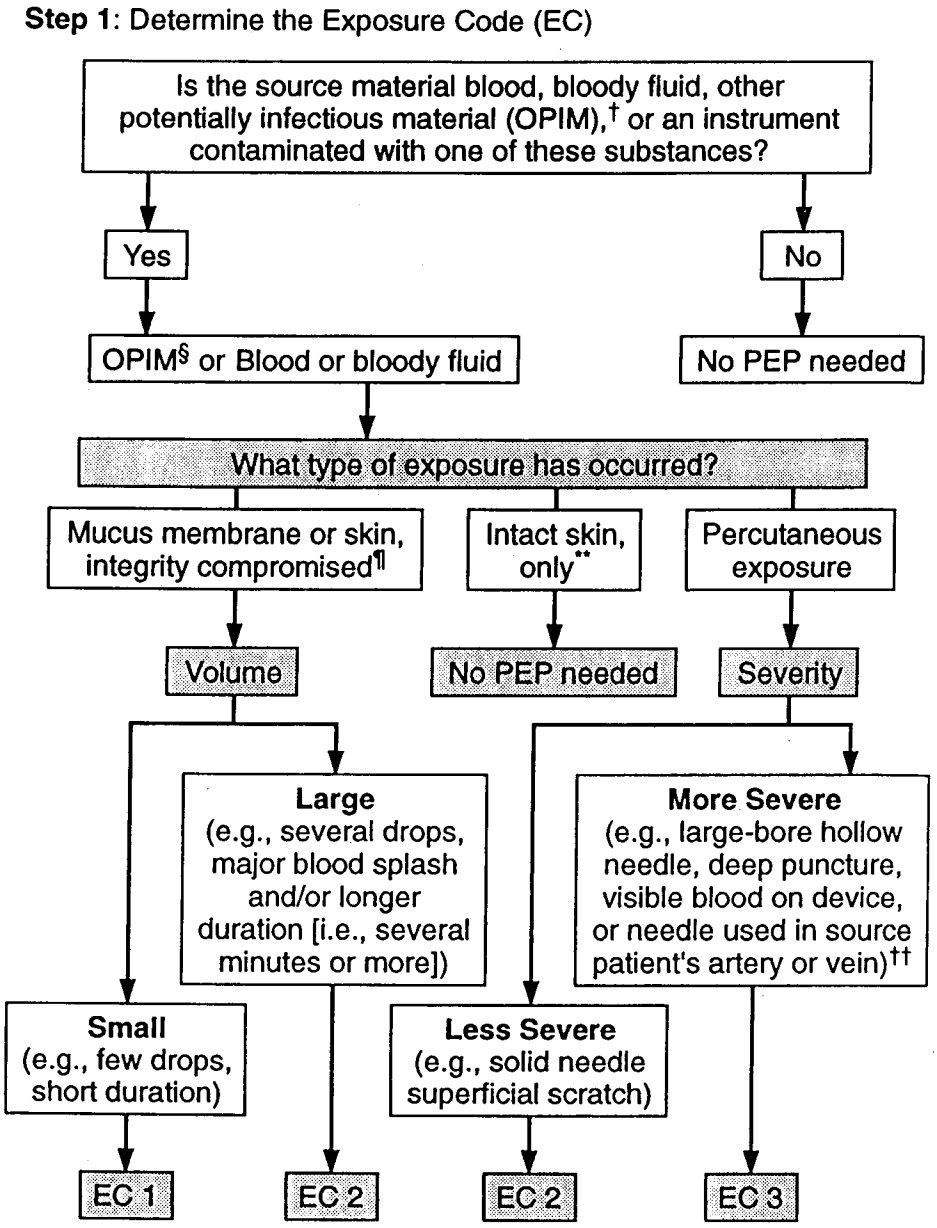


Fig. 19-1. Algorithm for determining the need for PEP after an occupational exposure. (*Continued on next page*)

evidence of enhanced activity with this combination and activity against many ZDV-resistant strains of HIV. The USPHS recognizes the fact that some clinicians may prefer to use other nucleoside agents or combinations of agents based on local knowledge and experience. The addition of a third drug, a PI, to the basic dual-drug regimen has been recommended to create the expanded triple-drug PEP regimen, thereby enhancing the antiretroviral activity of the basic regimen in higher-risk exposures. Currently, although indinavir (IDV) or nelfinavir is considered the PI of choice in the three-drug regimen for occupational exposures based on their more favorable toxicity profile and other characteristics, other drugs can be considered. Saquinavir's Fortovase soft-gel formula-

*This algorithm is intended to guide initial decisions about PEP and should be used in conjunction with other guidance provided in this Chapter.

