

Non-occupational Human Immunodeficiency Virus Post-exposure Prophylaxis

Introduction

The vast majority of human immunodeficiency virus (HIV) transmission worldwide occurs in non-occupational settings.¹ Of newly acquired infections in Australia, sexual contact between men accounts for more than 80% of cases, heterosexual contact for around 10% of cases and injecting drug use for around 5%.² Thus, appropriately targeted non-occupational HIV post-exposure prophylaxis (NPEP) could be a useful adjunct in the battle against HIV.

Evidence suggesting efficacy of HIV post-exposure prophylaxis (PEP) in HIV-exposed healthcare workers (HCWs)^{3,4} led to recommendations for occupational HIV PEP (OPEP) in most developed countries. However, NPEP recommendations have not appeared so readily; Australia being one of only seven countries in the world to have adopted national NPEP guidelines recommending its availability.⁵ The Australian National Council on AIDS, Hepatitis C and Related Diseases (ANCAHRD) NPEP guidelines⁶ address the practicalities of NPEP risk assessment, transmission risks and prescribing and are available online at URL: http://www.ancahrd.org/media_releases/bulletins/01/28_hiv_guidelines.pdf.

Definition and mechanism of action

HIV PEP is the term used to describe administering antiretroviral (ARV) therapy to individuals following potential or actual exposure to HIV infection. The observation that some HIV-exposed individuals develop antigen-specific CD8 T-cell responses without becoming chronically infected suggests that transient infection may have occurred in these subjects.^{7,8} Therefore, PEP may act, not to prevent, but to limit initial cellular infection and spread of virus, allowing the host's immune defences to clear the virus inoculum.⁹

History

As early as 1988, HIV PEP was administered to exposed HCWs,¹⁰ based on *in vitro* studies showing that reverse transcriptase inhibitors protected susceptible T-cells from viral replication and from the cytopathic effects of HIV.^{11,12} Criticisms of this practice^{13,14} were fuelled by a handful of case reports documenting PEP failure.¹⁵⁻¹⁹

However, the 1995 Centres for Disease Control and Prevention (CDC) case-control study reporting a reduction of occupational HIV transmission with the use of post-exposure zidovudine (AZT) therapy³ prompted countries around the world to develop policies on PEP for occupational exposures to HIV.

Although no data from randomised controlled trials supports the use of HIV PEP, research performed over the last two decades has suggested the use of ARV for this purpose may be appropriate.

Rationale for non-occupational post-exposure prophylaxis

(a) Studies of antiretrovirals in animal models

Early animal experiments attempting to prevent retroviral infection by administration of different ARV agents alone or in combination were generally unsuccessful.²⁰ Over the last decade, however, many primate studies have provided supportive evidence of reverse transcriptase inhibitor pre- and post-exposure prophylaxis efficacy. Single-agent PEP has been effective in preventing retroviral infection following both intravenous and mucosal simian immunodeficiency virus (SIV) and HIV-2 exposures.²¹⁻²⁹ The data from animal studies suggests that decreased PEP efficacy is associated with: (a) higher inoculum size; (b) longer interval between exposure and treatment; (c) shorter duration of treatment; and (d) lower doses of PEP agents.

(b) Studies of efficacy of antiretrovirals in preventing vertical transmission of HIV

The landmark ACTG 076 study demonstrated that administration of oral AZT to the mother before birth, intravenously during labour and delivery, and orally to the neonate for 6 weeks, reduced the rate of vertical transmission from 25.5% to 8.3%³⁰ To date, the relative impact of each of the three components of AZT prophylaxis in reducing the risk of mother-to-child transmission has not been quantified, although maternal viral load reduction is thought to have a considerable impact.³¹ The rationale for the neonatal AZT component is based on PEP efficacy data³¹ and its importance has been confirmed in an observational study where the mothers did not receive the pregnancy or intra-partum components.³² Furthermore, in the HIVNET 012 trial, a proportion of nevirapine's efficacy in preventing vertical HIV transmission was attributed to the neonatal dose acting as PEP.³³

