NCCHTA

21 January 2009

Research Protocol

Non-occupational post-exposure prophylaxis for HIV

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November 2007

1 Project title

Non-occupational post-exposure prophylaxis for HIV

2 Details of project team

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3 Planned investigation

3.1 Background

3.1.1 HIV

HIV (Human Immunodeficiency Virus) is a sexually transmitted and bloodborne virus primarily found in the blood, semen, or vaginal fluid of an infected person. HIV is transmitted in 2 main ways:

- Having sex (anal, vaginal, or oral) with someone infected with HIV.
- Sharing needles and syringes with someone infected with HIV.

HIV can also be transmitted through blood infected with HIV and being exposed as a fetus or infant to HIV before/during birth or through breast feeding. Any person is at risk of infection with the virus if he or she is exposed to HIV through sex or blood products.[1]

Seroconversion (converting from HIV negative to HIV positive) occurs when antibodies to HIV can be detected in the blood after infection with the virus. In individuals who become infected with HIV after exposure to the virus, about half to 90% experience an acute seroconversion illness, typically between two and six weeks after exposure to the virus. The onset is acute and the illness lasts for one to two weeks. Its severity varies from a mild glandular fever-like illness with fever, sore throat, lymphadenopathy, and a non-itchy maculopapular rash, to a severe illness associated with mucocutaneous ulceration and neurological manifestations that requires treatment in hospital.[2]

HIV has a prolonged ‘silent’ period during which it often remains undiagnosed, particularly since the seroconversion illness (if present) may have been very mild. More persistent or severe symptoms may not appear for 10 years or more after HIV first enters the body in adults, or within 2 years in children born with

HIV infection. This period of asymptomatic infection varies greatly in each person. Some people may begin to have symptoms within a few months, while others may be symptom-free for more than 10 years.[3]

HIV acts by attacking and destroying CD4 cells. These cells are a type of white blood cell called T-lymphocytes (or helper/inducer cells) important in the body's immune system. Their depletion during HIV infection results in susceptibility to infection from opportunistic diseases such as tuberculosis, pneumonia and some cancers.[4] A CD4 cell count (a measure of the number of CD4 cells in a specified volume of blood) gives a measure of the degree to which an individual's immune system is 'compromised'. It helps to identify periods in which an individual is more vulnerable to opportunistic infections, consequently helping inform decisions to initiate antiretroviral treatment and therapies to prevent these infections.[4] AIDS (Acquired Immunodeficiency Syndrome) is diagnosed in the UK when an HIV-infected individual presents with an AIDS-defining illness, such as *Pneumocystis carinii* pneumonia, pulmonary tuberculosis and extrapulmonary tuberculosis.[5]

Seroprevalence of HIV is the number of cases of HIV present in a specific population at a designated time, where a case is defined as someone who has HIV antibodies in their serum.[6] Information on the seroprevalence of HIV in the UK relies on case and test result reporting. However this can only give information on diagnosed infections. It is therefore supplemented by a programme of unlinked anonymous surveys (using the residue of specimens collected for routine testing for other purposes) which provide information about the total seroprevalence, including both diagnosed and undiagnosed infections, in population sub-groups.[6]

The most effective methods for preventing HIV infection are preventive behaviours including sexual abstinence, having sexual relations only with a non-infected partner, correct condom use, abstinence from drug-injection use and consistent use of sterile equipment when using injection drugs. However secondary prevention measures such as prophylactic antiretroviral drugs have been used to reduce the risk of HIV infection after occupational or non-occupational exposure.[7]

3.1.2 Patients

Globally there are an estimated 39.5 million people living with HIV. There were 4.3 million new infections in 2006 with 2.8 million (65%) of these occurring in sub-Saharan Africa and important increases in Eastern Europe and Central Asia, where there are some indications that infection rates have risen by more than 50% since 2004. In 2006, 2.9 million people died of AIDS-related illnesses.[8]

The most recent UK figures show that in 2005 there were over 7450 reports of new diagnoses of HIV infection. Thirty-two percent of these were in men who probably acquired their infection through sex with another man. Fifty-four percent acquired their infection heterosexually and about 2% through injecting drug use. Most of the heterosexuals were probably infected abroad. It is estimated there are about 63,500 HIV infected adults alive in the UK of whom about a third have not yet had their infections diagnosed.[5]

There are certain groups at higher risk of infection than others in the UK:

- Homosexual men (men who have sex with men, or MSM).
- Injecting drug users (IDU).
- Men and women who have lived as adults in countries where heterosexual transmission of HIV is common (notably South, East and Central Africa).
- Children, from their infected mothers during pregnancy.[1]

Table 1 shows the prevalence of HIV infection in different population sub-groups in the UK.[9]

Table 1: HIV seroprevalence in different population sub-groups in the UK

Community group	HIV seroprevalence (%)	
Homosexual men		
London	20.3	
Scotland	3.2	
Elsewhere	3.6	
Heterosexuals (region of birth)	Male (%)	Female (%)
UK	0.5	0.2
Rest of Europe	2.0	0.2
North America	2.9	0.1
Central and South America	2.4	0.9
Caribbean	1.2	1.0
North Africa and Middle East	0.5	0.4
Sub-Saharan Africa	6.9	11.3
South Asia	0.5	0.6
East and South East Asia	0.5	0.7
Australasia	0.8	0.1
Injecting drug users		
London	2.9	
Elsewhere in the UK	0.5	

3.1.3 Intervention

Post-exposure prophylaxis (PEP) for HIV is the prompt administration of antiretroviral therapy following known or potential exposure to HIV infection in an attempt to prevent the establishment of infection.[10] Animal models show that after initial exposure, HIV replicates within dendritic cells of the skin and mucosa before spreading through lymphatic vessels and developing into a systemic infection. This delay in systemic spread leaves a "window of opportunity" for PEP using antiretroviral drugs designed to block replication of HIV.[11] However, the evidence for the effectiveness of PEP in preventing seroconversion after non-occupational exposure to HIV is unclear.

Current UK guidance on PEP for non-occupational potential or actual exposure to HIV, based on the limited evidence available on the effectiveness of PEP after occupational exposure,[9;11;12] recommends combination therapies. Although there is no direct evidence that they are more effective in preventing HIV post-exposure than mono-therapies, combination therapies are more efficacious in treating HIV-infected patients and in preventing perinatal transmission than mono therapies, so it is theorised that a combination of drugs would enhance the effectiveness of PEP.[11] As yet no antiretroviral drug has been licensed for use after non-occupational exposure to HIV.[12] The current drug regime recommended for HIV PEP starter packs after non-occupational exposure[13] is:

- One combivir tablet (300mg zidovudine + 150mg lamivudine) b.d.
  plus
- Two Kaletra film-coated tablets (200mg lopinavir +50mg ritonavir) b.d.

Current UK guidance suggests that other drug combinations could be used where the physician considers them more appropriate for individual patients, such as including in the regimen ritonavir-boosted lopinavir, saquinavir or amprenavir.[12] However the current evidence on which drug regimen to use, the effectiveness of that regimen in preventing seroconversion following non-occupational exposure to HIV, and adherence rates to different regimens, is unclear.

There are potential risks associated with PEP following non-occupational exposure or potential exposure to HIV. The drugs used have side effects such as gastrointestinal upset (nausea and diarrhoea), diabetic exacerbation, dangerous interactions with other drugs, and nephrolithiasis.[11] These side effects can increase non-adherence, which in turn can lead to seroconversion of the patient and the development of drug-resistant strains.[11] There is also a potential increase in risk behaviours if PEP is perceived as preventing HIV infection.[7]

3.1.4 Costs

One cost estimate suggests the drug cost of a full 28-day course of PEP is approximately £600, whereas the lifetime costs of treatment for an HIV positive individual are estimated to be between £135,000 and £181,000.[9]

3.1.5 Current UK practice

Current UK practice for prescribing PEP after non-occupational exposure to HIV is based on guidance issued by the Department of Health[12] and guidelines from the British Association for Sexual Health and HIV (BASHH).[9]

The Department of Health guidance in 2004 states that the lack of evidence of effectiveness of PEP following non-occupational exposure to HIV prevents a recommendation either in favour of or against its use at that time.[12] It suggests that expert advice should be sought urgently from a physician experienced in the treatment of HIV (or paediatrician in the case of a child) in the event of any non-occupational exposure to HIV that is considered to carry a high risk of HIV infection.[12] For optimal efficacy PEP should ideally be started within an hour of exposure but as this timeframe is unlikely to be met in non-occupational exposures to HIV the risk of PEP failure is increased. However, longer periods from exposure should not be considered an absolute contraindication to PEP.[12] A risk assessment of the circumstances surrounding the exposure should be made by the physician considering prescribing PEP, to determine the risk of infection.[12] The guidance states that all the considerations that apply to the prescription of PEP after occupational exposure apply equally to non-occupational PEP from the point of a decision being reached that it is appropriate to prescribe it.[12] The current recommended drug regimen has been outlined in 3.1.3.