†Semen or vaginal secretions; cerebrospinal, synovial, pleural, peritoneal, pericardial, or amniotic fluids; or tissue.

§Exposures to OPIM must be evaluated on a case-by-case basis. In general, these body substances are considered a low risk for transmission in health-care settings. Any unprotected contact to concentrated HIV in a research laboratory or production facility is considered an occupational exposure that requires clinical evaluation to determine the need for PEP.

¶Skin integrity is considered compromised if there is evidence of chapped skin, dermatitis, abrasion, or open wound.

**Contact with intact skin is not nomally considered a risk for HIV transmission. However, if the exposure was to blood, and the circumstance suggests a higher volume exposure (e.g., an extensive area of skin was exposed or there was prolonged contact with blood), the risk for HIV transmission should be considered.

††The combination of these severity factors (e.g., large-bore hollow needle *and* deep puncture) contribute to an elevated risk for transmission if the source person is HIV-positive.

Fig. 19-1. *(Continued)*

tion has more bioavailability than Invirase and may be considered as an alternative for IDV. Also, although NNRTIs such as nevirapine and delavirdine are not recommended as initial PEP drugs of choice because of concerns about their side effects, they can be considered in particular situations. In general, clinical experience or judgment may influence an individual practitioner to use alternate drug combinations for either the "basic" or "expanded" PEP regimens.

Timing of Initiation of PEP After Exposure

PEP should be implemented as soon as possible after exposure, preferably within a few hours. Animal studies suggest that PEP is not effective when started after 24–36 hours, but the interval after which protection is lost in humans is unknown (47,48). PEP may be considered after a 1- to 2-week interval for the highest-risk exposures on the theoretical basis that treatment of acute HIV infection may be beneficial. The appropriate duration of PEP is unknown. Based on the CDC case-control study, a 4-week regimen is recommended.

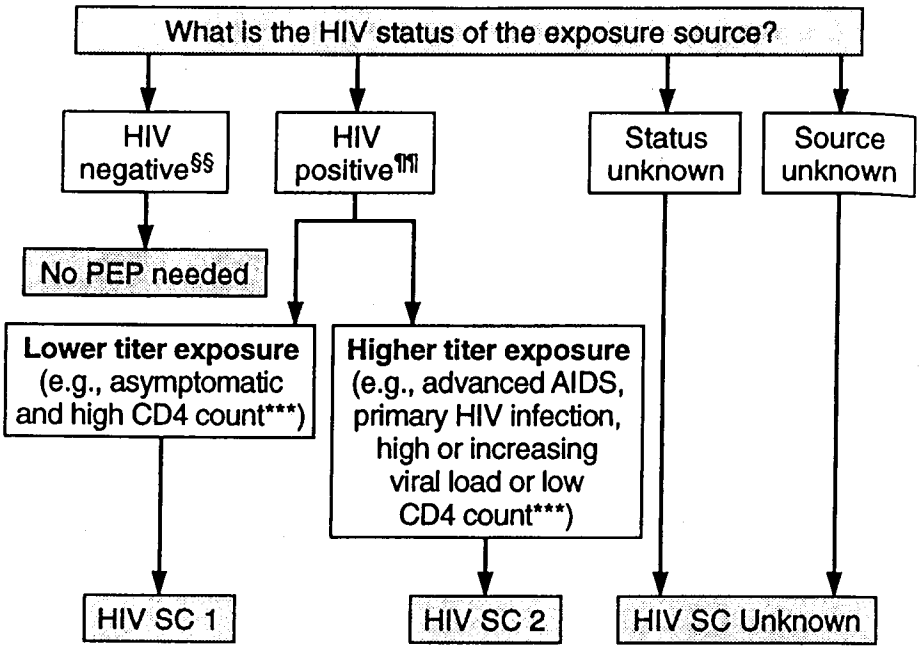
Other Elements of PEP Management

In addition to prescribing PEP medications, the following components of PEP management should also be addressed (46):

Appropriate Care of the Exposure Site

The wound should be cleaned with soap and water.