(c) Studies of occupational HIV post-exposure prophylaxis

The previously mentioned CDC study ultimately showed an 81% reduction of HIV transmission with AZT use in exposed HCWs.⁴ It is worthwhile to note, however, that there were several limitations to the study: cases and controls came from different populations; cases were identified retrospectively and actively reported, while controls were collected prospectively and reporting was voluntary; it was a retrospective study; and the study population was small. Despite these deficits, it remains the most convincing human PEP efficacy data available. The questionable ethics of withholding treatment likely to prevent transmission, in addition to the large numbers of exposed individuals needed to give a study of low-risk exposure adequate power, makes it unlikely that any randomised controlled trials of HIV PEP will ever be conducted. It is still unknown, however, if PEP efficacy in mucosal exposures can be extrapolated from non-mucosal exposures because of differences in the mucosal immune response.³⁴

Considerations for the use of Non-occupational Post-exposure Prophylaxis

Numerous factors involved in considering PEP for non-occupational exposures have been addressed in research settings (Figure 1). Clinicians must often make decisions based on minimal information regarding the source of exposure, further compounding an already difficult task.

Figure 1. Factors concerning NPEP availability & administration addressed by research studies

- Potential efficacy of NPEP (discussed above)
- Risk of HIV acquisition from the exposure
- Choice of drugs
- Number of drugs
- Timing
- Side effects
- Effect of NPEP availability on risk behaviours
- Follow up
- Costs

Risk of HIV acquisition from the exposure

The estimated probability of HIV transmission for various single HIV exposures is shown in Table 1. There are no published estimates on the risk of transmission via oral sex, although it is considered to be very low. There have, however, been reported cases of transmission via this route.³⁵ Other factors may also influence the risk of HIV transmission. For sexual exposures these include trauma, inflammatory genital disease and various characteristics of the uninfected host and virus itself.³⁶ Deep injuries with hollow bore needles directly into a vein or artery are associated with a higher transmission risk for percutaneous injuries.³ For all exposures, a high plasma viral load is associated with an increased risk of transmission.³⁷ Consideration of these factors, in addition to local HIV epidemiology, may facilitate risk assessment where the HIV status of the source is unknown.

Table 1. Estimated probability of HIV transmission by exposure (from⁶)

Exposure	Estimated risk HIV transmission per exposure
Receptive anal intercourse	≤ 3.0% (1/125 to 1/31)
Receptive vaginal intercourse	≤ 0.1% (1/2000 to 1/667)
Insertive anal or vaginal intercourse	≤ 0.1% (1/3333 to 1/1111)
Needle stick injury	≈ 0.3% (1/313)
Use of contaminated injecting drug equipment	≈ 0.6% (1/149)
Mucous membrane exposure	≈ 0.1% (1/1111)

Choice of drugs

Single agent AZT in HIV-exposed HCWs has failed as PEP in at least 13 individuals.^{15,16,38,39} Many reasons may account for these failures, including delayed treatment, large inoculum exposure and lower doses of drug than required being used for brief durations.⁴⁰

Resistance to ARV agents may also play a role in PEP failures, as a varying proportion of sexually transmitted HIV infections have been shown to be with viruses that show resistance to at least a single agent.⁴¹ Animal evidence suggests that PEP may still be effective following mucosal exposure when low-grade resistance to the employed PEP agent exists.²⁸ It remains unclear to what extent ARV resistance affects PEP efficacy, but it would seem prudent to construct PEP regimens based on the source individual's treatment history, where this is available.⁴² It has been argued that where there is no suspicion of possible AZT resistance, AZT should always be part of the initial PEP regimen as it is the only ARV agent for which PEP efficacy data are available.^{3,4}

Fusion inhibitors are biologically attractive PEP agents due to the early blockage of HIV entry into susceptible cells.⁴³ It should be noted, however, that none of the available antiretroviral agents are licensed for use as prophylactic agents.

