

As drug-resistant HIV strains become more common it will increasingly impact on PEP's effectiveness and the need for resistance-testing of 'source' individuals.

Won't demand for PEP be huge?

Concern about HIV infection is low outside populations seen as 'high risk'. Those from low risk groups requesting PEP are unlikely to meet the prescribing criteria. Among exposed health care workers (the one high risk group with easy access to PEP) take-up is low. Members of high risk groups are most likely to seek out PEP. In San Francisco where dedicated PEP clinics for sexual exposure have been operating, HIV incidence is high and the population of gay men is large, 401 requests were received in 15 months, with 309 people completing a course of PEP.

Where will the money for PEP come from?

Although seen as a preventative measure, PEP involves prescribing medicines to eradicate a virus inside the body and is therefore paid for out of treatment budgets. It remains to be seen whether in future a proportion of HIV prevention funds will be allocated to cover the cost of PEP.

Will people become repeat users of PEP?

Studies show those who have PEP once tend to subsequently take fewer sexual risks. Some PEP prescribing clinics set a limit on how often an individual is entitled to be receive PEP. It is likely that those requesting PEP more often than guidelines allow will simply go to another clinic or area to get it.

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Author: Richard Scholey.

Contributors: David Reid, Sigma Research, Julian Meldrum, Gay Men's and Living Well with HIV teams at Terrence Higgins Trust, London.

What would need to change if PEP for sexual exposure was to become more widely available?

In December 2003 an Expert Think Tank Seminar on PEP following sexual exposure hosted by Terrence Higgins Trust made the following recommendations for the future development of the availability of PEP to gay men in the UK:

- It is important that community based organisations both "sell" and advocate for the BASHH guidelines. The CHAPS partnership can play a crucial role in this.
- As part of a national programme on PEP, mass media adverts and small media leaflets will be made available. There will also be telephone and website-based information provision.
- There is a clear need for training and development around PEP following sexual exposure and/or the BASHH guidelines, for GUM practitioners, GPs, A&E departments and people delivering or involved in the day-to-day implementation of HIV prevention interventions to gay men.
- The CHAPS national programme on PEP must be targeted at both high prevalence areas and high-risk subgroups of homosexually active men.

In order to take these outcomes forward and to advise on the development of an inclusive CHAPS national programme on PEP, a (short-term) multi-agency specialist advisory group has been appointed.

Notes

1. HIV Post-Exposure Prophylaxis: Guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS (Dept of Health guidelines on PEP for occupational exposure; revised February 2004); available at: www.advisorybodies.doh.gov.uk/eaga/prophylaxisguidancefeb04.pdf (includes details of drugs prescribed for PEP and side effects).
2. Guidelines for PEP following sexual exposure will be available from the British Association for Sexual Health & HIV and its web site www.bashh.org
3. Of 702 individuals in a Californian study receiving PEP following possible sexual or IV drug-use exposure 7 people (or 1%) went on to become infected. All 7 were gay men receiving PEP following receptive anal intercourse (average time between exposure and first PEP dose was 45.5 hours). Two of the men had poor adherence to PEP, that of another was 'fair'. All 7 had unprotected anal intercourse in the 6 months prior to receiving PEP. Between PEP starting and their sero-conversion one reported additional high risk behaviour with a known HIV positive partner and 2 did so with partners of unknown status. *Roland ME et al. Seroconversion following non-occupational Post-exposure prophylaxis.* Eleventh Conference on Retroviruses & Opportunistic Infections, San Francisco, poster 888.2004.
4. Details of cohort studies of people receiving PEP after sexual exposure can be found in *HIV & AIDS Treatment Directory December 2002, National AIDS Manual, London pp 139-140.*
5. *Katz M et al. Post-exposure treatment of people exposed to the human immunodeficiency virus through sexual contact or injection-drug use.* New England Journal of Medicine 336:1097-1100,1997.
6. *Vittinghoff E et al. Per-contact risk of human immunodeficiency virus transmission between male sexual partners.* American Journal of Epidemiology 150: 306-311, 1999.
7. Sick leave and loss of production due to side effects is another factor and one Canadian study of PEP involving protease inhibitors estimated this added cost to be equivalent to the cost of the PEP drugs. *McLeod et al. Absenteeism adds significant cost to HIV needlestick prophylaxis.* XIV International AIDS Conference, Barcelona, abstract TuPeE5167, 2002.
8. For a cost-effectiveness analysis of the San Francisco PEP programme see *Steven D. Pinkerton et al Cost-effectiveness of Postexposure Prophylaxis After Sexual or Injection-Drug Exposure to Human Immunodeficiency Virus,* Archives of Internal Medicine 2004 164:46-54 (<http://archinte.ama-assn.org/cgi/content/abstract/164/1/46>).
9. *Harrison LH et al. Post-sexual exposure chemoprophylaxis (PEP) for HIV: a prospective cohort study of behavioural impact.* Eighth Conference on Retroviruses and Opportunistic Infections, Chicago, abstract 225, 2001.
10. Preliminary data from the 2003 *National Gay Men's Sex Survey*, London, Sigma Research.

