HIV Postexposure Prophylaxis in the 21st Century

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The administration of postexposure prophylaxis has become the standard of care for occupational exposures to HIV. We have learned a great deal about the safety and potential efficacy of these agents, as well as the optimal management of health-care workers occupationally exposed to HIV. This article describes the current state of knowledge in this field, identifies substantive questions to be answered, and summarizes basic principles of postexposure management.

Since 1988, institutions have been offering antiretroviral postexposure prophylaxis (PEP) for occupational exposures to HIV (1,2). Although much has been accomplished since 1990, many important questions remain: What are the initiating events in the pathogenesis of occupational HIV infection associated with a percutaneous exposure? What evidence supports the effectiveness of PEP in preventing occupational HIV infection? How can the use of PEP be improved by eliminating overtreatment? How can access to and use of expert consultants be facilitated? How can adherence to PEP medication regimens be improved? What is the relevance of the source patient's prior antiretroviral experience? How should occupational exposures be managed in pregnant health-care workers?

Pathogenesis

The early events in the pathogenesis of occupational HIV infection are incompletely characterized, although the last 10 years have seen substantial developments. Several studies have suggested an important role for the dendritic cell in the early events of infection. In the macaque simian immunodeficiency virus (SIV) model, dendritic cells, which are the first cells infected after intravaginal inoculation (3), can foster extensive viral replication when they interact with susceptible T cells (4). Another important piece of evidence underscoring both the role of the dendritic cell and the potential benefit of antiretroviral PEP comes from the studies of Pope et al., which demonstrated that infection of susceptible T cells by HIV-bearing dendritic cells could be blocked in vitro by the addition of antiretroviral agents to the culture system (4).

The role of host defense against HIV is also incompletely delineated. Ruprecht et al. were among the first to demonstrate efficacy of antiretroviral PEP in an animal system (a mouse model of retroviral infection). These investigators demonstrated that, for PEP to be effective, the mice needed to have intact cellular immunity (5). Clerici et al., who evaluated T cells from eight HIV-exposed but uninfected health-care workers, found that cells from six of the eight produced interleukin-2 when exposed to HIV peptide antigens, whereas cells from only one of nine unexposed controls mounted an interleukin-2 response (6). In follow-up studies from the same laboratories, investigators demonstrated that cytotoxic T-lymphocyte responses to HIV envelope peptides could be detected in 35% of occupationally exposed health-care workers, but in none of 20 health-care workers who had been exposed to blood from patients who did not have HIV infection (7). Administration of antiretroviral PEP to health-care workers who have sustained occupational HIV exposures may blunt this cellular response (8).

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Effectiveness of PEP in Preventing Occupational HIV Infection

The risk for occupational infection with HIV after a parenteral exposure to blood from an HIV-infected patient is approximately 0.3% (9). Because of this low rate of transmission and the difficulty in amassing a sufficient sample size of health-care workers with documented occupational HIV exposure, conducting a clinical trial is virtually impossible (2). During the past 10 years, however, evidence supporting the efficacy of PEP has come from three types of studies: in animal models; in preventing maternal-fetal transmission of HIV in humans; and a worldwide retrospective case-control study.

Animal Studies of PEP

Several recent studies have demonstrated the efficacy of various antiretroviral agents in preventing retroviral infections in animals. Bottiger et al. demonstrated that a 3-day course of the nucleoside analog BEA-005 (2,3'-dideoxy-3'-hydroxymethyl cytidine) prevented either SIV or HIV-2 infection (10). Tsai et al. demonstrated the efficacy of the nucleotide analog phosphonyl-methoxy-propyladenine (PMPA) (Tenofovir, Gilead Sciences, Foster City, CA) in preventing SIV infection in macaques (11). In subsequent studies, duration of PEP treatment influenced the success of chemoprophylaxis in this model; the timing of administration of the dose relative to exposure or infection is also critical. All the macaques treated for 28 days but only half the macaques treated for 10 days and none of those treated for 3 days were protected. Delaying PEP also was found to be detrimental: 100% of macaques that received PEP within 24 hours of intravenous infection with SIV remained uninfected, but 50% of the animals that received the first PEP dose 48 hours after infection and 25% of those that received the first dose 72 hours after infection were protected (12). In a similar study

presented at the 4th Decennial Conference, PMPA PEP was effective after vaginal inoculation of macaques with HIV-2. All animals treated within 36 hours of inoculation were protected, but one of four treated at 72 hours after inoculation became infected (13).