Number of drugs to use in NPEP regimen

Highly-active antiretroviral therapy (HAART) has been shown to reduce viral load, and limit the development of viral resistance, more effectively than monotherapy.⁴⁴ Based on this premise, the use of combination PEP regimens has been advocated.^{45,46}

Two-drug regimens are associated with fewer side effects than three-drug regimens,⁴⁶⁻⁴⁸ but the higher incidence of side effects does not appear to influence the rate of PEP discontinuation in HCWs.^{45,46} Therefore, some have argued that a triple drug regimen should be used for the more potent antiretroviral activity and for overcoming resistance, with discontinuation of the PI if intolerable side effects should intervene.^{45,46} However, French investigators have reported that three drug regimens carry an unacceptable risk of severe side effects.⁴⁹

Timing

The median time to receipt of NPEP in the Australian observational NPEP study was 23 hours.⁴⁸ Even greater delays have been reported in other countries⁴⁹⁻⁵¹ which is a concern given the indirect evidence from animal models suggesting that earlier treatment results in improved outcome.²⁶ Pathogenesis studies have indicated that for the first 1-3 days following mucosal SIV exposure in primates, virus remains concentrated at the site of infection and regional lymph nodes.⁵² It is unlikely that PEP initiation beyond 72 hours would be effective. Indeed, a prolonged (70-hour) delay between exposure and PEP initiation was the probable cause of a recently reported failure of triple-drug PEP following sexual exposure.⁵³ The recommended length of PEP treatment, again based on animal data,²⁶ is 28 days.⁶

Side effects

Serious side effects, which have been reported in individuals receiving PEP include nephrolithiasis, hyperbilirubinemia and pancreatitis.⁵⁴ Although these are reportedly rare, treatment modification is relatively common due to poor tolerance. Ceasing one drug (often the protease inhibitor (PI)) has been commonly employed in HCWs unable to tolerate the initial prescribed regimen.^{45,47,55-58} Overall, PI-containing regimens appear difficult to endure⁵⁵ with, both, nelfinavir and indinavir being discontinued in up to one-third of triple-drug PEP regimens.^{45,56,58} Even with single-agent AZT prophylaxis, albeit at higher doses than currently used in PEP regimens, side effects were common.^{38,59} Quirino and colleagues prospectively compared the tolerability of AZT, lamuvidine (3TC) and indinavir in HIV-infected subjects with those prescribed this regimen following an occupational exposure to HIV.⁵⁷ This study confirmed the much higher rate of side effects (70% vs. 11%) and cessation of drugs as a result of intolerance (57% vs. 7%) in the PEP group and HIV-infected group, respectively. The nature of side effects observed in those taking PEP are similar to those seen in the HIV-infected population.⁴⁷

It has been suggested that anxiety associated with inoculation injuries in HCWs may account for the high incidence of side effects observed during OPEP,⁵⁶ although similar high rates have been reported during NPEP. Overall, incidence, type and severity of side effects have been similar with NPEP to those observed in OPEP studies. However, in one observational study, those exposed occupationally were significantly more likely to experience side effects,⁶⁰ as were women in their analysis. Eighty percent of the Australian NPEP study⁴⁸ suffered side effects, while over 90% of OPEP and NPEP recipients in Canada reported intolerance of PEP drugs.⁶⁰ In both studies, side effects were more common in those receiving triple therapy compared with dual therapy, although the difference in the Canadian study was not significant.

Pharmacological properties⁶¹ and efficacy in preventing vertical HIV transmission,³³ initially suggested nevirapine may be an attractive prophylactic agent. However, following 12 cases of hepatotoxicity (one requiring liver transplantation) and 14 cases of severe skin

rashes (including up to 3 cases of Steven-Johnson syndrome) in healthy individuals receiving post-exposure nevirapine, its use in this setting is not generally recommended.⁶¹

Haematological and biochemical abnormalities appear to be reversible on cessation of PEP regimens^{38,62-66} and although the long-term effects of HIV PEP are unknown, to date, no teratogenic or oncogenic effects have been observed.³⁶

