HIV and postexposure prophylaxis

Paul Benn MB ChB MRCP, Department of Genitourinary Medicine, *Mortimer Market Centre, Camden PCT, London*

Martin Fisher MB BS FRCP, Department of Genitourinary Medicine, *Claude Nicol Centre, Brighton and Sussex University Hospitals NHS Trust, Brighton*

Clin Med 2008;8:319–22

Background

Postexposure prophylaxis (PEP) for HIV is readily available for healthcare workers following occupational exposure. The current Department of Health (DH) guidelines recommend triple combination therapy for 28 days initiated as soon as possible after the exposure, ideally within one hour.[1] The Chief Medical Officer has requested that PEP following non-occupational exposure should also be available from all trusts (UK guidelines are available[2]).

Epidemiology of HIV in the UK

The prevalence of HIV in the UK continues to increase. It was estimated that 73,000 adults in the UK were living with HIV by the end of 2006, one-third of them unaware of their HIV status. This total comprises:

- 52%: heterosexual men and women, most of whom acquired their infection outside the UK
- 43%: men who have sex with men
- 4%: injecting drug users.

It is estimated that 4% of black African, 0.4% of black Caribbean and 0.08% of white adults living in England, Wales and Northern Ireland are infected with HIV. The greatest prevalence of those individuals accessing care was among London residents (319 per 100,000 population). Further prevalence estimates can be obtained from the Health Protection Agency.[3]

Biology of HIV transmission

Models suggest that, following exposure, it takes 48–72 hours before HIV can be detected in regional lymph nodes and up to five days before HIV becomes disseminated and detected in the blood. This may therefore reflect a window of opportunity after an exposure during which an infection can be prevented using PEP.[4]

The risk of HIV transmission

In general the risk of transmission of HIV following an exposure is small. It depends upon the risk of exposure itself and, where HIV status of the source is unknown, the likelihood that they are HIV positive – which may be derived from HIV prevalence data. Risk estimates for HIV transmission following occupational exposure to HIV are derived from a case-control study which found them to be three and one per 1,000 for percutaneous needlestick and mucous membrane exposures, respectively.[5] Exposure characteristics associated with an increased risk of acquiring HIV are:

- deep injury
- visible blood on the device
- where the instrument has been placed in a source's artery or vein
- the source is known to have a terminal HIV-related illness.

If the exposure occurred with large volumes of blood and/or the source's viral load is high, the risk of transmission is likely to be greater.

The risk estimates for HIV transmission following an episode of unprotected sexual intercourse with an individual known to be HIV-positive are usually similar in magnitude to those following occupational exposure. However, the risk estimate for receptive anal intercourse with an HIV-infected individual is tenfold greater (1/33) (Table 1). The risk of transmission of hepatitis B and C following a percutaneous injury is greater than for HIV (Table 2). Exposure to other bodily fluids (Table 3) may also result in HIV transmission.

Viral load

The likelihood of HIV transmission also depends on the infectiousness of the source and the susceptibility of the exposed individual. The former is particularly influenced by viral load.[5,6] It is

Table 1. Risk estimates of HIV transmission per exposure with an individual known to be HIV-positive.

Type of exposure	Estimated risk of HIV transmission per exposure (%)
Blood transfusion (one unit)	90–100
Receptive anal intercourse	0.1–3.0
Receptive vaginal intercourse	0.1–0.2
Insertive vaginal intercourse	0.03–0.09
Insertive anal intercourse	0.06
Receptive oral sex (fellatio)	0–0.04
Needlestick injury	0.3 (95% CI 0.2–0.5%)
Sharing injecting equipment	0.67
Mucous membrane exposure	0.09 (95% CI 0.006–0.5%)

CI = confidence interval.

Table 2. Comparative risk estimates for transmission of blood-borne viruses following percutaneous injury. Data adapted from Reference 25.

Blood-borne virus	Estimated risk of transmission per exposure
Hepatitis B (E Ag +ve)	1 in 3
Hepatitis C	1 in 30
HIV	1 in 300

Ag = antigen.

recognised that primary HIV infection may play a key role in ongoing HIV transmission since the viral load around the time of infection may be extremely high. Following initiation of combination antiretroviral therapy, the decline in viral load in other body fluids such as genital tract secretions parallels that seen in the plasma. Most individuals with an undetectable plasma viral load also have an undetectable genital tract viral load. However, in some people it is possible to detect replicative competent virus or separate virus evolution within these compartments.[7,8] Therefore, whilst effective antiretroviral therapy is likely to reduce the likelihood of HIV transmission, an undetectable viral load does not mean an individual is non-infectious. This may be further influenced by non-adherence to antiretroviral therapy and the ability of antiretroviral agents to penetrate other body compartments.[9]

Occupational exposures to HIV in the UK

A voluntary reporting system for occupational exposures (England, Ireland and Wales) to blood-borne viruses was established in July 1997. Between 2002 and 2005 there was an increase in the number of nursing and medical professionals reporting exposures to blood-borne viruses. During the same period a total of 303 healthcare workers in the UK reported exposures to HIV.[10] The voluntary nature of this surveillance means that the number of healthcare workers potentially exposed to HIV is likely to be underestimated.

By the end of 2005 there had been five documented cases and a further 16 probable cases of occupationally acquired HIV infections in healthcare workers in the UK,[10] most of them presumed to have been infected outside the UK. Two of the five documented cases had received PEP, one with zidovudine (AZT) monotherapy, the other with combination therapy.[11,12]

Table 3. Body fluids and materials which may pose a risk of HIV transmission if there is significant occupational exposure.

- Amniotic fluid
- Blood
- Cerebrospinal fluid
- Exudative or other tissue fluid from burns or skin lesions
- Human breast milk
- Pericardial fluid
- Peritoneal fluid
- Pleural fluid
- Saliva in association with dentistry (likely to be contaminated with blood, even when not obviously so)
- Semen
- Synovial fluid
- Unfixed human tissues and organs
- Vaginal secretions
- Any other body fluid if visibly bloodstained

Evidence supporting the use of postexposure prophylaxis

In a recent Cochrane review no prospective randomised controlled trials to determine the efficacy of PEP were identified. It was recognised that such a study would be neither ethical nor practical, requiring a very large sample size to show an effect.[13] A case-control study conducted in healthcare workers suggested that the use of AZT for PEP after percutaneous exposure to HIV-infected blood was associated with a significant decrease in the risk of HIV transmission (odds ratio 0.19 (95% confidence interval 0.06–0.52%).[5] In addition, mother-to-child transmission studies where only the neonate received antiretroviral therapy have also demonstrated a protective effect.[14] Many, but not all, animal models using intravenous and percutaneous inocula and models mimicking sexual exposures show protective benefits of antiretroviral therapy. One study demonstrated that both time to initiation and duration of PEP influence its effectiveness, with delays and shorter courses reducing it.[15]

PEP is not 100% effective and individuals have acquired HIV despite commencing PEP following both occupational and sexual exposures. Delayed initiation of PEP, poor adherence and completion rates, presence of resistant virus in the source and further high-risk exposures may explain some transmissions.[10,16]

Ensuring the timely use of postexposure prophylaxis

Animal models suggest that the time to initiation of PEP influences its effectiveness.[15] The DH guidelines[1] recommend that PEP is commenced within one hour of exposure. This clearly requires effective care pathways within trusts and availability of starter packs to facilitate 24-hour access. Awareness of local and national guidelines among healthcare workers is also important. However, studies demonstrate a lack of awareness of PEP among healthcare professionals.[17] Significant delays in initiating PEP are not uncommon.[10] Previous studies also suggest possible delays in the time to initiation of PEP in individuals presenting following sexual exposure compared with those following occupational exposure.[18] PEP is generally not recommended when an individual presents more than 72 hours after the exposure.

Ensuring appropriate use of postexposure prophylaxis

Many exposures to blood-borne viruses are avoidable: in 2004 and 2005 up to one-third of the reported exposures among healthcare workers were due to non-compliance with universal precautions.[10] An HIV test in the source undertaken, with consent, may completely avoid the need for PEP where the result is negative. If the source is unable to provide consent, HIV testing can be undertaken only if it is for their immediate clinical benefit.[19] Consent should be obtained by a healthcare worker other than the one who has sustained an injury, with appropriate explanation of the rationale for testing. It is very uncommon for source patients to decline testing.

Furthermore, rapid point-of-care testing for HIV in the source can avoid or significantly reduce the duration of PEP in such cases.[20] Significant delays between the source testing negative for HIV and the healthcare worker stopping

PEP are not uncommon.[10] Ideally, all individuals requesting PEP should undergo HIV testing at baseline (or as soon as possible) to exclude pre-existing HIV infection, particularly in cases of possible sexual exposure.