Step 2: Determine the HIV Status Code (HIV SC)



§§A source is considered negative for HIV infection if there is laboratory documentation of a negative HIV antibody, HIV polymerase reaction (PCR), or HIV p24 antigen test result from a specimen collected at or near the time of exposure and there is no clinical evidence of recent retroviral-like illness.

¶¶A source is considered infected with HIV (HIV positive) if there has been a positive laboratory result for HIV antibody, HIV PCR, or HIV p24 antigen or physician-diagnosed AIDS.

***Examples are used as surrogates to estimate the HIV titer in an exposure source for purposes of considering PEP regimens and do not reflect all clinical situations that may be observed. Although a high HIV titer (HIV SC 2) in an exposure source has been associated with an increased risk for transmission, the possibility of transmission from a source with a low HIV titer also must be considered.

Fig. 19-1. ***(Continued)***

Evaluation of the Source and Exposed Individuals for Evidence of Blood-borne Infection, Including HIV

The source individual should be informed of the exposure, and, once informed, and consent is obtained, should be tested for HIV infection. Because source testing can take some time, and given that PEP may not be effective after 24 hours, clinicians may have to make a decision about PEP based on incomplete information. If the source individual is found to be HIV-infected, the exposed individual should be tested for HIV as soon as possible after the exposure and, if seronegative, should be retested periodically for a minimum of 6 months after exposure (e.g., 6 weeks, 12 weeks, and 6 months after exposure). Confidentiality of the source and

Step 3: Determine the PEP Recommendation

EC	HIV SC	PEP recommendation
1	1	**PEP may not be warranted.** Exposure type does not pose a known risk for HIV transmission. Whether the risk for drug toxicity outweighs the benefit of PEP should be decided by the exposed HCW and treating clinician.
1	2	**Consider basic regimen.**[†††] Exposure type poses a negligible risk for HIV transmission. A high HIV titer in the source may justify consideration of PEP. Whether the risk for drug toxicity outweighs the benefit of PEP should be decided by the exposed HCW and treating clinician.
2	1	**Recommend basic regimen.** Most HIV exposures are in this category; no increased risk for HIV transmission has been observed but use of PEP is appropriate.
2	2	**Recommend expanded regimen.**[§§§] Exposure type represents an increased HIV transmission risk.
3	1 or 2	**Recommend expanded regimen.** Exposure type represents an increased HIV transmission risk.
Unknown		If the source or, in the case of an unknown source, the setting where the the exposure occurred suggests a possible risk for HIV exposure and the EC is 2 or 3, consider PEP basic regimen.

[†††]Basic regimen is four weeks of zidovudine, 600 mg per day in two or three divided doses, *and* lamivudine, 150 mg twice daily (adult doses).

[§§§]Expanded regimen is the basic regimen plus *either* indinavir, 800 mg every 8 hours, *or* nelfinavir, 750 mg three times a day (adult doses).

Fig. 19-1. ***(Continued)***

exposed individuals should be maintained. If the HIV status of the source patient is unknown, decisions about PEP should be made on a case-by-case basis, considering the risk of transmission from the exposure and the likelihood that the source patient is HIV infected. The possible need for prophylaxis against hepatitis B virus should also be considered.

Drug Toxicity Monitoring

Such monitoring should include a complete blood count and renal and hepatic chemical function tests at baseline and 2 weeks after starting PEP. HCWs receiving PEP for occupational exposures may be enrolled in a confidential registry developed by the CDC, Glaxo Wellcome, and Merck to assess toxicity (telephone, 888-737-4448 [888-PEP-4HIV], or write The HIV PEP Registry, 1410 Commonwealth Drive, Suite 215, Wilmington, NC 28405). The Food and Drug Administration (telephone, 800-332-1088) and/or the manufacturer should be informed of unusual or serious

and unexpected toxicity from antiretroviral drugs. In addition, pregnant HCWs who are exposed to antiretrovirals as a consequence of PEP should be reported to the Antiretroviral Pregnancy Registry (telephone, 800-722-9292, ext. 39437, or write Antiretroviral Pregnancy Registry, Post Office Box 13398, Research Triangle Park, NC 27709-3398). Finally, HCWs receiving PEP who seroconvert should be encouraged to call the CDC at 404-639-6425 about a protocol to evaluate such events.