Effect of NPEP availability on risk behaviours

Concerns have been expressed that the availability of NPEP may undermine primary prevention efforts and lead to increases in sexual risk-taking behaviour.⁹ Nonetheless, sexual exposure to HIV may inadvertently occur in those who have adopted safe sexual practices, such as condom breaks and slippages, which occur in 1 - 7% of episodes and 3 - 15% of episodes of intercourse, respectively.^{67,68} Data regarding sexual behaviour in situations where there is access to PEP is conflicting. Cross-sectional surveys carried out in San Francisco before and after a PEP awareness campaign⁶⁹ suggested that knowledge of PEP availability in San Francisco did not affect self-reported risk behaviour. Another cross-sectional survey in California revealed that knowledge of HIV PEP did not have an effect on condom use among serodiscordant couples.⁷⁰ Other studies have shown the majority of individuals report a decline in risk behaviour with awareness of PEP availability.^{71,72} In Australia, however, a recent increase in unprotected sex with casual partners has been reported among men who have sex with men (MSM).⁷³ Similar findings have been reported overseas⁷⁴ and attributed to optimism among MSM of reduced HIV transmission risk with HAART. It is impossible to discern how much the availability of PEP has directly impacted on increases in high-risk behaviour,⁴⁹ although repeat presentations by individuals for PEP are not uncommon,^{48,50} in some cases up to four times.⁷² This sobering data highlights the necessity of risk-reduction counselling as an integral part of any PEP program to reduce the likelihood of future exposures.⁶

Follow-up

Delayed HIV seroconversion has been reported in animal models treated with PEP.²⁹ Thus, current Australian recommendations suggest that individuals who have received PEP should have HIV antibody testing performed at 6 months following the exposure.⁶

NPEP Costs

The provision of PEP for HCWs and AZT for pregnant women have been shown to be cost-effective measures.^{75,76} The assessment of benefits due to PEP in non-occupational situations, however, is difficult due to the lack of data proving its efficacy. Some authors have suggested PEP for sexual exposures to HIV would be prohibitively expensive,⁷⁷⁻⁷⁹ whereas others have argued that clear eligibility criteria and guidelines would allow such a program to be affordable⁸⁰ by limiting availability to the highest risk exposures with a source likely to be HIV-infected.^{81,82} To minimize costs of a NPEP program, a Swiss group implemented a policy which included active contacting of source individuals and free, anonymous HIV testing.⁸³ Over 40% of sources whose serostatus was initially unknown were contacted and tested, which avoided PEP initiation, or allowed its discontinuation, in almost 95% of these exposures. In contrast, of those sources unable to be tested, PEP was prescribed in over 80%. They concluded that the contact and test policy was feasible and, on modelling, resulted in a 31% cost reduction. However, costs associated with serious side effects, and their impact on quality of life, were not included in the analysis. Notably, MSM sexual contacts were significantly less likely than other groups to be available for testing. Thus, a policy such as this may have limited utility in Australia as gay males receive the majority of PEP prescriptions⁴⁸ and comprise the vast majority of HIV-infected individuals.² Four weeks of dual therapy costs approximately \$600, with an additional \$500 for the course if a third agent is added. Laboratory tests and physician consultations are an additional expense, potentially putting excessive strain on an already overburdened health budget, especially if offered indiscriminately.

Studies of non-occupational HIV post-exposure prophylaxis

An observational study⁴⁸ was initiated in Australia to monitor implementation of the New South Wales Health Department NPEP guidelines in October 1998.⁸⁴ By the end of 2002, 819 individuals had received PEP. Over 80% of prescribed PEP was after male homosexual exposure and only 35% of PEP participants overall reported their sources were HIV infected. Overseas studies have concurred that most individuals presenting for NPEP are unaware of their source's HIV status.⁴⁹⁻⁵¹ In the Australian study to date, there have been no HIV seroconversions directly attributed to treatment failure.