The BASHH guidelines make recommendations for the use of PEP following potential sexual exposure to HIV (PEPSE).[9] The recommendation is that PEPSE is given within 72 hours following unprotected vaginal or anal intercourse with an HIV positive source or receptive anal intercourse with a source of unknown HIV status but from a group of >10% HIV prevalence. It is suggested that patients complete 4 weeks of antiretroviral therapy and re-attend for HIV testing at 3 months and 6 months post-exposure.[9] The recommended drug regimen has been outlined in 3.1.3.

A recent audit of practice against these guidelines suggests that PEPSE is being prescribed and dispensed as the BASHH guidelines suggest, but that completion rates of the full course of medication (53%, 95% CI 40.84 to 64.21) and attendance for 3 and 6 months post-exposure HIV testing (12%, 95% CI 5.56 to 21.29) are low.[14]

3.1.6 Rationale for the study

There is growing clinical and patient enthusiasm for the use of non-occupational post-exposure prophylaxis to prevent HIV infection but the reduction in the risk of seroconversion may be small, therapy can have unpleasant side effects and may inhibit the adoption of safer sexual behaviours. There has been no systematic review of the existing literature. Research is therefore needed to synthesise the available evidence on the effectiveness, harms and cost-effectiveness of non-occupational post-exposure prophylaxis for HIV.

From the perspective of the patient the pressing clinical issue is to prevent HIV infection. The wider NHS perspective is the most appropriate and cost effective use of expensive anti-retroviral drugs.

3.2 Research Aim

The aim of this project is to evaluate the effects of non-occupational post-exposure prophylaxis for HIV with a course of anti-retroviral therapy.

3.3 Objectives

The main objectives will be as follows:

- To review the evidence on the effectiveness of non-occupational post-exposure prophylaxis for HIV;
- To summarise the best relevant evidence on the harms of non-occupational post-exposure prophylaxis for HIV;
- To review the evidence on the costs and cost-effectiveness of non-occupational post-exposure prophylaxis for HIV.
- To make recommendations for future research.

If appropriate, and if sufficient time and resources allow, an additional aim will be to develop an economic evaluation or adapt an existing one to model costs and cost-effectiveness in preventing seroconversion after non-occupational post-exposure prophylaxis for HIV.

Existing research
Preliminary scoping searches of key databases (Medline, PubMed, Cochrane, DARE, NHS EED and Embase) have been undertaken and show that there are some studies considering non-occupational post-exposure prophylaxis for HIV. However, the results suggest that there is no existing systematic review of the literature although a Cochrane protocol has been registered (Effectiveness and safety of HIV post-exposure prophylaxis after sexual, injecting-drug-use or other non-occupational exposure. 2005[7]). The UK Guideline for the use of post-exposure prophylaxis for HIV following sexual exposure[9] by the British Association for Sexual Health and HIV (BASHH) is based upon a non-systematic review of the literature and a combination of biological plausibility, cohort studies, data from post-exposure prophylaxis in other settings and expert opinion.

No randomised studies have investigated the efficacy of non-occupational post-exposure prophylaxis. One cohort study has been identified. In a study of men who have sex with men (MSM) in Brazil (n=200), individuals were given PEPSE supplies to commence immediately after an eligible sexual exposure.[15] There were 11 HIV seroconversions, 10 among non-PEP users and 1 that was a PEP failure. The overall seroincidence was 2.9 per 100 person-years (95% CI 1.4,5.1). The expected number of new HIV infections and corresponding expected seroincidence based on the authors previous work were 11.8 and 3.1 respectively ($p>0.97$). PEP following sexual exposure was found to be safe and not associated with an increase in reported high-risk behaviours. However, study authors concluded that as the occurrence of new HIV infections did not differ from what had previously been observed in this cohort in the absence of PEP, this intervention would have a limited public health impact.