HIV Postexposure Counseling and Education

HIV-exposed HCWs should be counseled about the prevention of secondary transmission, particularly during the initial 6–12 weeks after exposure when seroconversion might occur. Specifically, sexual abstinence and the use of condoms should be encouraged, and breast-feeding and the donation of blood, plasma, organs, tissue, or semen should be discouraged. Exposed HCWs should also be encouraged to seek medical advice if the following signs and symptoms of acute HIV infection appear: fever, rash, myalgia, fatigue, malaise, or lymphadenopathy. Information about adherence to the PEP regimen and management of side effects should emphasize the need to complete the full course of the regimen, the potential side effects and drug interactions, and ways in which these can be minimized and monitored. The potential toxicities of, required monitoring for, and drug interactions to consider with antiretroviral therapy are described in detail in Chapters 16 and 17. It is worth reiterating that drinking at least 48 ounces of fluid per 24-hour period can limit the incidence of nephrolithiasis associated with indinavir and that prescription antimotility agents may be helpful in limiting the diarrhea associated with nelfinavir, saquinavir, and ritonavir. When recommending or offering PEP, exposed persons should also be informed that knowledge about the efficacy and toxicity of PEP is limited.

PEP FOR HIV EXPOSURES IN CHILDREN

In addition to its published recommendations for occupational PEP, the USPHS has recently published a statement on the management of nonoccupational exposures to HIV (48A). The CDC's position on "nonoccupational PEP" is as follows:

> "currently, the use of antiretroviral drugs for nonoccupational exposures to HIV should be considered a clinical intervention of unproven efficacy. Individual practitioners and their patients may opt to consider its use in specific circumstances following exposures to HIV that carry a particularly high risk of infection, but only after careful consideration of the potential risks and benefits and with a full awareness of the many gaps in our current knowledge [7]."

PEP for exposed children should be initiated in close consultation with a physician expert in the care of HIV-infected children.

Principles for Pediatric PEP

Currently, the only FDA-approved drug for HIV infection prophylaxis in the pediatric population is ZDV in the PACTG 076 regimen (49) for prophylaxis in infants born to HIV-infected mothers during the first 6 weeks of life. Because there have been no other studies of PEP in the pediatric age group, clinicians who wish to offer other potential PEP drug options to their pediatric

patients should take into account both the PEP recommendations for HCWs with occupational exposures (45,46), the most current guidelines on HIV antiretroviral therapy in children (50), and the statement on management of nonoccupational exposures to HIV (48A).

Some recommended drugs are not yet FDA-approved for use in children or in all age groups among children. These recommendations were based on ongoing studies or studies that have recently been completed. Based on these sources (45,46,50), principles for PEP and HIV therapy would include the following:

1. ZDV should be a component of any drug regimen used for PEP.
2. The effectiveness of combination therapy is greater than that of monotherapy to treat HIV infection. Similarly, the effectiveness of combination PEP is assumed to be greater than that of monoprophylaxis to prevent HIV infection. Dual- or triple-drug combinations are recommended for treatment of HIV-infected pediatric patients. Triple-drug combinations that include a PI are superior to the dual NRTI combination regimens alone in reducing viral load to undetectable levels and increasing CD4+ lymphocyte number (51). The triple regimen consisting of a PI and two NRTIs is "able to reduce HIV RNA to undetectable levels in some children" (52,53).
3. Monotherapy for HIV infection should be avoided. Similarly, it is assumed that monoprophylaxis to prevent HIV infection should be avoided, except in the case of perinatal transmission. Prophylaxis with ZDV is recommended during the first 6 weeks for an HIV-exposed infant after birth to an HIV-infected mother. If the infant is documented to be HIV-infected during this 6-week perinatal period, he/she should be put on the dual NRTI combination regimen of ZDV and 3TC (50). As some women are receiving combination antiretroviral therapy during pregnancy for their own health (54), some clinicians have elected to administer combination antiretroviral prophylaxis instead of ZDV monoprophylaxis to the infants during the first 6 weeks of life. It should be emphasized that no published data exist upon which to base recommendations for antiretroviral prophylaxis for the infant other than ZDV prophylaxis during the first 6 weeks of life. Prior maternal ZDV treatment may result in ZDV resistance in infants. However, such resistance has not been shown to account for most perinatal HIV infections (55). Also, duration of prior ZDV therapy in women with advanced HIV disease has not been associated with diminished ZDV efficacy for reduction of transmission (56). Based on such data, current guidelines do not recommend that antiretroviral prophylaxis regimens for perinatally exposed newborn infants should be based on maternal antiretroviral use (50). They caution, however, that the "perinatal transmission of antiretroviral-resistant HIV isolates" should be monitored (50). A clinical trial comparing ZDV monoprophylaxis with combination drug prophylaxis (ZDV prophylaxis in addition to NVP administered to the HIV-infected mother during labor and NVP given to the neonate) to reduce perinatal transmission is ongoing.
4. Because the duration of PEP is only 4 weeks, drugs that do not require graded dosing schemes and are maximally effective throughout the entire course should be considered drugs of choice for PEP.