In the event of an exposure to HIV it is essential to undertake a case by case risk assessment of the exposure and where the likelihood that the source is HIV positive if their HIV status is unknown. This must be compared with the possibility of toxicity from PEP – for example, nevirapine given for PEP has been associated with significant toxicity.[18]

Key Points

- **The risk of acquiring HIV following an exposure is generally small**
- **A risk–benefit analysis of post exposure prophylaxis is required for each case**
- **Many occupational exposures are avoidable and HIV testing of the source with consent can avoid or reduce the duration of postexposure prophylaxis**
- **Regular follow up is required to monitor for possible toxicity and adherence**

KEY WORDS: antiretroviral therapy, HIV, occupational exposure, post exposure prophylaxis, sexual exposure

Which postexposure prophylaxis regimen?

The principles for selecting which regimen to use for PEP are in general similar to those for the treatment of chronic HIV infection: potency, pill burden, dosing schedule and tolerability. The current DH guidelines recommend a combination of Truvada (a fixed dose combination of tenofovir disoproxil and emtricitabine) and Kaletra for four weeks as soon as possible after an exposure.[1] (It must be noted that the use of these agents for PEP is outside their licence.)

Adverse effects

All antiretroviral agents have been associated with side effects. Truvada rarely can cause a reversible proximal tubulopathy including Fanconi syndrome. Kaletra not uncommonly causes diarrhoea and other gastrointestinal disturbances.[21] Previous studies suggest that PEP is often poorly tolerated, with individuals frequently reporting side effects and poor completion rates.[18] Non-completion of PEP may potentially reduce its efficacy so it is important proactively to manage side effects with antidiarrhoeals and antiemetics.

Kaletra is metabolised through the cytochrome p450 enzyme system so it is important to consider the potential for drug-drug interactions. This may either reduce the efficacy (eg anti-epileptics, oral contraceptive pill) or increase the risk of toxicity (eg methadone, Viagra and recreational drugs such as ecstasy).[22] Kaletra may also cause lipid elevations and insulin resistance, and may impact upon other medical conditions such as diabetes.[21]

Other considerations

Resistance in the source

Surveillance of resistance in antiretroviral therapy naive individuals demonstrates that it is present in a significant minority (ca 10%) in the UK.[23] The choice of PEP regimen should be supported by local resistance prevalence data. Where resistance is suspected in the source, the regimen should be tailored accordingly, with advice from local virologists or HIV specialists.

Pregnancy

Pregnancy does not preclude the use of PEP but expert advice should be sought.

Healthcare workers and exposure prone procedures

Healthcare workers need not refrain from performing exposure prone procedures pending follow-up of occupational exposure to an HIV-infected source. The combined risks of contracting HIV infection from the source and then transmitting this to another patient is so low as to be considered negligible. However, in the event of the worker being diagnosed as HIV-positive, such procedures must cease in accordance with the DH guidance.[24]

Follow-up

Regular follow-up during the course of PEP is required to monitor for possible toxicity and adherence (Table 4). This may be undertaken by occupational health, genitourinary medicine or infectious disease departments according to local expertise. Individuals should be advised to seek medical advice for further

Table 4. Laboratory and clinical follow-up.

Baseline	• Full blood count • U&Es, LFTs, glucose and lipids • HIV Ab/Ag, hepatitis B and C serology • STI screen (as clinically indicated) and syphilis
Baseline to 4 weeks	Regular review to assess for toxicity and adherence, including: • full blood count • U&Es, LFTs, glucose and lipids
Three months	• HIV Ab/Ag test, 3 months after exposure (no PEP) • HIV Ab/Ag test, 3 months after completion of PEP • Hepatitis B and C serology

Ab = antibody; Ag = antigen; LFTs = lung function tests; PEP = postexposure prophylaxis; STI = sexually transmitted infection; U&Es = urea and electrolytes.

assessment should they experience symptoms and/or signs of HIV seroconversion. A follow-up HIV antibody test should be performed three months after the conclusion of PEP to exclude infection.

Conclusions

It is essential to provide regular training regarding universal precautions for healthcare workers to minimise the number of exposures to blood-borne viruses. All trusts need to make certain that there are local care pathways to ensure appropriate and timely PEP. Close links between occupational health, genitourinary medicine, infectious diseases, microbiology and virology departments are required. Strategies to improve adherence, follow-up rates and completion of PEP are important; they may include the development of designated clinics for individuals receiving PEP. Future surveillance is essential to monitor the demand, use and efficacy of PEP.