The HIV & AIDS charity for life

Terrence Higgins Trust 52-54 Grays Inn Road, London WC1X 8JU

Tel: 020 7831 0330 Fax: 020 7816 4552 Email: info@tht.org.uk

Website: www.tht.org.uk Helpline: 020 7242 1010 12 noon - 10pm daily

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PEP: Post Exposure Prophylaxis following sexual exposure to HIV

Post Exposure Prophylaxis (PEP) has been available to health workers exposed to HIV for many years; it has been far less available to people exposed sexually. This briefing, primarily for sexual health promotion workers, focuses on PEP following sexual exposure. It does not address PEP for health workers following occupational exposure (e.g. needlestick injury or contact with blood), nor does it go into detail about drugs prescribed for PEP. Information on these are signposted at the end of the briefing.

The first UK guidelines for PEP following sexual exposure are in development, with publication by the British Association for Sexual Health & HIV (BASHH) due in 2004 and available through the association's web site www.bashh.org

What is PEP?

PEP involves taking anti-retroviral drugs for a limited time (usually 28 days) soon after exposure to HIV in an attempt to prevent HIV infection. The hope is that the drugs inhibit HIV from reproducing before it can enter cells and establish infection in the body. The earliest form of PEP was a month-long course of AZT (zidovudine) offered to health care workers exposed to HIV at work. Now it usually contains two or three anti-retroviral drugs and is sometimes given to prevent infection following exposure after sex or IV drug taking.

How might it work?

It is believed that after entering the body it may take between 48 and 72 hours before HIV can be detected within lymph nodes and up to 5 days before detection in the blood. For PEP to prevent infection it would need to be taken during this 'window of opportunity'. Animal studies suggest the greater the delay in giving PEP the less likely it is to be effective. Health care workers given PEP often begin treatment one or two hours after exposure. Animal research is cited by some to suggest PEP may be ineffective if administered later than 24 to 36 hours; others believe PEP becomes less effective or entirely ineffective after 72 hours. Some hospitals will not offer PEP later than 24 to 48 hours. Department of Health/Expert Advisory Group on AIDS (EAGA) guidelines on PEP in occupational settings from 2004⁽¹⁾ state that PEP may be justified as late as two weeks after exposure. Studies on primates suggest that the longer PEP is taken, the greater its effectiveness; 28 days is recommended.

What PEP involves

Guidelines on drug prescribing for PEP for occupational exposure, including possible side effects, can be found in the Department of Health/EAGA document from 2004. Until the BASHH guidelines⁽²⁾ are published later in 2004 there are no UK guidelines for drug prescribing following sexual exposure. It is believed that monotherapy (one anti-HIV drug) is the least effective, frequently duotherapy (two drugs) is prescribed and many consider a three drug combination best (this is recommended in the UK occupational exposure guidelines). Drug combinations inadequate to treat established HIV infection may be adequate to prevent infection. AZT with 3TC is not sufficient to treat established HIV infection but is given as PEP. This mirrors other infections such as tuberculosis and malaria where drug regimes that prevent infection are insufficient to treat established infection.

HIV testing is often carried out before the first PEP dose to check that the person is not already infected. This prevents waste and ensures an already infected person is not given medication (e.g. PEP consisting of AZT and 3TC duotherapy) inadequate to treat established HIV infection. To gauge PEP's effectiveness follow-up HIV tests are carried out at 1, 3 and 6 months.

Does PEP work?

The belief that PEP stops infection is based on 'biological plausibility' - i.e. it is reasonable to assume PEP could work based on what the drugs achieve when used by people with HIV. This is supported by some (but not all) studies

of primates infected with a simian retrovirus (SIV) similar to HIV and given PEP. Questions remain whether conclusions drawn from PEP's effect on SIV and primates can be transferred to HIV and humans.

There is no incontrovertible evidence showing PEP works in adult humans or, if it does, to what extent. There are documented cases of PEP failing to prevent infection in health care workers after occupational exposure despite being taken within and for the required time period. Failures have also been seen in those taking PEP after sexual exposure⁽³⁾

With no formal studies of PEP for sexual exposure its effectiveness remains unproven. For this reason EAGA does not advocate for or against PEP after sexual exposure. When looking at human PEP research, comparisons are problematic due to wide variations in:

- **Drugs prescribed.**
- **Length of time between exposure and start of PEP.**
- **Levels of adherence to PEP.**
- **Different types of exposure (occupational or a variety of sexual exposures).**

Also the HIV status of the supposed 'source' of infection is often unknown.

The research

The first study suggesting PEP prevents HIV infection came when month-long AZT monotherapy was shown to reduce infection rates by 80% among health care staff. This encouraged PEP use in medical settings and helped establish it for babies born to infected women. Evidence also shows that 3TC and

Nevirapine have a preventative effect when given to babies breastfed by infected women.

Cohort studies exist of people receiving PEP following sexual exposure.⁽⁴⁾ These show no or only isolated cases of sero-conversions among those completing PEP. Cohort studies have included hundreds of people but thousands are needed for reliable conclusions on PEP's effectiveness.

Current thinking on whether PEP is effective (and to what degree) is based on:

- **Biological plausibility (what can be expected to occur in the absence of firm data).**
- **Existing cohort studies of people taking PEP.**
- **Studies of PEP in primates.**
- **Expert opinion.**
- **Data on PEP from other settings (e.g. use with new-born babies of HIV-infected women).**

Side effects of PEP

Side effects are generally the same as those experienced by people taking anti-retroviral drugs for established infection. Longer term side effects are rarely seen among PEP users. The 28 day regime is insufficient time to produce effects such as heart disease, diabetes, liver problems or lipodystrophy (changes in body shape due to abnormal fat deposits around the body). However, rare cases exist of serious side effects occurring within days or a couple of weeks of starting some PEP drug combinations, including lipodystrophy and serious liver damage. Metabolic abnormalities (such as increased levels of fats in the blood) have been seen while taking PEP.

Far more common are side effects typical of starting anti-HIV medications (diarrhoea, nausea, headaches and vomiting), serious enough to prevent many from completing PEP. Studies show around 20% (up to 40% when protease inhibitors are used) discontinue PEP due to side effects. Some drugs seem better tolerated than others.

Under what circumstances is PEP given?

The Department of Health/EAGA document of 2004 gives guidelines for use of PEP after occupational exposure and the Department of Health advised

every NHS Trust in 2000 to develop a PEP policy and protocol for work place exposure. Until the arrival of the 2004 BASHH guidelines PEP following sexual exposure is not yet governed by nationally agreed protocols.