5. Dual NRTI drug combinations are the second choice for HIV treatment of HIV infection when compared with triple combinations and are considered the "basic" PEP regimen for lower-risk HIV exposures. 3TC and ZDV comprise the dual-drug "basic" regimen of choice for PEP. In addition, other ZDV-containing dual NRTI drug combinations have been tested in children, including ZDV and ddI; and ZDV and ddC. The FDA has approved ddI as an HIV therapy in children more than 3 months of age and has approved the similar use of ddC in children more than 13 years of age. ddC is not available in a liquid preparation commercially, although it can be obtained through a compassionate-use program of the manufacturer (Hoffman-LaRoche Inc., Nutley, NJ) (50). The following dual combinations are not recommended: d4T and ZDV, ddC and ddI, ddC and d4T, and ddC and 3TC (50).
6. Triple-drug combinations are used as part of the "expanded" PEP regimen for higher-risk HIV exposures and are considered the first-choice regimen for HIV treatment. The triple-drug combination of choice is a highly active PI and two NRTIs (including ZDV). An alternate triple-drug combination is nevirapine (NVP) plus two NRTIs (including ZDV). The dual NRTI combination of choice is noted earlier. ZDV and ddC is a less preferred choice for use in combination with a PI (50). The PI of choice for PEP is nelfinavir. Ritonavir is the second-choice PI because its dosing schedule requires a stepwise increase over the first 5 days of therapy because of its possible side effects. Although no protease inhibitor is FDA-approved for infants under 2 years of age, the current treatment guidelines (50) recommend the use of pediatric formulations of ritonavir and nelfinavir in infants, with the understanding that "optimal dosing of these agents in young infants has not been defined" but is "under study in clinical trials." NVP, an NNRTI, is recommended as an "alternative" to a PI and is not a first-choice drug because of its potential side effects and the fact that the PIs are more accessible. However, NVP is an important alternative because it is fast-acting, is potent, and has been shown to have prophylactic efficacy in animal studies (57). The combination of NVP, ZDV, and ddI has produced substantial and sustained suppression of viral replication in two of six infants treated at less than 4 months of age (58). Although the liquid preparation of NVP is unavailable commercially, it can be obtained through a compassionate-use program of the manufacturer (Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) (50).

Age-Specific Considerations for PEP in Children

The choice of drugs available for treatment of HIV is more limited for children than for adults. Some drugs available for treatment of adults are not FDA-approved for children, are not recommended for children, or lack formulations suitable for small children. The age of the child at time of exposure may dictate which drugs can be used for HIV treatment or PEP. Pediatric antiretroviral therapy is a rapidly evolving field. Clinicians faced with a decision about PEP should consult a physician with expertise in pediatric HIV care. No definitive recommendations exist for PEP in older infants and in children. However a reasonable approach must take into account which pediatric formulations are available

in a particular area, which are available through compassionate-use programs, which are accessible in the appropriate time frame for PEP, and which have age-appropriate dosing schemes available for the child in question. Table 19-3 lists those antiretroviral drugs that have been FDA-approved for children by age category. In general, the suggested drugs of choice for the "basic" pediatric PDP dual-drug regimen in lower-risk exposures include ZDV and 3TC. The suggested drugs of choice in the "expanded" pediatric triple-drug regimen for higher-risk exposures include the "basic" regimen and Nelfinavir or Ritonavir (see Table 19-4). Other second-choice or alternate drugs have been described in the previous section. The dosing for the antiretroviral drugs used in pediatric PEP is generally the same for that used to treat pediatric HIV infection, and the duration of treatment is usually 4 weeks. The main exception to the 4-week duration of prophylaxis is the recommended 6-week course of perinatal ZDV monotherapy.