An interesting addition to the arsenal of NPEP data was reported at the 9th Conference on Retroviruses and Opportunistic Infections last year.⁷¹ HIV-negative, homosexual men (n=202) were enrolled in a non-randomised study, given a 4-day starter pack of AZT and 3TC and instructed to begin PEP immediately following sexual exposure of a mucous membrane to blood or semen. PEP was initiated 110 times by 73 individuals and over 90% of exposures were considered by the investigators to be eligible for PEP. During the follow-up period there were 11 HIV seroconversions; 10 in non-PEP users and one in an individual who had taken PEP. This individual was later found to be infected with virus carrying the M184V mutation, conferring high-level resistance to 3TC. The seroincidence was 4.1 and 0.7 per 100 person years for those who never used PEP and for PEP users, respectively. The major limitation of this of this report was that no risk behaviour data was presented, thus risk behaviour differences between the two groups may have accounted for differences in infection rates, rather than the effect of PEP.

Post-exposure prophylaxis for injecting drug use exposures

Intuitively, the probability of HIV infection following use of contaminated injection drug equipment would be expected to be similar to that of parenteral occupational exposures. In one model, the measured risk was slightly higher,⁸⁵ which may reflect the greater volume of blood transferred in sharing of needles.⁸⁶ The published NPEP data suggests that provision of PEP for this scenario occurs infrequently.⁴⁸⁻⁵⁰

Post-exposure prophylaxis following sexual assault

Several issues not encountered following consensual sexual exposures may complicate risk assessment and recommendation for prophylaxis in the sexual assault scenario. Emotional distress and poor recollection of the events⁸⁷ lead to difficulties in risk assessment. Many victims will also suffer psychosomatic symptoms,⁸⁸ which may compound the already high rate of side effects experienced in those taking PEP. In addition, genital trauma as a result of sexual assault, although occurring in the minority of cases,⁸⁹ may facilitate HIV acquisition.⁹⁰ The most difficult aspect of risk assessment is the unknown HIV serostatus of the perpetrator in most cases.⁹⁰ Few documented cases of HIV transmission following sexual assault have been reported;⁹¹⁻⁹³ none of which have occurred in Australia. Sexual assault victims were observed to receive follow-up PEP after the starter pack significantly less often than individuals exposed via other routes,⁹⁴ perhaps reflecting victims' efforts to forget the traumatic experience which led to its administration. Men, and those suffering anal assaults, are more likely to commence HIV PEP following sexual assault⁹⁵⁻⁹⁸ suggesting that appropriate risk assessment is occurring in this scenario. Unfortunately, sexual assault physicians face significant dilemmas when addressing this issue with their patients as discussing an unproven intervention in the setting of a low HIV risk may create both added anxiety and unsubstantiated hope.

Guidelines for non-occupational post-exposure prophylaxis

Australian guidelines for the use of NPEP have undoubtedly impacted on its use locally. Although triple drug regimens have accounted for the majority of prescriptions in the Australian NPEP study,⁴⁸ significant increases in the prescription of two-drug versus three-drug regimens were observed following the 2001 release of the ANCAHRD guidelines⁶ which state that two-drug PEP regimens are adequate for most exposures. Three-drug regimens for NPEP, recommended in the 1998 French national guidelines, increased almost 40% after release of this policy, although post-guideline prescriptions were more commonly for less risky exposures.⁴⁹ In contrast, the UK has no such guidelines⁹⁹ and wide variation in NPEP prescribing practice has been observed,¹⁰⁰ highlighting the utility of national policy on NPEP.

Conclusion

The growing body of research on non-occupational post-exposure prophylaxis combined with occupational data suggests that NPEP may be effective, feasible and cost-effective when applied to high-risk HIV exposures, although the lack of NPEP efficacy data have hindered introduction of national guidelines in most countries. HIV risk-reduction strategies should not be usurped by the availability of NPEP, which, in turn, must incorporate these strategies to avoid ongoing risk exposures. Ultimately, primary prevention efforts hold the key to stemming the spread of HIV, but in isolated high-risk exposures when these strategies fail, non-occupational post-exposure prophylaxis may prove to be a useful tool in the fight against HIV/AIDS.

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