References

1 HIV postexposure prophylaxis: Guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS. www.dh.gov.uk/en/index.htm

2 Fisher M, Benn P, Evans B; Clinical Effectiveness Group (British Association for Sexual Health and HIV) *et al.* UK Guideline for the use of post-exposure prophylaxis for HIV following sexual exposure. *Int J STD AIDS* 2006;17:81–92. www.bashh.org/guidelines/ceguidelines.htm

3 *Testing times – HIV and other sexually transmitted infections in the United Kingdom: 2007 annual report.* www.hpa.org.uk/infections/topics_az/hiv_sti/publications/AnnualReport/2007/HIVSTIs_AR2007.pdf

4 Spira AI, Marx PA, Patterson BK *et al.* Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. *J Exp Med* 1996;183:215–25.

5 Cardo DM, Culver DH, Ciesielski CA *et al.* A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med* 1997; 337:1485–90.

6 Gray RH, Wawer MJ, Brookmeyer R *et al.* Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1 discordant couples in Rakai, Uganda. *Lancet* 2001;357:1149–53.

7 Vernazza L, Troiani L, Flepp MJ *et al.* Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. *AIDS* 2000;14:117–21.

8 Chun TW, Davey RT Jr, Ostrowski M *et al.* Relationship between pre-existing viral reservoirs and the re-emergence of plasma viremia after discontinuation of highly active anti-retroviral therapy. *Nat Med* 2000;6:757–61.

9 Drumond JB, Yeh RF, Patterson KB *et al.* Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. *AIDS* 2007;21: 1899–907.

10 Eye of the needle. United Kingdom Surveillance of Significant Occupational Exposures to Blood Borne Viruses in Healthcare Workers November 2007. www.hpa.org.uk/publications/2006/eye_needle/pdf/eye_needle.pdf

11 Heptonstall J, Gill ON, Porter K, Black MB, Gilbart VL. Health care workers and HIV: surveillance of occupationally acquired infection in the United Kingdom. *Commun Dis Rep CDR Rev* 1993;3:R147–53.

12 Hawkins DA, Asboe D, Barlow K, Evans B. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. *J Infect* 2001; 43:12–5.

13 Young TN, Arens FJ, Kennedy GE, Laurie JW, Rutherford GW. Antiretroviral post-exposure prophylaxis (PEP) for occupational HIV exposure (Review). Cochrane Database of Systematic Reviews 2007(1). www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002835/pdf_fs.html

14 Sperling RS, Shapiro DE, Coombs RW *et al.* Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1996;335:1621–9.

15 Tsai CC, Emau P, Follis KE *et al.* Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. *J Virol* 1998;72:4265–73.

16 Roland ME, Neilands TB, Krone MR *et al.* Seroconversion following nonoccupational postexposure prophylaxis against HIV. *Clin Infect Dis* 2005;41:1507–13.

17 Chen MY, Fox EF, Rogers CA. Post-exposure prophylaxis for human immunodeficiency virus: knowledge and experience of junior doctors. *Sex Transm Infect* 2001;77:444–5.

18 Benn P, Mercey D, Brink N, Scott G, Williams IG. Prophylaxis with a Nevirapine-containing triple regimen after exposure to HIV-1. *Lancet* 2001;357:687–8.

19 GMC guidance. *Serious communicable diseases.* www.gmc-uk.org/guidance/archive/serious_communicable_diseases_1997.pdf

20 Landrum ML, Wilson CH, Perri LP, Hannibal SL, O'Connell RJ. Usefulness of a rapid human immunodeficiency virus-1 antibody test for the management of occupational exposure to blood and body fluid. *Infect Control Hosp Epidemiol* 2005; 26:768–74.

21 Kaletra Summary of Product Characteristics. Electronic Medicines Compendium 2007, August 8. http://emc.medicines.org.uk/

22 Liverpool University Website. HIV drug interactions website. www.hiv-druginteractions.org/

23 UK Collaborative Group on HIV Drug Resistance; UK Collaborative HIV Cohort Study; UK Register of HIV Seroconverters. Evidence of a decline in transmitted HIV-1 drug resistance in the United Kingdom. *AIDS* 2007;21:1035–9.

24 Department of Health. *HIV Infected Health Care Workers: guidance on management and patient notification.* London: DH, 2005.

25 Department of Health. *Guidance for clinical health care workers: protection against infection with blood-borne viruses.* London: DH, 1998.