Term Infants From Birth Through Less Than 3 Months of Age

ZDV is the only FDA-approved antiretroviral drug for both HIV therapy and prophylaxis from the time of birth. ZDV monopro-

Table 19-3. FDA-approved antiretrovirals for children by age category

Drug	0–3 Months	3 Months to 2 Years	>2 Years
	NRTIs		
ZDV	Yes	Yes	Yes
3TC	No[a]	Yes	Yes
ddI	No	Yes	Yes
d4T	Yes[b]	Yes	Yes
ddC	No	No	Yes[c]
	NNRTIs		
Nevirapine[d]	Yes[d]	Yes	Yes
Delaviridine	No	No	No
	Protease inhibitors		
Nelfinavir	No	No	Yes
Ritonavir	No	No	Yes
Indinavir[e]	No	No	No
Saquinavir	No	No	No

Note: information in this table may change over time and the clinician is encouraged to review prescribing and toxicity information before prescribing these drugs.

[a] Use of 3TC recommended in children < 3 months of age, despite absence of FDA approval (50).

[b] FDA-approved for children ≥ 5 weeks of age.

[c] FDA-approved for children ≥ 13 years of age.

[d] Recommended as an alternate for PI (50) and recommended for children ≥2 months of age.

[e] Recommended for older children who can chew tablets or swallow capsules (50).

Table 19-4. Suggested "basic" and "expanded" PEP regimens for nonoccupational pediatric exposures

Regimen Category	Application	Drug Regimen[a]
"Basic"	HIV exposures for which there is a recognized transmission risk (see Fig. 19-1)	Four weeks (28 days) of both zidovudine (ZDV) and lamivudine (3TC)
"Expanded"	HIV exposures that pose an increased risk for transmission	"Basic" regimen plus either nelfinavir or ritonavir[b]

[a] See formulary for drug doses depending on age of child.
[b] Indinavir is recommended as a second-line PI agent for older children who can tolerate swallowing solid tablets or caplets.

phylaxis for the first 6 weeks after birth is the current recommendation for HIV-exposed infants born to HIV-infected mothers. In addition, experts feel that enough data exist on 3TC dosing for infants under 3 months of age to consider it safe to use for therapy of HIV-infected infants (50). (See Table 19-5 for 3TC dose under study for infants less than 3 months of age.) For infants exposed to HIV after birth, dual prophylaxis with AZT and 3TC might be considered the PEP "basic" regimen of choice in this and other age groups. d4T is also FDA-approved in children more than 5 weeks of age but is not recommended in combination with AZT (50). An "expanded" regimen for infants using a PI or NVP and two NRTIs (including ZDV) might be considered for higher-risk exposures if appropriate dosing schemes become available for younger infants and liquid formulations can be obtained in the short time frame required to administer PEP.

Term Infants From 3 Months of Age to Children Less Than 2 Years of Age

ZDV, 3TC, ddI, and d4T are the only FDA-approved antiretrovirals for HIV therapy in this age group. However, specific formulations of nelfinavir and ritonavir are recommended for use in "older infants" (50), and, as mentioned earlier, a liquid preparation of NVP is available through a compassionate-use program for infants through the Boeringer-Ingelheim pharmaceutical company. The "basic" and "expanded" pediatric PEP regimens in Table 19-4 are suggested for this age group.

Children 2 Years of Age to 13 Years of Age

ZDV, 3TC, ddI, d4T, nelfinavir, and ritonavir have been FDA-approved for therapy of HIV infection in this age group. The "basic" and "expanded" pediatric PEP regimens in Table 19-4 are suggested for this age group; however, indinavir is recommended as a second-line PI agent for older children who can tolerate swallowing solid tablets or capsules. NVP can be obtained through the compassionate-use program.