Efficacy in Preventing Maternal-Fetal Transmission of HIV

Progress has been made in the past 10 years in preventing the transmission of HIV from infected mothers to their offspring. In the United States, the incidence of perinatally transmitted HIV infection declined by two thirds from 1992 to 1997 (14). In the groundbreaking AIDS Clinical Treatment Group (ACTG) protocol 076, zidovudine (ZDV) was administered to mothers before birth and during labor and delivery and to the newborns for 6 weeks after birth (15). For mother-offspring pairs in the treatment arm of this study, the risk for vertical transmission of HIV was reduced by 67% (15). Since publication of the ACTG 076 trial, several studies have confirmed and extended these initial results (14,16-30). Wade et al. demonstrated that administration of antiretroviral agents to the newborn within the first 48 hours of life significantly reduced the risk for perinatal HIV transmission (31). Several recent studies have evaluated combinations of antiretroviral agents (23,24), altered dosing schedules (22,28-31), delivery strategies (19,20), or short-term administration of nonnucleoside reverse transcriptase inhibitors (25)—all with similar success (Table). As in the study by Wade and colleagues, in some of these studies only the infant received the agents (22). These studies effectively dispel the early concern that, because of their mode of action, antiretroviral agents (in particular, nucleoside analogs) could not be effective in prophylaxis (2). Further, the studies that show a preventive effect when the drugs are administered only to newborns offer definitive proof that PEP (at least for vertical exposure) can be effective in humans.

Table. Clinical trials assessing the efficacy of antiretroviral agents in preventing maternal-fetal transmission of HIV

Study (ref)	Regimen[a]	Timing[b]	Outcome (%)
Connor (15)	ZDV	A+L+P	8.3 vs 25.5
Shaffer (28)	ZDV	A+L	9.4 vs 18.9
Wiktor (29)	ZDV	A+L	12.2 vs 21.7
Dabis (30)	ZDV	A+L+P	18.0 vs 27.5
Wade (31)	ZDV	A+L+P	6.1 vs 26.6
	ZDV	L+P	10.0 vs 26.6
	ZDV	P (<48 hr)	9.3 vs 26.6
	ZDV	P (>72 hr)	18.4 vs 26.6
Bulterys (22)	ZDV	A+L+P	8.2 vs 15.5
	ZDV	L+P	8.6 vs 15.5
	ZDV	P	8.1 vs 15.5
Saba (23)	ZDV+3TC	A+L+P	52 (reduction)
	ZDV+3TC	L+P	40 (reduction)
	ZDV+3TC	L	no reduction
Blanche (24)	ZDV+3TC	A+L+P	2.6
	ZDV	A+L+P	6.5
Guay (25)	ZDV	L+P	25.1
	NVP	L+P	13.1

[a]ZDV = zidovudine (azidothymidine); 3TC = lamivudine; NVP = nevirapine

[b]A - Prenatal therapy (usually beginning at 36 weeks); L - Therapy during labor and delivery; P - Postpartum treatment of infant.

The Retrospective Case-Control Study

The third piece of evidence supporting the efficacy of antiretroviral PEP comes from the retrospective case-control study of health-care workers who sustained occupational exposures to HIV (32). In this study, cases of occupational infection were matched with controls from the Centers for Disease Control and Prevention (CDC)'s ongoing study of self-reported occupational HIV exposures. This study identified four factors associated with the risk for occupational infection and also found that ZDV PEP was associated with an >80% reduction in infection risk (32). Despite these limitations (33), the study findings are extremely important, as no other data directly address this issue.

Overtreatment and the Use of Expert Consultants

A concern in the prescribing and administration of PEP is that the persons who are asked to prescribe PEP are often not familiar with the drugs. Emergency room staff or occupational medicine personnel may be called on to prescribe drugs for PEP but have limited experience with the drugs and their toxicities and, because these occurrences are rare, often are unfamiliar with what constitutes an exposure. Occupational HIV exposures are crisis situations demanding immediate, decisive action. Indirect evidence that the primary prescribers may not be entirely familiar with the optimal management strategies for PEP comes from the University of California at San Francisco prophylaxis hotline. In 1997, in 58% of the calls to the hotline, staff recommended either stopping or not starting PEP (34). In 1998, 59% of calls were handled similarly (D. Bangsberg, pers. comm.). These problems could at least in part be averted by providing ready access to expert consultants.

The choice of agents for PEP is also a source of confusion and an area in which expert consultants could provide substantial assistance. To err on the conservative side of the issue, providers may assume that more is better. Adding additional agents, however, may mean that the health-care worker is unable to adhere to the regimen. For most exposures, only two agents are necessary (35). For more complicated situations (e.g., a source patient with extensive antiretroviral experience), expert consultation is essential.

Finally, the duration of PEP is somewhat controversial. In some maternal-fetal studies, a short course was effective (e.g., two doses of nevirapine) (25). In certain animal studies, shortened courses were effective (10), but in others, the shortened course was associated with decreased efficacy (12). Providing a regimen to which the exposed health-care worker can adhere is of paramount importance. Without definitive data to demonstrate the safety of shorter courses, the "traditional" 28-day course of PEP is preferable.