One study has investigated side effects after a change in post-exposure prophylaxis regimen due to a high incidence of intolerable side effects and also assessed the number of individuals completing prescribed post-exposure prophylaxis before and after this change.[16]

There are some non-controlled studies. One showed seroconversion in 7 subjects out of 702 exposed subjects who received post-exposure prophylaxis after non-occupational exposure (1%; 95%CI 0.4%, 2%).[17] In a study of post-exposure prophylaxis for sexually abused children there were no seroconversions after six months post-assault in 17 children given post-exposure prophylaxis.[18]

One cost-effectiveness study conducted in the USA estimated that a post-exposure prophylaxis programme prevented an estimated 1.26 HIV infections, saved 11.74 QALYs and averted $281323 in future HIV-related medical care costs. The overall cost-utility ratio was $14449 per QALY saved.[19] A study conducted in France found that post-exposure prophylaxis after receptive anal intercourse with an HIV-infected individual was cost-saving in men and women, with a negative ratio of €22,141 and €22,031 per QALY saved, respectively.[20] Post-exposure prophylaxis prescribed for an intravenous drug user having shared needles with an HIV-infected individual was also found to be cost saving, with a negative ratio of €1,141 per QALY saved.[20]

Other relevant studies listed on NRR as complete may be due for publication in the near future.

3.4 Research Methods

3.4.1 Systematic Review

The systematic review will be undertaken in accordance with the NHS Centre for Reviews and Dissemination guidelines,[21] and published criteria for appraising economic evaluations.[22;23]

3.4.1.1 Literature search

Literature will be identified from several sources including electronic databases, bibliographies of articles and consultation with experts in the area. A comprehensive database of relevant published and unpublished articles will be constructed using the Reference Manager software package.
The searches carried out will include:

- General health and biomedical databases: Medline; Embase; PubMed (previous 6 months); Cochrane Library.
- Specialist electronic databases: Database of Abstracts of Reviews of Effectiveness (DARE); Cochrane Library; Health Technology Assessment Database (HTA); NHS Economic Evaluation Database (NHS EED); EconLit; Specialist HIV databases such as AEGIS (Aids Education Global Information System and UNESCO's HIV/AIDS database.
- Contact with individual experts and those with an interest in the field.
- Checking of reference lists.
- Research in Progress: National Research Register (NRR).

All databases will be searched from inception to the current date. In the first instance searches will be conducted in all languages with non-English language articles set to one side in a separate foreign language reference database. The primary focus will be English language articles but the need to include non-English articles will be considered in the light of what is found and within the constraints of available time for translation.

3.4.1.2 Study inclusion

Specific inclusion criteria will be defined. The full literature search results will be screened by one reviewer and checked by a second reviewer to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two reviewers against the inclusion criteria. Disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

The planned inclusion/exclusion criteria for the systematic reviews are shown in Table 2.

Table 2: Inclusion criteria for the systematic review

Population	Humans with non-occupational exposure to HIV. This may be by: • unprotected sexual exposure (oral, vaginal, anal), either voluntary or rape, with a HIV-infected partner or partner of unknown HIV status; • exposure to a needle contaminated by known or potentially infected substance in a non-occupational setting.
Intervention	Any anti-retroviral drug regimen administered as post-exposure prophylaxis for a short period (28 days) to HIV-negative people potentially exposed to HIV through unprotected sexual contact or use of a potentially contaminated needle or potentially contaminated biological fluid.
Comparator	• no intervention • group not receiving PEP • a different post-exposure prophylaxis regimen
Outcomes	• HIV seroconversion frequency • Adverse effects and complications of post-exposure prophylaxis • Adherence to post-exposure prophylaxis • Health-related quality of life. • Costs or some measure of cost effectiveness
Design	RCT, CCT, cohort study or case control. Cost-effectiveness /utility studies. Descriptive studies with no control group will be excluded.

3.4.1.3 Data extraction

The extraction of studies' findings will be conducted by two reviewers using a pre-designed and piloted data extraction form to avoid any errors. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

3.4.1.4 Quality assessment

The methodological quality of included studies will be assessed using formal tools specific to the design of the study and focusing on possible sources of bias. Quality assessment of RCTs will be conducted using criteria developed by NHS Centre for Reviews and Dissemination[21] and observational studies will be assessed using criteria developed by Spitzer[24] (Appendix 1). Quality assessment of economic evaluations will be conducted using a checklist adapted from those developed by Drummond et al[22] and Philips et al.[23] Study quality will be assessed by two reviewers. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration involving a third reviewer.