Guidelines are recommendations that clinicians follow at their discretion, not rules or standards. Australia, several European countries and some American bodies already have guidelines for non-occupational PEP prescribing.

The following are considered before PEP is given:

- **'Has the person presented soon enough after exposure for PEP to work?'**
- **'Was the 'source' HIV positive?'**

If the 'source' is identified as HIV positive, disease stage, treatment history and viral load may be taken into account, as can evidence of drug resistance in the 'source's' virus strain. If the 'source' is uninfected, PEP is not given or is stopped. Except in known sero-discordant relationships, ascertaining the HIV status of the 'source' individual may be problematic. Whether the 'source' came from a high prevalence population or region can be used to judge the likelihood they had HIV.

- **'Does the candidate for PEP have HIV already?'**

If so, PEP is not only unnecessary but could have adverse effects - some PEP combinations are inadequate to treat HIV infection. HIV tests (with results within hours) before PEP establish HIV status before time for PEP runs out.

The following points are also usually considered when assessing PEP eligibility;

- **Type of sex act and whether 'insertive' or 'receptive' (vaginal, anal, oral).**
- **Whether ejaculation into the body occurred.**
- **Whether physical trauma (e.g. bleeding) or violence (e.g. rape) occurred.**
- **Will the person be able to adhere to 28 days of anti-retroviral therapy and possible side effects?**
- **Will the person consent to HIV testing before PEP starts and for follow-up tests at 1, 3 and 6 months?**

The risk of HIV being passed on

When considering PEP it is useful to consider the estimated risk of infection from various types of contact with an HIV positive individual. Epidemiological studies vary considerably in these estimates. The most frequently cited place the odds of infection after unprotected receptive anal sex with an infected partner at between 1 in 125 to 1 in 31 episodes of such sex.^{(5) (6)}

Since these estimates were calculated before the arrival of viral load-reducing treatments, the likelihood of transmission per exposure may now be lower. However, when an infected partner has a high viral load it is believed the likelihood of infection is much higher. In comparison, only three infections are estimated to occur for every 1,000 occupational needlestick injuries.

All commonly judged to be lower risk than receptive anal intercourse are:

- **Insertive and receptive vaginal sex (unless accompanied by trauma).**
- **Insertive anal sex.**
- **Insertive or receptive oral sex.**

However, factors such as viral load, skin trauma, whether ejaculation occurred or duration of intercourse may change the level of risk involved in each sex act.

Where PEP guidelines do exist they tend towards the following:

- **Receptive anal sex - PEP recommended.**
- **Oral sex (including receptive or with ejaculation into the mouth) - PEP not recommended.**
- **Insertive anal or insertive and receptive vaginal sex - somewhere between 'recommended' and 'not recommended'.**

With the latter a case by case risk analysis is used, especially if other factors increase risk. Prescribers often err on the side of caution, giving PEP if the 'source' is known to be HIV positive or there is a reasonable risk of this. If the 'source' is of unknown HIV status but not from a high HIV prevalence group or area PEP is often only considered for receptive anal sex.

How does someone get PEP?

PEP can be prescribed by hospitals (including A&E departments and GUM or HIV clinics) and General Practitioners experienced in treating HIV. Some have suggested that clinics which prescribe PEP appear reluctant to get a reputation for doing so out of concern they will be attract large numbers wanting it. Formal and open PEP prescribing policies for sexual exposure are rare, in part due to lack of evidence that PEP works and potential drug toxicity.

Success in getting PEP following sexual exposure can depend on:

- **Finding a clinic/clinician within the necessary time period.**
- **Knowing which clinics/clinicians are most likely to prescribe PEP.**
- **Knowing risk factors that make a clinician more likely to prescribe PEP.**

Anecdotal evidence suggests that success in obtaining PEP largely depends on the determination to get it and willingness to say those things (truthful or not) that make PEP prescription most likely. Saying 'the condom broke with someone I know to have HIV' may be more persuasive than 'I had a casual sex with someone whose HIV status I don't know.' As with accessing health care in general, PEP access appears easier for the well-informed and well-connected to the medical profession.

Is PEP cost-effective?

The cost of PEP is far more frequently discussed when the exposure is sexual rather than occupational. A 28 day course of PEP costs on average £750 (but half this if 2 nucleoside analogue drugs are used). This figure does not include staff costs and HIV testing.⁽⁷⁾

Current estimates put the cost of HIV treatment at around £10,000 per year, which set against the cost of PEP seems a powerful argument in its favour. However, due to HIV's low transmission rate the vast majority of those receiving PEP would never have become infected had they not received it. In many cases PEP is prescribed when the 'source' individual will not even have HIV, further reducing cost effectiveness.

Key factors remain how likely the 'source' individual is to be HIV positive and whether the sex act is high risk. In low HIV prevalence populations chances that a 'source' is infected are low enough to make PEP seem not cost effective. This is less true of groups such as gay men or some UK African communities where prevalence rates reach double figures in some areas. Although unethical to some, restricting PEP to those at highest risk (either by group or sexual act) makes both economic and clinical sense. Only if PEP became much cheaper would large scale use make financial sense.

Some studies take into account the economic cost of HIV-related illness/death (e.g. lost productivity and tax revenue); this results in PEP appearing more cost-effective. Cost effectiveness appears greatest when PEP is restricted to exposure following receptive anal intercourse.⁽⁸⁾

Does PEP encourage more sexual risk-taking?

Research contradicts the assumption that PEP access increases sexual risk-taking.⁽⁹⁾ No study shows overall increased risk-taking among those who have had PEP. Some individuals show greater subsequent risk taking but this is outweighed by reduced risk-taking within the group. PEP offers opportunities for counselling, information and behavioural interventions with potential for reducing risk-taking; experience of 28 days of anti-retroviral treatment may also result in less risk-taking.

Who knows about PEP?

Knowledge of PEP is no longer confined to the medical profession or health promoters. A 2003 survey⁽¹⁰⁾ showed 21.2% of UK gay men know about PEP, rising to 60.4% of men diagnosed with HIV. Of gay men,

- **0.7% have tried to get PEP**
- **0.4% report taking it**
- **4.8% know someone who has received it.**

Among men who already know about PEP,

- **3.1% had tried to get it**
- **2.1% report taking it**
- **22.9% know someone who has received it.**

Men who last tested HIV negative or who had never tested report strong motivation to access PEP. Asked if they would consider trying to get it if they thought they had been exposed to HIV, men replied;

- **'Yes' 70.8%**
- **'Maybe' 27.2%**
- **'No' 2%**

Men with high levels of education were almost three times more likely to know about PEP than those with low levels. Articles about PEP appear occasionally in the mainstream, gay and HIV press. Campaigns publicising PEP to gay men have been run in other countries, including Australia, Denmark and the US. Knowledge of PEP is therefore widely, but not equally, disseminated.

Will PEP use lead to more drug resistant HIV?

If PEP is effective, the HIV entering the body is eliminated and what no longer exists cannot become drug-resistant. There is an erroneous belief that, after taking anti-retrovirals as part of PEP, an individual can become resistant to these drugs. But after PEP the anti-viral drugs disappear from the body, leaving no 'memory' behind that would interfere with HIV treatment later. Someone who has successfully taken PEP is, just like any other HIV negative individual, incapable of exhibiting any kind of 'drug resistance'.

Drug resistance can arise:

1) If the person given PEP already has HIV. PEP may not be sufficient therapy to suppress viral reproduction, potentially allowing the virus to develop resistance to the drugs used in the PEP combination.

2) If PEP fails to prevent an infection. Then the virus has encountered the drugs, survived and may develop resistance. This is possible if someone does not complete the PEP course or does not take PEP as instructed. Alternately, if the strain of HIV entering the body is already resistant to any of the drugs in the PEP combination, PEP is more likely to fail and the person will be infected with this drug-resistant strain.