Relevance of the Source Patient's Experience with Antiretroviral Agents

An issue that frequently arises in centers treating large numbers of patients with HIV infection is whether the PEP regimen should be altered for exposures to a patient who has extensive experience with antiretroviral agents. Some instances of PEP failure have been associated with genotypic or phenotypic resistance to the agent(s) selected for PEP (35). Instances have been reported in which PEP failure was ascribed at least in part to isolates resistant to one or more of the three drugs in the standard regimen (36). Conversely, especially in the maternal-fetal studies, genotypic resistance

has not precluded a beneficial drug effect (17). For example, in the ACTG-076 study, ZDV therapy was effective despite the fact that HIV isolates from 25% to 30% of the women demonstrated genotypic resistance to ZDV (17). If a source patient has a resistant isolate, expert consultation should be sought with an HIV specialist. Tailoring the PEP regimen to the source patient's antiretroviral experience makes intuitive sense. If the source patient is controlled on therapy (i.e., has a low or undetectable viral burden), working with the expert consultant to select a regimen based on the source patient's drugs is also reasonable.

Tailoring regimens for all health-care workers who have exposures to antiretroviral-experienced patients may lead to the administration of newer, less well-tested, and potentially more toxic agents to the exposed health-care workers, clearly increasing their risk. However, a patient who is breaking through on therapy (i.e., has a high viral titer despite treatment) may not always have resistant isolates. Treatment failures may be due to poor adherence with treatment regimens rather than viral resistance (37,38), and circulating isolates (i.e., wild-type virus) may be nonresistant. In addition, some evidence indicates that resistance disappears rapidly after treatment is stopped (39), so that aggressive selection of PEP agents may not be necessary. Nonetheless, the most recent U.S. Public Health Service guideline for managing health-care workers who have sustained occupational HIV exposures recommends adding an agent from a class of drugs to which the source patient's isolate has not been exposed when resistance is highly suspected or known (35). Based on the new information cited above, such an agent should be added only if resistance is documented.

PEP in Pregnant Health-Care Workers

The administration of antiretroviral PEP to pregnant health-care workers who have sustained an occupational exposure to HIV has long been a matter of controversy. Information about the risks of administering these agents to pregnant women has been extremely limited, but a few basic principles should be applied. First, pregnancy per se should not preclude PEP for an exposed health-care worker. Second, the decision whether PEP should be administered to a pregnant health-care worker should be hers, after she has had the benefit of thorough counseling about risks for infection and adverse drug effects for herself and her fetus. Third, the regimen offered to a pregnant health-care worker should be the one with the best chance of preventing infection. Fourth, pregnant workers electing PEP should be followed scrupulously for signs of adverse events. Recently, concern has been expressed about potential for mitochondrial toxicity in infants born to mothers receiving antiretroviral agents. In the French cooperative study evaluating the administration of antiretroviral agents to prevent maternal-fetal HIV transmission, two infant deaths among children who did not acquire HIV infection were ascribed to progressive neurologic disease (40). After this cohort was screened for elevated lactate levels, six additional cases of potential mitochondrial toxicity were identified (40). Four patients had received ZDV alone, and four had received the ZDV/3TC combination. Three of the additional six cases had neurologic findings including status epilepticus, myopathy, seizures, spastic diplegia, and febrile seizures (40). The U.S. Food and Drug Administration has evaluated postmarketing data from manufacturers of nucleoside analogs and has not identified additional deaths in this dataset. The U.S. Public Health Service has also examined data from CDC surveillance, CDC studies of maternal-fetal transmission, the National Institutes of Health's ACTG Studies, and the large database from the Women and Infants Transmission Study without identifying additional deaths attributable to mitochondrial disease. These data provide some reassurance, but the French findings indicate that additional scrutiny is warranted.

Conclusions

We have made substantial progress in our management of occupational exposures to HIV since the 1990 Decennial Conference. The rationale for offering PEP to health-care workers after documented occupational exposures to HIV now seems much more solid than in 1990. Nonetheless, several important questions remain unanswered: How are the generally encouraging data generated from animal studies and from studies of the efficacy of antiretroviral agents in preventing vertical transmission of HIV in humans relevant to the use of chemoprophylaxis after sexual exposures to HIV? What roles will new agents (e.g., BEA-005 or PMPA) play in postexposure management? Why do patients coinfected with hepatitis C and HIV have such differing prognoses and disease progression?

Several basic principles should be followed in postexposure management of occupational exposures to HIV. First, ensure that treatment is immediately accessible. Second, make certain an exposure has occurred (using expert consultants whenever necessary). Third, if PEP is administered, select a regimen to which the health-care worker can adhere (dependent on the source patient's therapy and viral level). Fourth, learn to anticipate and treat side effects prophylactically. Fifth, monitor the health-care worker closely for adherence with the regimen and for adverse drug effects.

Finally, regardless of the development of successful postexposure management strategies, we need to continue to invest a substantial effort in preventing occupational exposures to bloodborne pathogens. Several institutions have worked aggressively to reduce these exposures, some with great success (41-44). We need to learn from our colleagues' experiences and continue to minimize such occupational exposures.

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