Should emergency departments offer postexposure prophylaxis for non-occupational exposure to HIV?

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Introduction

In 1998 the US Centers for Disease Control and Prevention (CDC) first recommended that institutions provide postexposure prophylaxis (PEP) for occupational exposure to HIV.[1] Many emergency departments (EDs) have developed protocols for the distribution of medications to health care workers who have sustained high-risk injuries with contaminated blood and body fluids. However, only a very small proportion of HIV cases are occupationally related. Worldwide surveillance reports from December 1984 until September 1997 list 94 documented and 170 possible cases of occupationally acquired HIV. Only 1 documented and 2 possible infections had been reported in Canada.[2] In contrast, in 1999 it was estimated that 49 800 people in Canada were living with HIV and 4190 had become infected.[3] Should protocols be developed for those seeking prophylaxis for non-occupational exposures? The CDC did publish guidelines for the use of PEP for non-occupational exposures to HIV in 1998,[4] but these guidelines are not definitive; they state only that "because the therapy remains unproven and can pose risks, physicians should consider its use only in individual circumstances when the probability of HIV infection is high, the therapy can be initiated promptly, and adherence to the regimen is likely. It should not be used routinely and should never be considered a form of primary prevention."[5] The 2002 summary and recommendations can be viewed on the CDC Web site (www.cdc.gov/hiv/pubs/facts/petfact.htm).

Uncertainty in the emergency department

For a variety of reasons, physicians are often asked to provide antiretroviral medications in the emergency setting. It is well recognized that there are many difficulties distributing PEP for non-occupational exposures to HIV through primary care practices or HIV clinics. Therapy must be initiated in a timely fashion, and exposures frequently occur after usual office hours. Furthermore, individuals may desire relative anonymity, thereby seeking treatment from someone other than their established health care worker.[6] Should EDs extend their PEP programs to individuals with high-risk non-occupational exposures to HIV? The following cases are provided to help define a clinical context in which emergency physicians may be asked to initiate PEP in the ED.

Case 1a

A 25-year-old male presents to the ED of a large urban centre at 0200 h Saturday night. He states that he works in a "gay bath house" and while cleaning the washrooms he sustained a needlestick injury from a used syringe. He was counselled by his family physician to present immediately to the ED to receive appropriate therapy. He is immunized against tetanus and hepatitis B, and was HIV negative when tested 3 weeks earlier.

Case 1b

A 6-year-old child is found playing with a discarded syringe in a playground. She states that she pricked her finger with the needle.

Case 2

A 32-year-old heterosexual male presents to the ED. Two hours after engaging in unprotected vaginal intercourse with a new partner, he learned that she is HIV positive. He is otherwise healthy, without any risks for hepatitis or HIV.

Case 3

A 34-year-old female injection drug user (IDU) shared a needle with an HIV-positive friend. She has not used any

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drugs in many years. She last tested negative for HIV one year ago.

Case 4

A 24-year-old female student presents to the ED 1 hour after being sexually assaulted. In addition to other therapies and counselling, should she be offered PEP for possible HIV exposure?

What is the risk of HIV transmission?

Determining the relative risk associated with an exposure to HIV may be difficult, but it is important to estimate prior to prescribing PEP. Estimated risks have been published for a variety of contacts (Table 1[7–17]). Blood and body fluids containing visible blood, as well as semen and vaginal secretions are considered potentially infectious. Feces, mucous, saliva, sweat, urine and vomitus have an extremely low risk of infection unless they are contaminated with blood.[18] For sexual exposures, the highest risk is associated with receptive anal intercourse with a symptomatic partner.[4,19] The risk of infection of receptive anal intercourse with an HIV-positive asymptomatic partner is estimated to be similar to the risk of a needlestick injury in the clinical setting. Seroconversion does occur with oral–genital exposures, although the risk is low and poorly quantified.[4] Mathematical modelling has estimated the risk of a shared injection with an HIV-positive individual as 0.67% per incident.[15] In contrast, the risk after exposure to a discarded needle in the outdoor setting has not been estimated and is likely small.[16,20] It is hypothesized that the lag time and the exposure of the virus to environmental factors will decrease the likelihood of HIV transmission. In approximately 600 documented exposures in both children and adults there have not been any cases of seroconversion.[21–23] Finally, the risk of transmission of HIV from a bite is also low because enzymes in saliva inhibit the growth of HIV.[3] Documented cases of HIV transmission by human bites have been associated with blood-tinged saliva.[17] Therefore, only if a break in the skin of an HIV-positive source or bloody saliva is present should PEP administration be considered.[16]

How should we interpret these risks? One expert panel stated "we recommend PEP after a sporadic exposure with a risk of infection of about 0.3% or greater. If the risk of infection is moderate, in the range of 0.10% to 0.30% we do not believe the evidence currently warrants a recommendation for PEP in all cases. . . . all persons exposed should be informed of the risks and benefits of PEP, so that decisions can be individualized".[19]

What is the rationale for PEP?

Animal models, using simian immunodeficiency virus (SIV), have demonstrated the potential effectiveness of antiviral regimes. The mechanism of SIV infection is unclear. However, investigators have shown a 2- to 3-day lag from the time of inoculation to the time that virus is detected in regional lymph nodes or cells.[24,25] Chemoprophylaxis taken shortly after exposure may halt HIV replication or block

Table 1. Estimated risk of infection after exposure to an HIV positive source

Type of exposure	Per-contact risk	Reference
Receptive anal intercourse; asymptomatic source	0.008–0.032	<7>
Receptive anal intercourse (1° HIV infection)	0.1–0.3	<8>
Insertive anal intercourse	0.0003	<9>
Receptive vaginal intercourse	0.0005–0.002	<4,10–13>
Insertive vaginal intercourse	0.0003–0.0009	<10–13>
Oral intercourse*	Not quantified, low risk. Increased risk if lesions or sores in mouth	<3,14>
Needle sharing	0.0067 (mathematical modelling data)	<15>
Occupational percutaneous exposure	0.003	<1>
Bite	No contact with blood — low risk	<3,16,17>

* Case reports in literature. Identified as an independent risk factor in 3 of 24 epidemiologic studies.

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the dissemination of HIV to susceptible T cells.[24,26–28] Several studies have also shown that initiation of antiretrovirals may be effective in preventing SIV infections in these models.[29–35] After HIV infection has been established, viral replication is rapid, and there may be a theoretical advantage in those who seroconvert to the initiation of antiretroviral and the limitation of proliferation.[1] Treatment of animals with zidovudine within 24 hours, and continued for 28 days, was more effective than treatment after 72 hours.[4] It is unclear how much direct impact animal studies should have on recommendations for treatment of exposed individuals.[19,36,37] However, there is evidence to suggest that not everyone who is exposed to HIV will become infected. Case reports have documented that health care workers who have been exposed to HIV may be sensitized to viral antigens but never seroconvert.[38–40]

How effective is treatment?

There is no direct evidence to support the use of PEP for non-occupational exposures to HIV. The rationale for therapy is extrapolated from human trials involving occupational exposure or vertical transmission. The evidence of effectiveness of PEP for occupational exposures was reviewed in a case–control study by Cardo and colleagues,[41] which prospectively followed health care workers with percutaneous exposure to HIV-infected blood. The study compared 33 cases to 665 controls. Participants were treated with non-standardized doses of zidovudine, and the overall risk of seroconversion was reduced by 81% (95% confidence interval [CI], 48%–94%).[41] Failures of PEP have been reported in both the occupational and non-occupational setting. Increased risk of HIV transmission was associated with antiretroviral resistance in the source, a high HIV titre or large inoculum exposure, route of exposure, delay in initiation of PEP, and short duration of therapy.[2,18,41–44]

Chemoprophylaxis studies have also been conducted in HIV-infected pregnant women. In a prepartum and perinatal study of 447 HIV-positive women more than 14 weeks pregnant treated with zidovudine, the relative risk reduction in neonatal infection was 67.5% (95% CI, 40.7%–82.1%).[45] Studies of abbreviated therapy with zidovudine have demonstrated a 50% reduction in vertical transmission.[46–50] Transmission was also decreased by 50% when zidovudine and lamivudine were administered in pregnancy, labour and 1-week postpartum, and by 37% if started in labour and continued for one week postpartum.[18] Although the data from these studies may not be analogous to other exposures, it does provide indirect evidence of the potential effectiveness of prophylaxis.

What is the downside of PEP therapy?

Drug toxicity, side effects and interactions are some of the most serious concerns when prescribing PEP. Case series have estimated that severe reversible adverse events occur in 0.9% of persons receiving 3-drug therapies (95% CI, 0.5%–1.5%).[51,52] The BC Centre for Excellence in HIV/AIDS estimates that long-term adverse events may occur in 1 in 5000 cases of PEP, with a risk of death between 1:15 000 and 1:150 000 (http://cfeweb.hivnet.ubc.ca/).

In the San Francisco PEP Study, 78% of participants who were treated for non-occupational exposures completed therapy.[53] Side effects included nausea (52%), fatigue (44%), headache (24%), diarrhea (15%) and anorexia (12%). Reversible laboratory abnormalities were seen in <2% of cases. In persons receiving PEP for occupational exposures, compliance ranged from 43% to 79%, and the side-effect profile was similar.[18,54–58] Noncompliance was frequently attributed to the significant side-effect profile, with 2-drug regimes better tolerated than 3-drug regimes.[18,52,57,59] Only 6% of workers had laboratory abnormalities, and all serious adverse events resolved within 6 months.[57]

Of note, serious side effects have been reported with the use of nevirapine, which has been prescribed for occupational exposures to HIV. In 2000, there were 2 published reports of life-threatening hepatotoxicity, 10 cases of mild-to-moderate hepatotoxicity, 14 cases of serious skin reactions (including Stevens–Johnson Syndrome) and 1 case of rhabdomyolysis.[60–62] One case of ototoxicity has also been reported in 23-year-old female treated for PEP with stavudine, lamivudine and nevirapine.[63]

In non-occupational exposures, concerns have been raised regarding drug resistance, especially when detailed information regarding contacts may be difficult to obtain.[53,64] When it is available, it is important to note any viral resistance to PEP medications and to tailor regimes accordingly. As well, there is the potential for individuals to develop viral resistance if they seroconvert after noncompliance with therapy[19] or if PEP does not suppress infection.[53]

Finally, EDs and health care facilities must be prepared to develop and initiate protocols that will allow for the timely implementation of therapy, counselling and follow-up. Time delays seeking therapy may be considerable. The San Francisco PEP Study had a median time from exposure to treatment of 33 hours.[53] As with occupational injuries, therapy should begin as soon as possible because it is believed there is little benefit in offering therapy if it be-

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gins more than 72 hours after the exposure.[4,19,37] Therefore, PEP programs must be able to offer a supply of medications readily. Many emergency programs designed for health care workers provide an initial 3- to 5-day supply of medications. However, cost may be considerable for non-occupational programs. It is estimated that a 28-day course of medications costs between $300 and $1200.[65]

Who should provide PEP?

EDs have played an important role in the initial management of occupational exposures, and it would appear reasonable for them to develop policies to define how high-risk non-occupational exposures to HIV should be treated. Many centres consider the therapy experimental and require formal consent.[4] It is important that community resources, HIV specialists and primary care physicians with a special interest in HIV therapy play a major role in the development of any program offering PEP, in order to ensure that individuals receive adequate monitoring, counselling and follow-up. Patients should be followed for a minimum of 6 months. The median interval to seroconversion was 25 and 46 days in studies involving health care workers.[1,66] It is estimated by the CDC that 95% of health care workers with occupational exposures became HIV positive within 6 months, and the majority experienced a syndrome compatible with infection.[1] Delayed seroconversion has been reported in 3 cases, all of which became seropositive by 12 months.[1]

Should we treat non-occupational exposures? Will PEP undermine primary prevention?

Several issues should be considered when discussing the issue of PEP with patients. In populations at risk, expert consensus maintains that primary prevention is essential and PEP is neither a feasible nor an effective mechanism to decrease the rate of new infections. Educational and risk-reduction programs are estimated to avert 10 times more cases than PEP programs.[67] Therefore, if PEP programs are implemented it is essential that new resources be made available rather than diverting funding from primary prevention initiatives.

There is also concern that misconceptions about the effectiveness of PEP might encourage high-risk activities. In a 1997 survey of 540 gay and bisexual men, 3% had already used PEP and 26% planned to use PEP. Those who planned to use PEP were younger, less well educated and more likely to use injection drugs.[68] Similarly, in a survey of 54 men who have sex with men (MSM), 15% had taken "a chance of getting infected when having sex" because of the availability of new therapies.[4]

It is clear that for individuals who repeatedly engage in high-risk activities, PEP is not appropriate. However, in cases of isolated exposure, where the risk of transmission of HIV is similar or higher than for occupational exposure, should PEP be offered? Most health care workers are empathetic to a colleague who sustained a work-related injury. This empathy, however, may not extend to an individual who has participated in a high-risk activity. Although physicians may not condone the behaviours exhibited by an individual with non-occupational exposures, they continue to have an obligation to act in the best interest of the patient. PEP should be considered as one of the therapies available to this population when they have an isolated, high-risk exposure to HIV.

Are PEP protocols necessary? Are non-occupational PEP programs feasible?

There is a need for EDs to review the issue of PEP for non-occupational exposures to HIV because patients will present for counselling and potential therapy. A 1998 survey of 78 EDs in Massachusetts showed that 52% had had patient requests for PEP for non-occupational reasons. However, only 15% of these EDs had established written protocols for drug distribution.[69] In the UK, the request for PEP increased 4-fold between 1997 and 1999, with most of the requests coming from HIV-discordant couples.[70] In a survey from France, usage of PEP increased 9-fold between 1997 and 1999.[51]

Programs are in place in many sites. For example, the San Francisco PEP Study enrolled 401 participants between December 1997 and March 1999.[53] Participants were primarily male (91%), and 93.5% sought treatment after sexual exposure. Fifty-seven percent were uncertain of the source's HIV-infection status. The median time to treatment was 33 hours. In total, 309 (78%) participants completed 4 weeks of therapy. A second PEP course was provided to 12% of participants. All participants were provided with 5 risk-reduction counselling sessions. After 6 months of follow-up, no patient had seroconverted, although the study did not have adequate power to define this risk.

Case discussions

Case 1a

A 25-year-old male presents to the ED of a large urban centre at 0200 h Saturday night. He states that he works in

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a "gay bath house" and while cleaning the washrooms he sustained a needlestick injury from a used syringe. He was counselled by his family physician to present immediately to the ED to receive appropriate therapy. He is immunized against tetanus and hepatitis B, and was HIV negative when tested 3 weeks earlier.

Case 1b

A 6-year-old child is found playing with a discarded syringe in a playground. She states that she pricked her finger with the needle.

Cases 1a and 1b raise the issue of the use of PEP for needlestick injuries from an unknown source. Neither the American Academy of Pediatrics[20] nor the BC Centre for Excellence in HIV/AIDS (http://cfeweb.hivnet.ubc.ca/) recommend the use of PEP when there is no available history regarding time or use of the abandoned syringes. However, a survey of pediatric infectious disease and emergency medicine specialists indicated that 83% and 56% respectively would offer PEP in the first 24 hours after a needlestick exposure.[71]

In the first scenario, the treating physician may choose to consider seroprevalence rates for HIV. One must be cautious interpreting the data because seroprevalence can only be estimated and surveys are prone to bias in reporting and delays in publication. Furthermore, information is unavailable for many regions in Canada. HIV prevalence rates in IDUs for 1997 were 19.5% in Montreal, 23% in Vancouver, 9% in Quebec City and 8.6% in Toronto. In Ottawa, Victoria and Montreal, the seroprevalence rate in needle-exchange programs was 20%. Prevalence rates for MSM who are also IDUs may be higher, up to 25%.[3,72] In comparison, seroprevalence of IDUs in New York City is estimated at 41%–48%.[19] The distribution of new infections has changed, with a 30% increase in new infections per year among MSM and a 27% decline in infections among IDUs between 1996 and 1999.[3] Appropriate therapy for the individual with a needlestick injury from an unknown source may be highly dependent on the community. Probability of HIV transmission would also be estimated to be higher if the syringe had only recently been discarded.

Case 2

A 32-year-old heterosexual male presents to the ED. Two hours after engaging in unprotected vaginal intercourse with a new partner, he learned that she is HIV positive. He is otherwise healthy, without any risks for hepatitis or HIV.

This case addresses the moderate-risk exposure to HIV. The male patient had unprotected intercourse with a seropositive female. The risk is felt to be lower for female-to-male transmission, and would be estimated to be somewhat less than 0.1%. In this case, the risks and benefits of therapy were discussed and the patient chose to initiate therapy. Baseline bloodwork was performed, and follow-up arrangements were made with a primary care provider with an interest in HIV. Other individuals may have chosen not to begin PEP medications.

Case 3

A 34-year-old female IDU shared a needle with an HIV-positive friend. She has not used any drugs in many years. She last tested negative for HIV one year ago.

This case represents re-initiation of high-risk behaviour by an IDU. The patient's friend was confirmed to be HIV positive, was noncompliant with follow-up and was not on any medications. The estimated risk of this exposure was 0.67%. The patient received extensive counselling and was referred to a detoxification program. She did not know her HIV serostatus, and baseline testing was performed. She was started on standard PEP medications, and follow-up was arranged.

Case 4

A 24-year-old female student presents to the ED 1 hour after being sexually assaulted. In addition to other therapies and counselling, should she be offered PEP for possible HIV exposure?

PEP for possible HIV exposure is only one component of a comprehensive rape-treatment program. It may be argued that discussion of HIV infection would create needless concern where none existed. Yet studies from the United States have reported that up to 40% of survivors of sexual assault feared contracting HIV.[73] "The fear of contracting an STD, particularly HIV infection, following rape appears to be a significant stressor adding to the incidence, prevalence and severity of psychiatric morbidity in rape survivors." [73] Counselling should be used to educate individuals about the physical and psychological issues associated with the assault. Included in the discussion should be the risks of HIV infection, the meaning of antibody tests, the issue of linked versus anonymous testing and the efficacy of PEP therapy.

Estimation of the risk of exposure is difficult. Frequently, the serostatus of the assailant is unknown. In Canada, the risk of HIV transmission is estimated to be greater than 0.2% (2 per 1000 contacts).[65] Other issues that must be taken into account include the type of exposure or contact, the body fluid involved and route of exposure, the nature of the associated physical injuries and the number of assaults. In sexual assault, the risk of transmission is felt

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to be higher than with consensual receptive vaginal intercourse due to the significant tissue trauma and contact with lesions and blood that may result from violent attacks. Concomitant infection with chlamydia, gonorrhea, trichomonas or bacterial vaginosis may also increase the victim's susceptibility to infection.[9]

Despite concerns regarding HIV transmission, published studies show that compliance with PEP is poor. A sexual-assault service in Vancouver reviewed 258 people who were seen by the service. Seventy-one accepted HIV prophylaxis. Twenty-nine of the 71 continued drug therapy for more than 5 days. Only 8 completed the full 4-week therapy and follow-up.[74] Those at higher risk for HIV exposure were more likely to complete treatment. A similar study of 376 individuals was conducted in San Francisco. Sixty percent of eligible persons were offered PEP, and 32% began therapy. Only 38% returned for 1-week follow-up and received an additional 3 weeks of therapy.[75]

Physicians and counsellors should be aware that, due to the stress of the event, sexual assault survivors might have difficulty making informed decisions about the appropriateness of initiating PEP.[9] In situations in which the risk of exposure may be significant, the survivor should be encouraged to begin medication as soon as possible and to seek further counselling regarding its continuation. During follow-up counselling the overall risks and benefits could be explained more thoroughly. Providing PEP, along with medical care, counselling and other therapies may help individuals regain a sense of control and allay some of their anxieties.

Summary

- Based on the CDC guidelines, there is no conclusive data to recommend the initiation of PEP for possible non-occupational exposures to HIV.[4,5]
- PEP is not a primary prevention measure for HIV.
- PEP does not replace adherence to harm-reduction behaviours. Participants should be carefully evaluated for behaviours that may lead to recurrent exposure, and counselling should be provided to all individuals.
- Prior to initiating therapy, physicians should evaluate the risk of transmission and the time elapsed since exposure.
- Antiretroviral therapy should be initiated in consultation with experienced providers who will provide ongoing consultation, follow-up and treatment. Monitoring must include a complete blood count and renal and liver function testing upon initiation of therapy and again at 2 weeks.[4]
- Medical evaluation should continue for a minimum of 6 months, with HIV-antibody testing at 6 weeks, 12 weeks, 6 months and one year. Patients should be monitored for signs of acute HIV infection and, if necessary, re-tested.

Key words: HIV, postexposure prophylaxis, non-occupational exposure, HIV exposure, antiretroviral therapy

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