Adolescents

Adolescent dosages should be prescribed according to Tanner staging of puberty and not by age (50). Therefore those in Tanner

Table 19-5. Oral doses of antiretroviral drugs most often used for postexposure prophylaxis

Drug Preparations	Neonatal Dose	Pediatric Dose	Adult Dose
Nucleoside analog reverse transcriptase inhibitors (NRTIs)			
Zidovudine (AZT, ZDV, Retrovir) 10 mg/mL syrup 100-mg capsules 300-mg tablets	2 mg/kg q6h	90–180 mg/m^2 q6–q8h	200 mg tid or 300 mg bid
Lamivudine (3TC, Epivir) 10 mg/mL solution 150-mg tablets	2 mg/kg q12h[a]	4 mg/kg q12h	150 mg bid (body weight ≥ 50 kg), 2 mg/kg BID (body weight <50 kg)
Protease inhibitors			
Indinavir (Crixivan) 200 mg, 400-mg capsules	None	500 mg/m^2 q8h[a]	800 mg q8h
Saquinavir (Invirase) 200-mg capsules	None	None[a]	600 mg q8h
Saquinavir (Fortavase) 200-mg soft-gel capsules	None	None[a]	1200 mg tid
Nelfinavir (Viracept) 200 mg/tsp powder 250-mg tablet	10 mg/kg TID[a]	20–30 mg/kg tid	750 mg tid

[a] Dose is under study or will be studied in clinical trials.

stages I and II should be dosed according to pediatric schedules and those in Tanner V should be dosed using adult schedules (50). Adolescents undergoing growth spurts (Tanner III girls and Tanner IV boys) should be closely monitored for medication efficacy and toxicity when using adult or pediatric dosing guidelines (50).

Considerations for Determining Level of Risk in Nonoccupational HIV Exposures and the Appropriateness of Administering

The same considerations mentioned in determining level of risk for occupational exposures (see Fig. 19-1) as well as those delineated for specific pediatric exposures in the epidemiology section of this chapter should be taken into account when assessing risk for HIV transmission in pediatric exposures. In addition, the CDC has described the following factors (7) that can be applied to any

nonoccupational exposure, including those involving the pediatric age group: "(1) the likelihood that the source is infected with HIV; (2) the likelihood of transmission, including the many cofactors that might increase or decrease transmission risk; (3) characteristics (e.g., viral load, stage of infection) of an HIV-positive source; (4) isolated versus recurrent HIV exposures; (5) time delay between possible exposure and presentation for medical care; and (6) ability to adhere to the antiretroviral regimen." For example, in sexual abuse cases, one may want to know whether the abuse was acute or chronic. PEP will have a higher probability of being effective if an acute exposure has occurred and medication can be administered promptly. Was the exposure known to be associated with exchange of semen or blood? If the status of the perpetrator is unknown, what is the seroprevalence of HIV in the community where the child lives, or is the perpetrator known to take part in behaviors that would put him/her at risk for HIV infection? Similarly, for a situation where bottles containing expressed milk may have been switched, one would want to know the seroprevalence of HIV in the community and the HIV serostatus of the sources involved. Other important factors include the number of breast milk exposures, the presence of cracked or bleeding nipples in the mother providing the breast milk, and the oral hygiene status of the infant or child (e.g., presence of inflamed gingiva secondary to teething). If the source was found to be HIV-infected, it would also be important to determine her viral load because this would have an effect on risk of transmission. Each case must be evaluated individually, taking into account the specifics of each situation.

Prophylaxis for Infectious Agents Other Than HIV After Accidental Needlesticks with Discarded Needles

Recommendations for management of these exposures have been delineated (35). Because hepatitis B virus may survive on fomites for at least several days, one should check the hepatitis B virus vaccination status of the child. For children who have completed their hepatitis B virus immunization regimen, no further action is needed. Children who have not completed their regimen should receive an additional hepatitis B virus vaccination and should be scheduled to receive their remaining doses. Experts differ in the need to administer hepatitis B immune globulin (HBIG) to children who have not completed the hepatitis B virus immunization regimen. Tetanus toxoid and tetanus immune globulin should be administered based on the vaccination history of the person who has been stuck. It is thought that the risk for transmission for hepatitis A virus and hepatitis C virus through discarded needles is very low. Therefore administration of immune globulin for hepatitis A virus is not recommended (35). The need to test for hepatitis C virus is controversial (35). Should the clinician elect to test for hepatitis C virus, it should be done at time of injury and 6 months later with a confirmatory test for positive tests (35).

Prophylaxis for Hepatitis B Virus in Cases of Sexual Assault or Abuse in Children

The CDC has published guidelines (34) regarding such evaluation. In summary, it recommends initial, 2-week, and 12-week follow-up examinations to determine the presence of various STD infections. With regard to hepatitis B virus prophylaxis, it recommends that "sexual contacts of patients who have acute hepati-

tis B virus should receive HBIG and begin the hepatitis B vaccine series within 14 days after the most recent sexual contact" (34).

PREVENTING EXPOSURES

HCWs

General preventive measures to keep in mind include strict adherence to "universal precautions," avoiding the recapping of needles, properly restraining patients when drawing lab samples, and being well trained in doing procedures involving sharps. Gloves are unnecessary for handling breast milk "except in situations where exposures to breast milk might be frequent, for example, in breast milk banking" (2). HCWs with abraded skin or another condition that compromises the integrity of the epidermis should be especially cautious to avoid such contact.

Children in Hospital Settings

Used needles should be rapidly disposed of in sharps containers, and such containers should be placed in locations that are out of the reach of children. To avoid switching bottles of breast milk or having infants breast-feed from the wrong mother, there should be a good system for labeling bottles of breast milk and assuring that the correct bottle is administered to the correct child (e.g., compare name on label on bottle with name on patient identification bracelet).

Children Outside of Hospital Settings

Needlesticks

Children should be educated to avoid playing in areas known to be frequented by injecting drug users and to avoid playing with discarded needles and syringes because it may not be always feasible to monitor children during all their activities. However, some needlestick-related injuries may be impossible to avoid (59). Needle exchange programs may play a role in decreasing the number of discarded needles in public places (35).

Breast-Feeding Infants or Administering Expressed Breast Milk

All expectant mothers should be encouraged to be tested for HIV infection. If infected, mothers in industrialized countries should be discouraged from breast-feeding, and clinicians should provide education to HIV-infected mothers about feeding options. Breast milk alternatives should be affordable and easily accessible to all HIV-infected women. Every effort should be made to avoid exposure to contaminated breast milk. Anyone providing day-care services involving more than one child should have procedures in place to avoid switching bottles among their infants. Specifically, all bottles should be labeled with the child's name and used for the intended child (60). Women who choose to use wet nurses, particularly in areas with high HIV seroprevalence, should be made aware of the possibility of HIV transmission through this route.

SUMMARY

Adequate emphasis should be placed on preventing exposures to HIV in both occupational and nonoccupational settings. PEP may be recommended for higher- and lower-risk occupational exposures to HIV. In general, either a "basic" or "expanded" com-

Table 19-6. Summary of recommendations for postexposure prophylaxis after exposure to HIV

- Chemoprophylaxis should be considered for exposed workers after exposures that pose a risk for HIV transmission. In a situation where the risk is remote, PEP is not needed (see Fig. 19-1).
- Although its effectiveness in nonoccupational exposures is unproven, the use of PEP in such situations may be considered on a case-by-case basis taking into account the risks and benefits.
- ZDV should be considered for all PEP regimens, and 3TC should usually also be used for lower-risk exposures ("basic" regimen). In addition, a protease inhibitor should be considered for exposures with the highest risk of transmission ("expanded" regimen) (see Table 19-2).
- PEP should be initiated promptly, preferably within a few hours postexposure. PEP should be administered for 4 weeks, if tolerated.
- If PEP is used, drug toxicity monitoring should include a complete blood count and renal and hepatic chemical function tests at baseline and 2 weeks after starting PEP.
- If the source patient's HIV status is unknown, initiating PEP should be decided on a case-by-case basis, based on the exposure risk and the likelihood of HIV infection in the source patient.
- Persons with exposures to HIV should receive follow-up counseling and medical evaluation, including HIV-antibody tests at baseline and periodically for at least 6 months after exposure (e.g., 6 weeks, 12 weeks, 6 months) and should observe precautions to prevent possible secondary transmission.
- Persons who receive PEP are encouraged to be enrolled in anonymous registries. For occupational exposures, (1-888-737-4448) and, in 1999, for nonoccupational exposures (1-877-448-1737)
- Updated information about PEP can be obtained from the internet at CDC's home page (http://www.cdc.gov).

From Refs. 45 and 46.

bination antiretroviral regimen is recommended for prophylaxis, depending on level of risk, and should be continued for 4 weeks. Nonoccupational PEP should be considered a clinical intervention of unproven efficacy. The therapeutic principles established for occupational exposures (46) and pediatric HIV therapy (50) may be applicable to nonoccupational exposures to HIV in children. Determining the level of risk in these situations must be done on a case-by-case basis. Table 19-6 summarizes the important points to keep in mind for PEP.

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DISCLAIMER

The use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

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Handbook of Pediatric HIV Care

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