3.4.1.5 Data synthesis

The methods of data synthesis will be determined by the nature of the studies identified through searches and included in the review. Quantitative synthesis of results e.g. meta-analysis, will be considered if there are several high quality studies of the same design and sources of heterogeneity will be investigated by subgroup analyses if applicable. The results of any included studies suitable for quantitative synthesis will also be summarised in a narrative form along with a narrative synthesis of the results from studies for which quantitative synthesis is not possible. All results will also be tabulated (see Appendix 2).

3.4.2 Economic evaluation

Where appropriate, and if time and resources allow, an economic model will be devised by adapting an existing cost-effectiveness model or constructing a new one using the best available evidence to determine cost-effectiveness in a UK setting. Data on resource use and costs will be from the published literature and NHS sources where appropriate and available. The perspective of the economic analysis will be that of the NHS and Personal Social Services. Effectiveness data will be from published studies and used in conjunction with other relevant data (eg resource use, unit costs) to populate the model to obtain measures of cost-effectiveness. If available, quality of life information will be obtained from the literature or other sources to calculate cost-utility estimates in terms of cost per quality adjusted life year (QALY). The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

3.4.3 Ethical arrangements

No specific ethical arrangements necessary.

3.4.4 Outputs of the review

In addition to the preparation of the HTA Short Report, the findings of this project will be disseminated through papers submitted to relevant peer reviewed journals.

4 Project management and milestones

Project management and milestones

Major Milestones	Date
Development of protocol	December 2007
Drafting of final report	April 2008
Submission and dissemination of report	May 2008

Competing Interests: No member of the team has registered any competing interests.

5 Advisory Group

Representatives and other potential users of the review from different professional backgrounds and opinions will be invited to provide expert advice to support the project. Experts will be asked to provide comments on a version of the protocol and of the final report, as well as advising on the identification of relevant evidence. All experts will be asked to register competing interests and to keep the details of the report confidential.

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Appendix 1: Quality assessment

a. Quality criteria for assessment of experimental studies (NHS CRD)[21]

Item	Judgement*
1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

* adequate, inadequate, not reported, unclear

b. Quality criteria for assessment of observational studies

These quality criteria were adapted from Spitzer and colleagues.[24] The original checklist was modified to include items of particular relevance to assessing observational studies.

1. Does the trial use proper random assignment?
   A study with proper random assignment would include multiple conditions with random assignment and would use an appropriate method for the assignment (e.g., random numbers table, computer generated, etc.) with allocation concealment.
2. Did the study use proper sampling?
   A study with proper sampling would allow for all patients to be equally likely to enter the study (e.g., patients selected consecutively or randomly sampled).
3. Was the sample size adequate?
   Proper sample size enables adequately precise estimates of priority variables found to be significant (e.g., can compute CI within relatively small range or relatively small SEM).
4. Were the criteria for definition or measurement of outcomes objective or verifiable?
   Good outcome measures would be defined by clear methods for measuring outcomes (i.e., an operational definition) that are public, verifiable and repeatable.
5. Were outcomes measured with blind assessment?
   In studies with blind assessment those evaluating outcomes are unaware of the treatment status of those being evaluated.
6. Were objective criteria used for the eligibility of subjects?
   Good eligibility criteria would use clear, public, verifiable characteristics that are applied for inclusion and exclusion.
7. Were attrition rates (%) provided?
   A study should report the number of patients who could not be contacted for outcome measures or later, e.g., drop-outs or withdrawals due to treatment toxicity.
8. Were groups under comparison comparable?
   Comparable groups show similar results across a reasonable range of baseline characteristics that could be expected to affect results.
9. Are the results generalisable?
   Generalisable results come from a sample population that is representative of the population to which results would be applied.

Appendix 2: Data extraction form – Generic Sample

Reference and Design	Intervention	Participants	Outcome measures
Author: Year: Country: Study design: Number of centres: ? Funding:	Intervention: Control: Other interventions used:	Number of Participants: Intervention: Control: Sample attrition/dropout: Sample crossovers: Inclusion criteria for study entry: Exclusion criteria for study entry: Characteristics of participants:	Primary outcomes: Secondary outcomes: Method of assessing outcomes: Adverse symptoms: Length of follow-up: Recruitment dates:

Results

Primary Outcomes	Intervention	Control	P Value

Comments:

Secondary outcomes	Intervention	Control	P value
			P=0.87

Comments:

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments
Allocation to treatment groups:
Blinding:
Comparability of treatment groups:
Method of data analysis:
Sample size/power calculation:
Attrition/drop-out:

General comments
Generalisability:
Outcome measures:
Inter-centre variability:
Conflict of interests: