

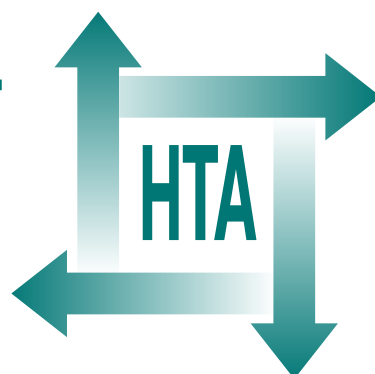
## **Non-occupational postexposure prophylaxis for HIV: a systematic review**

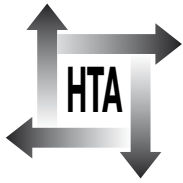
J Bryant,\* L Baxter and S Hird



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# Non-occupational postexposure prophylaxis for HIV: a systematic review

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The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 07/40/01. The protocol was agreed in December 2007. The assessment report began editorial review in May 2008 and was accepted for publication in August 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report. The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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## Abstract

### Non-occupational postexposure prophylaxis for HIV: a systematic review

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**Objective:** To review the evidence on the clinical effectiveness and cost-effectiveness of non-occupational postexposure prophylaxis (PEP) for HIV.

**Data sources:** Eleven electronic databases were searched from inception to December 2007.

**Review methods:** Selected studies were assessed, subjected to data extraction using a standard template and quality assessment using published criteria. Studies were synthesised using a narrative approach with full tabulation of results from all included studies.

**Results:** One clinical effectiveness study meeting the inclusion criteria was identified, a cohort study of PEP in a high-risk HIV-negative homosexual male cohort in Brazil. The quality of the study was generally weak. Seroincidence in the cohort as a whole (2.9 per 100 person-years) was very similar to that expected in this population (3.1 per 100 person-years,  $p > 0.97$ ), despite the seroconversion to HIV being 1/68 in the PEP group and 10/132 in the group not receiving PEP. High-risk sexual activities declined over time for both PEP and non-PEP users. Four economic evaluations met the inclusion criteria of the review. The methodological quality of the studies was mixed. The studies are constrained by a lack of published data on the clinical effectiveness of PEP after non-occupational exposure, with effectiveness data derived from one study of occupational PEP. Their generalisability to the UK is not clear. Results suggest that PEP following non-occupational exposure to HIV was cost saving for

men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not; heterosexuals after unprotected receptive anal intercourse; and intravenous drug users sharing needles with a known HIV-positive person. PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex, and ‘other’) and was possibly cost-effective for intravenous drug users and high-risk women. Four additional studies were identified giving further information about adverse events associated with PEP after non-occupational exposure to HIV. The majority of participants experienced adverse events with the most common being nausea and fatigue. Rates were generally higher in participants receiving triple therapy than in participants receiving dual therapy. Completion of PEP therapy was variable, ranging from 24% to 78% of participants depending on type of therapy. Toxicity was the main reason for discontinuation of treatment.

**Conclusions:** It is not possible to draw conclusions on the clinical effectiveness of non-occupational PEP for HIV because of the limited evidence available. The review of cost-effectiveness suggests that non-occupational PEP may be cost-effective, especially in certain population subgroups; however, the assumptions made and data sources used in the cost-effectiveness studies mean that their results should be used with caution.







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## List of abbreviations

3TC	lamivudine	MSA	metropolitan statistical areas
AIDS	acquired immunodeficiency syndrome	MSM	men who have sex with men
ART	antiretroviral therapy	Nfv	nelfinavir
BASHH	British Association for Sexual Health and HIV	PEP	postexposure prophylaxis
CCT	controlled clinical trial	PEPSE	PEP following potential sexual exposure to HIV
d4T	stavudine	PI	protease inhibitor
ddI	didanosine	RCT	randomised controlled trial
HIV	human immunodeficiency virus	QALY	quality-adjusted life-year
IDU	injecting/intravenous drug user	ZDV	zidovudine

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS) or it has been used only once or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.





## Executive summary

### Background

Human immunodeficiency virus (HIV) is a sexually transmitted and bloodborne virus found primarily in the blood, semen or vaginal fluid of an infected person. It is transmitted in two main ways: by having unprotected sex (anal, vaginal or oral) with someone infected with HIV or by sharing needles and syringes with someone infected with HIV. Postexposure 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. The effectiveness of PEP in preventing seroconversion (i.e. converting from HIV negative to HIV positive, with the detection in the blood of antibodies to HIV) after non-occupational exposure to HIV is unclear.

### Objectives

The main aim of this study was to review the evidence on the clinical effectiveness and cost-effectiveness of non-occupational PEP for HIV.

### Methods

A systematic review of the evidence was undertaken using a priori methods.

### Data sources

Eleven electronic databases were searched from inception to December 2007. Bibliographies of related papers were assessed for relevant studies and experts contacted to identify additional published references.

### Study selection

Studies were included if they fulfilled the following criteria:

- Intervention: any antiretroviral drug regimen administered as non-occupational PEP 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.

- Participants: humans with non-occupational exposure to HIV through unprotected sexual exposure (oral, vaginal, anal), either voluntary or rape, with an HIV-infected partner or partner of unknown HIV status; humans with exposure to a needle contaminated by a known or potentially infected substance in a non-occupational setting.
- Comparator: no intervention; group not receiving PEP; a different PEP regimen.
- Outcomes: HIV seroconversion frequency; adverse effects and complications of PEP; adherence to PEP; health-related quality of life; costs or some measure of cost-effectiveness.
- Design: randomised controlled trial, controlled clinical trial, cohort study or case-control study; cost-effectiveness/utility studies; economic evaluations; prospective observational studies for adverse events.

Studies identified were assessed for inclusion in two stages with titles and abstracts and full papers of retrieved studies assessed independently by two reviewers, with differences in decisions resolved through discussion or through recourse to a third independent reviewer.

### Data extraction and quality assessment

Data were extracted by two reviewers using a data extraction form developed a priori. Any disagreements were resolved through discussion or through recourse to independent assessment by a third reviewer. The methodological quality of the studies included in the systematic review was assessed by means of modified quality assessment tools using individual components of methodological quality rather than relying on summary scores. The quality criteria were applied by two reviewers, with any disagreements resolved through discussion or through recourse to a third independent reviewer.

## Data synthesis

Studies were synthesised using a narrative approach with full tabulation of results from all included studies.

## Results

### Number and quality of studies

One clinical effectiveness study meeting the inclusion criteria for the review was identified. This was a cohort study of PEP in a high-risk HIV-negative homosexual male cohort in Brazil. The methodological quality and the quality of reporting of the study were generally weak.

Four economic evaluations met the inclusion criteria of the review (three conducted in the US and one in France). The methodological quality of the studies is mixed. Each of the studies is constrained by a lack of published data on the clinical effectiveness of PEP after non-occupational exposure, with effectiveness data derived from one study of occupational PEP. Their generalisability to the UK is not clear.

### Summary of clinical effectiveness

Seroincidence in the cohort as a whole (2.9 per 100 person-years) was very similar to that expected by the study authors in this population (3.1 per 100 person-years,  $p > 0.97$ ), despite the seroconversion to HIV being 1/68 in the PEP group and 10/132 in the group not receiving PEP. The study reported that, on average, high-risk sexual activities declined over time for both PEP and non-PEP users. The study authors concluded that a public health PEP programme would not have a major impact on HIV transmission in the study population.

### Summary of cost-effectiveness

Results from the included economic studies suggest that PEP following non-occupational exposure to HIV is cost saving for men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not; heterosexuals after unprotected receptive anal intercourse; and intravenous drug users sharing needles with a known HIV-positive person.

PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex, and ‘other’). PEP following non-occupational exposure to HIV was possibly cost-effective for intravenous drug users and high-risk women.

## Adverse events

Four additional studies (two comparative studies and two observational studies) were identified that supplied further information about adverse events associated with PEP after non-occupational exposure to HIV. The majority of participants experienced adverse events with the most common being nausea and fatigue. Rates were generally higher in participants receiving triple therapy than in participants receiving dual therapy. Completion of PEP therapy was variable, ranging from 24% to 78% of participants depending on type of therapy. Toxicity was the main reason for discontinuation of treatment.

## Conclusions

It is not possible to draw conclusions on the clinical effectiveness of non-occupational PEP for HIV because of the limited evidence in terms of quantity and quality of studies. Only one cohort study was identified that met the inclusion criteria for the systematic review. Cost-effectiveness has been assessed in four economic evaluations using evidence on effectiveness taken from the use of PEP in the occupational setting. Results are consistent across studies and suggest that non-occupational PEP may be cost-effective, especially in certain population subgroups. Although the studies have been conducted in an appropriate way and may have internal validity in terms of the structure of the model and plausible results, the assumptions and data sources mean that results should be used with caution. The generalisability to the UK of studies conducted in the US is not clear as sexual behaviour and HIV incidence may not be similar.

## Suggested research priorities

The most important research need is to establish the clinical effectiveness of non-occupational PEP within the UK. Ongoing research in the form of the NONOPEP project, an MRC-funded surveillance programme of PEP for non-occupational exposure to HIV, will address aspects of clinical effectiveness in terms of seroconversion rates in people who take PEP compared with those who do not and evaluate problems associated with taking antiretroviral medications. This project is due for submission shortly. Data generated from this study can then be assessed and used to inform future economic modelling of the cost-effectiveness of non-occupational PEP in the UK.

# Chapter I

## Aim of the review

The aim of this project is to evaluate the effects of non-occupational postexposure prophylaxis (PEP) for human immunodeficiency virus (HIV) with a course of antiretroviral therapy.

The main objectives are as follows:

- to review the evidence on the clinical effectiveness of non-occupational PEP for HIV
- to summarise the best relevant evidence on the harms of non-occupational PEP for HIV
- to review the evidence on the costs and cost-effectiveness of non-occupational PEP 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 PEP for HIV.



## Chapter 2

# Background

### Description of underlying health problem

Human immunodeficiency virus is a sexually transmitted and bloodborne virus found primarily in the blood, semen or vaginal fluid of an infected person. HIV is transmitted in two main ways:

- by having unprotected sex (anal, vaginal or oral) with someone infected with HIV
- by sharing needles and syringes with someone infected with HIV.

Human immunodeficiency virus can also be transmitted through blood infected with HIV and being exposed as a fetus or infant to HIV before/during birth or through breastfeeding. Any person is at risk of infection with the virus if he or she is exposed to HIV through unprotected sex, contaminated blood products or HIV-infected bodily fluids.<sup>1</sup>

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 30–70% experience an acute seroconversion illness, typically between 2 and 6 weeks after exposure to the virus. The onset is acute and the illness lasts for 1–2 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.<sup>2</sup>

Human immunodeficiency virus has a prolonged 'silent' period during which it often remains undiagnosed, particularly as 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 whereas others may be symptom-free for more than 10 years.<sup>3</sup>

Human immunodeficiency virus acts by attacking and destroying CD4 (cluster of differentiation) cells. These cells are a type of white blood cell called T lymphocytes (or helper/inducer cells), which are 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.<sup>4</sup> 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.<sup>4</sup> Acquired immunodeficiency syndrome (AIDS) is diagnosed in the UK when an HIV-infected individual presents with an AIDS-defining illness, such as *Pneumocystis carinii* pneumonia, pulmonary tuberculosis or extrapulmonary tuberculosis.<sup>5</sup>

The 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.<sup>6</sup> 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 subgroups.<sup>6</sup>

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.<sup>7</sup>

## Epidemiology

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.<sup>8</sup>

The most recent figures for the UK estimate that in 2006 there were 73,000 people living with HIV in the UK, around one-third of whom had not yet been diagnosed. There were an estimated 7800 reports of new diagnoses of HIV infection in 2006. A total of 59% of these were among heterosexuals, 36% in men who have sex with men (MSM) and 2.5% in intravenous drug users. In terms of ethnic group, 46% of persons newly diagnosed were black African and 42% were white.<sup>9</sup>

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

- homosexual men (MSM)
- injecting drug users (IDUs)
- 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 and birth.<sup>1</sup>

Table 1 shows the prevalence of HIV infection in different population subgroups in the UK.<sup>10</sup>

## Description of the intervention

Postexposure prophylaxis 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.<sup>11</sup>

**TABLE 1** HIV seroprevalence in different population subgroups in the UK

Community group	HIV seroprevalence (%)	
<b>Homosexual men</b>		
London	20.3	
Scotland	3.2	
Elsewhere	3.6	
<b>Heterosexuals (region of birth)</b>		
	<b>Male</b>	<b>Female</b>
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
<b>Injecting drug users</b>		
London	2.9	
Elsewhere in the UK	0.5	



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.<sup>12</sup> 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,<sup>10,12,13</sup> recommends combination therapies. Although there is no direct evidence that they are more effective in preventing HIV post exposure than monotherapies, combination therapies are more efficacious in treating HIV-infected patients and in preventing perinatal transmission than monotherapies and so it is theorised that a combination of drugs would enhance the effectiveness of PEP.<sup>12</sup> As yet, no antiretroviral drug has been licensed for use after non-occupational exposure to HIV in the UK.<sup>13</sup> The current drug regimen recommended for HIV PEP starter packs after non-occupational exposure<sup>14</sup> is:

- one Combivir® (GlaxoSmithKline) tablet (300 mg zidovudine + 150 mg lamivudine) twice daily, plus
- two Kaletra® (Abbott) film-coated tablets (200 mg lopinavir + 50 mg ritonavir) twice daily.

Current UK guidance suggests that other drug combinations could be used when the physician considers them more appropriate for individual patients, such as including in the regimen ritonavir-boosted lopinavir, saquinavir or amprenavir.<sup>13</sup> 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. The guidance is based upon effectiveness of antiretroviral therapy in individuals chronically infected with HIV and on limited data of toxicity in PEP.

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.<sup>12</sup> These side effects can increase non-adherence,

which in turn can lead to seroconversion of the patient and the development of drug-resistant strains.<sup>12</sup> There is also the potential for an increase in risk behaviours if PEP is perceived as preventing HIV infection.<sup>7</sup>

## 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<sup>13</sup> and guidelines from the British Association for Sexual Health and HIV (BASHH).<sup>10</sup>

The Department of Health guidance (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.<sup>13</sup> It suggests that expert advice should be sought urgently from a physician experienced in the treatment of HIV (or a 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.<sup>13</sup> For optimal efficacy PEP should ideally be started within an hour of exposure, but as this time frame 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.<sup>13</sup> A risk assessment of the circumstances surrounding the exposure should be made by the physician considering prescribing PEP, to determine the risk of infection.<sup>13</sup> The guidance states that all of 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.<sup>13</sup> The current recommended drug regimen has been outlined in the previous section.

The BASHH guidelines make recommendations for the use of PEP following potential sexual exposure to HIV (PEPSE).<sup>10</sup> 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 reattend for HIV testing at 3 months and 6 months post exposure.<sup>10</sup> The recommended drug regimen has been outlined in the previous section.

A recent audit of practice against these guidelines suggests that PEPSE is being prescribed and dispensed as the BASHH guidelines recommend, but that completion rates for the full course of medication [53%, 95% confidence interval (CI) 40.84–64.21] and attendance for 3 and 6 months postexposure HIV testing (12%, 95% CI 5.56–21.29) are low.<sup>15</sup>

A survey of UK genitourinary medicine clinics in 1999 found that there were 242 requests for prophylactic antiretroviral drugs made at 56 clinics following a potential non-occupational exposure to HIV.<sup>11</sup> In total, 60% of these requests were made to nine clinics, six of which were located in the London area. The survey also found that there had been a fourfold increase in the number of requests for prophylactic antiretroviral drugs and a sevenfold increase in the number of prescriptions between 1997 and 1999.<sup>11</sup> Most of the requests had come from HIV-serodiscordant couples who had either had unprotected sex (13 cases, 29%) or had condom breakage during sex (10 cases, 22%).

## Costs

One cost estimate suggests that the drug cost of a full 28-day course of PEP is approximately £600 (not including staff time,) whereas the lifetime costs of treatment for an HIV-positive individual are estimated to be between £135,000 and £181,000.<sup>10</sup>

## Issues specific to non-occupational HIV exposure

There are a number of factors specific to non-occupational HIV exposure that impact on establishing the effectiveness of PEP in this situation or that have particular implications which are different from those in occupational exposures.<sup>16</sup>

## Ethical issues

The study types available to investigate the efficacy of PEP for non-occupational exposures are limited as it is not deemed ethical to randomly allocate subjects to an intervention or a control group after such an exposure. No controlled trials are likely to take place for this reason.<sup>7</sup>

## Time from exposure to PEP initiation

As mentioned in the section on current UK practice, current UK guidance on the use of PEP for non-occupational exposure to HIV recommends that PEP should be considered when individuals present within 72 hours of exposure.<sup>10</sup> This contrasts with guidance for initiation of treatment within 1 hour of occupational exposure.<sup>13</sup> The average length of time between non-occupational exposure and presentation at health services is unknown. One study of requests for PEP from UK genitourinary medicine clinics found that the time interval between exposure and request was known for 141 out of 242 requests for PEP.<sup>11</sup> Out of these 141 requests, 116 (82%) were made within 48 hours.

## Potential multiple exposures to HIV pre- and post-PEP initiation

Unlike occupational exposure to HIV in which the exposure incident will usually be a single exposure, non-occupational exposures to HIV can be multiple.<sup>16</sup>

There is a possibility that HIV infection could take place as a result of another exposure immediately before the exposure that led to PEP being sought.<sup>16</sup> Individuals presenting for PEP after non-occupational exposure who subsequently seroconvert have reported additional potential exposures (with partners known to be HIV positive or with unknown HIV status) between initiating the PEP regimen and their subsequent seroconversion.<sup>16</sup> This, combined with potential multiple exposures before PEP, makes it difficult to determine whether seroconversion resulted from failure of PEP or from other exposures.<sup>16</sup>

## Virus concentration

A high plasma viral load in the source may increase the risk of transmission.<sup>10</sup> Although low or undetectable plasma viral loads probably reduce the risk, transmission may still be possible.<sup>10</sup> Although viral loads in the genital tract normally correlate with plasma viral loads, it is possible to have a detectable genital viral load with an undetectable plasma viral load.<sup>10</sup> This may be important in non-occupational exposures, where the exposures may be repeated.

## Knowledge of HIV status of source

In many circumstances the estimated risk of HIV transmission following non-occupational exposure is greater than that following occupational exposure in which PEP is routinely considered (*Table 2*).<sup>10</sup> Homosexual men having unprotected receptive anal intercourse with a known HIV-positive source have an estimated risk of transmission of 3% (or a 1 in 33 chance of infection).<sup>10</sup> This compares with an estimated risk of transmission of 0.3% (1 in 333 chance of infection) following a needlestick injury when the source is HIV positive.<sup>10</sup>

In occupational exposure the HIV status of the source may already be known or there may be an opportunity to establish the HIV status of the source. In non-occupational exposure the HIV status of the source may also be known, for example in known HIV-discordant partners. However, the HIV status of the source may not be known and it may be very difficult or impossible to find out. This could make calculating the estimated risk of transmission after non-occupational exposures less accurate. The proportion of requests for PEP after non-occupational exposure for which the HIV status of the source is unknown is not currently established.

Furthermore, knowledge of the HIV status of the source is important because it may lead to better prescribing of antiretrovirals, for example in cases in which the source is known to have a drug-resistant strain of HIV. This can lead to higher adherence to medication and potentially greater effectiveness in preventing seroconversion.

## Concomitant exposures to other pathogens

Risky sexual behaviour places individuals at risk of sexually transmitted infections other than HIV, such as gonorrhoea and syphilis.<sup>13</sup> Exposure through sharing drug-injecting equipment can expose a person to the risk of other bloodborne infections such as hepatitis B and C.<sup>13</sup> Epidemiological studies have shown that the presence of other sexually transmitted infections enhances HIV transmission.<sup>10</sup>

## The impact of local trauma on the risk of transmission

Breaches in the mucosal barrier as a result of trauma (e.g. following sexual assault or first intercourse) may increase the risk of HIV acquisition.<sup>10</sup> Menstruation or other bleeding may also facilitate transmission.<sup>10</sup>

## Non-compliance with therapy and follow-up testing

As mentioned previously in the section on description of the intervention, the drugs used to prevent HIV seroconversion have side effects such as gastrointestinal upset (nausea and diarrhoea), diabetic exacerbation, dangerous interactions with other drugs and nephrolithiasis.<sup>12</sup> Because of this the BASHH guidelines state that these potential side effects need to be considered in situations in which the presenting patient is in a state of acute anxiety but the assessment of risk of transmission is low.<sup>10</sup>

**TABLE 2** Risk of HIV transmission following an exposure from a known HIV-positive individual<sup>10</sup>

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.

Patients have cited side effects as a reason for discontinuing PEP after sexual exposure.<sup>15</sup> The BASHH guidelines recommend that at least 75% of people receiving PEP following sexual exposure to HIV should complete the 4-week course of HIV therapy, and at least 75% should attend for a 3- and 6-month follow-up HIV test.<sup>10</sup> However, one study<sup>15</sup> found that only 53% (95% CI 40.84–64.21) of patients completed therapy and only 12% (95% CI 5.56–21.29) attended for both a 3- and 6-month follow-up HIV test. They speculate that this low completion rate may reflect recipients independently clarifying their source's HIV status, poor documentation of adherence and/or a high default rate from follow-up, with patient-perceived low risk, inadequate recall of non-attendees and a mobile population also contributing.<sup>15</sup>

Poor adherence to PEP regimens is important as it may theoretically result in the acquisition of a drug-resistant virus should the individual become HIV infected.<sup>10</sup>

### **Behavioural impact of PEP availability and programmes**

There are concerns that the availability of PEP for non-occupational exposure to HIV will reduce commitment to primary prevention strategies such as using a condom during sex or avoiding needle sharing when injecting drugs. This could lead to a rise in the frequency of high-risk behaviours, thereby adding to, rather than lessening, HIV transmission.<sup>10,17</sup> The most desirable outcome is that promoting PEP will cut rates of HIV infection in exposed individuals and reinforce safer sexual behaviour.<sup>17</sup>

A number of possible scenarios have been envisaged including:

- no impact of availability of PEP on behaviour
- negative impact: availability of PEP results in an increase in risky behaviours
- positive impact: the 'close call' may act to motivate and sustain risk reduction in individuals who have engaged in risk behaviour.<sup>10</sup>

Currently there is conflicting evidence with different studies providing evidence for each of the three scenarios.<sup>10</sup> At the moment there are no data suggesting that a significant number of individuals will repeatedly present for PEP following non-occupational exposure.<sup>10</sup>

Another possible outcome of PEP for non-occupational exposures is that the overall number of HIV infections remains unchanged because the numbers protected by PEP are counterbalanced by additional infections in individuals whose risk behaviour is increased by awareness of PEP but who then fail to use it.<sup>17</sup> There is the potential for PEP to cause net harm by protecting only a few individuals at the expense of adverse effects on behaviour and increased HIV transmission in the wider community.<sup>17</sup> There are also implications for the cost and cost-effectiveness of non-occupational PEP, particularly if the awareness of availability of PEP for non-occupational exposures leads to increased demand from those with a low-risk exposure.<sup>17</sup> Although these are important concerns there does not appear to be much evidence to support or refute them.

### **Rationale for the study**

There is growing clinical and patient enthusiasm for the use of non-occupational PEP to prevent HIV infection, although the reduction in the risk of seroconversion may be small, therapy can have unpleasant side effects and other issues as described may impact on effectiveness. No systematic review of the existing literature has been identified. Research is therefore needed to synthesise the available evidence on the effectiveness, harms and cost-effectiveness of non-occupational PEP 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 antiretroviral drugs.

## Chapter 3

# Methods

The a priori methods used for the review are outlined in the research protocol (see Appendix 1). This was sent to members of the advisory group for the review for expert comments (see Acknowledgements). Helpful comments were received relating to the general content of the research protocol; no specific problems with the proposed methods of the review were identified.

Some changes, additions or points of clarification were made to the methods discussed in the original protocol.

- It was felt important that a comparator group of some sort was included in any study that was considered for inclusion as evidence of clinical effectiveness. This could be either a group not receiving PEP, either through study design or by individual choice not to receive medication, or a group receiving an alternative drug regimen. As such, several studies that initially appeared to meet the inclusion criteria were excluded on the basis of not reporting relevant outcomes for comparator groups.
- The main outcome of interest to assess the clinical effectiveness of non-occupational PEP for HIV was the HIV seroconversion rate. However, adverse events are also an important outcome measure and to supplement the limited adverse event data from the clinical effectiveness section of the report additional studies were sought. Studies that did not report the main outcome of interest (seroconversion rates) but which did present adverse event data for both an intervention group and a comparator group were included for adverse events, as were prospective observational studies that met the inclusion criteria in terms of population and intervention.

The research methods used for the systematic reviews are summarised below.

### Search strategy

The following databases were searched for published studies and ongoing research, from inception to December 2007: the Cochrane

Library (Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials), MEDLINE (Ovid), EMBASE (Ovid), PubMed, NHS Economic Evaluations Database (NHS EED), NHS Health Technology Assessment database (NHS HTA), Database of Abstracts of Reviews of Effectiveness (DARE), EconLit, National Research Register (NRR), Current Controlled Trials and ClinicalTrials.gov. Grey literature and conference proceedings were also searched. Searches were restricted to the English language and to human studies. Bibliographies of identified papers were assessed for other relevant studies. Investigators of studies were not contacted because of time constraints. Further details, including key search terms, can be found in Appendix 2.

### Inclusion and data extraction process

Titles and abstracts of studies identified by the search strategy were screened independently for inclusion by two reviewers. The full text of potentially eligible studies was obtained and examined independently for inclusion by two reviewers. Data from each of the included studies were extracted by two reviewers on standard data extraction forms. Any disagreements were resolved by consensus or arbitration by a third reviewer if necessary.

The process for identifying and including studies is illustrated in Appendix 2, *Figure 1*. The primary reason for excluding studies was that they did not meet the inclusion criteria; for example they did not have a comparator group or results were not presented separately for the intervention and comparator groups. A list of studies excluded at various stages of the process can be found in Appendix 3.

### Quality assessment

The methodological quality of included studies was assessed using modified formal tools specific to the design of the study and focusing on possible sources of bias. The clinical effectiveness study

was assessed for quality using criteria developed by Spitzer *et al.*<sup>18</sup> Quality assessment of economic evaluations was conducted using a checklist adapted from those developed by Drummond and Jefferson<sup>19</sup> and Philips and colleagues.<sup>20</sup>

Quality criteria were applied to each included study independently by two reviewers. At each stage any differences in opinion were resolved through discussion or if necessary by arbitration by a third reviewer.

## Inclusion criteria

The inclusion criteria used for studies of the clinical and cost-effectiveness of non-occupational PEP for HIV are shown below.

### Intervention

- Any antiretroviral drug regimen administered as non-occupational PEP 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.

### Population

- Humans with non-occupational exposure to HIV. This may be by:
  - unprotected sexual exposure (oral, vaginal, anal), either voluntary or rape, with an HIV-infected partner or partner of unknown HIV status

- exposure to a needle contaminated by a known or potentially infected substance in a non-occupational setting.

### Comparator

- No intervention.
- Group not receiving PEP.
- A different PEP regimen.

### Outcomes

- HIV seroconversion frequency.
- Adverse effects and complications of PEP.
- Adherence to PEP.
- Health-related quality of life.
- Costs or some measure of cost-effectiveness.

### Study type

- Randomised controlled trial (RCT), controlled clinical trial (CCT), cohort study or case-control study.
- Cost-effectiveness/utility studies.
- Economic evaluations.
- Prospective observational studies for adverse events.

### Data synthesis

Synthesis of data was through narrative review with full tabulation of results of all included studies. Full data extraction forms are shown in Appendices 4 and 5. Meta-analysis was not possible because of the limited data found.



# Chapter 4

## Clinical effectiveness

### Quantity and quality of research available

One published study met the inclusion criteria for the review, which was a cohort study conducted by Schechter and colleagues<sup>21</sup> in Brazil (Table 3, Figure 1 in Appendix 2 and Appendix 4).

The methodological quality and the quality of reporting of the included study were generally weak (Table 4).

Significant selection bias may have occurred during the recruitment of study participants. Participants were recruited from an unreported number of eligible participants of a previous HIV seroincidence study of MSM. A total of 250 of those deemed eligible were contacted by telephone and the first 200 to agree to participate were included in this study. The authors do not report the total number of eligible participants in the previous study or how the 250 eligible participants that were telephoned were selected, nor do they

**TABLE 3** Details of included study

Study	Population	Intervention	Comparison	Outcome measures
Schechter et al. 2004 <sup>21</sup>	Brazilian cohort of 200 high-risk men who have sex with men (MSM)	28-day course of PEP after potential high-risk exposure to HIV (zidovudine 300 mg and lamivudine 150 mg orally, fixed-dose combination tablet twice daily)	Non-PEP users	Reported behaviour, PEP utilisation, adverse events, incident HIV infection

**TABLE 4** Quality assessment of included study

	Yes	U/I/S <sup>a</sup>	No	DK/NR <sup>b</sup>	N/A	Comments
Proper random assignment			No			
Proper sampling		U				250 potential participants invited to participate by telephone; first eligible 200 who agreed were enrolled. Participants were given PEP to begin after an eligible exposure
Adequate sample size		U				Authors comment that the 109 exposures for which PEP was taken represent a small proportion of the total eligible exposures that occurred during the study
Objective outcomes		I				Self-reported high-risk sexual activity
Blind assessment			No			
Objective eligibility criteria	Yes					
Reported attrition	Yes					
Comparability of groups	Yes					
Generalisability		U				Limited to men who have sex with men from a previously known high-risk cohort, aged 18–35 years

a U/I/S, uncertain/incomplete/substandard.  
b DK/NR, don't know/not reported.

report any attempt to minimise volunteer bias. No power calculation is provided to justify why 200 participants were needed.

Participants allocated themselves to the intervention or the control group depending on whether or not they initiated chemoprophylaxis after an eligible exposure by taking the 4-day supply of PEP that they had been given. If PEP was initiated, after 4 days the participant was assessed by study personnel to establish whether the exposure was considered a high enough risk to warrant a further 24 days of PEP. Further selection bias may have occurred at this point as the authors do not report what was considered to be a high-risk exposure or the procedure by which study personnel made such decisions. However, the authors do report the demographic and behavioural characteristics of all study participants, which suggests that there were no significant differences between those who did and those who did not use PEP over the course of the study.

The authors do not report blinding of study participants or personnel. Although it would not have been possible to have fully blinded both study personnel and participants, it may have been possible at the routine follow-up appointments to have blinded personnel to PEP use by participants. This could have reduced potential detection bias.

In the analysis the authors report that two participants had no follow-up data and were therefore excluded from analysis, meaning that an intention to treat analysis was not conducted. The authors report the seroincidence rate (incidence of seroconversions per 100 person-years) for all of the study participants together, compared with the expected number of incident HIV cases in the absence of PEP (modelled from the previous HIV incidence study). The authors state that they did this because of a lack of a control group (participants not taking PEP). However, the reported results seem to suggest that there is a control group with follow-up data (participants who

did not initiate PEP after an eligible exposure). It is therefore not clear why the authors did not calculate the incidence of seroconversion for those who took PEP and for those who did not take PEP, to give an estimate of the effectiveness of PEP in preventing seroconversion for non-occupational exposures.

This study reports the use of PEP amongst a well-established cohort of high-risk sexually active MSM, aged 18–35 years, in Rio de Janeiro, Brazil. The study cohort may have some similarities with populations of MSM living in other big cities, although the limited age range of study participants prevents generalisation to populations of MSM as a whole. It is also not possible to generalise the findings of this study to the population as a whole, in which potential exposure to HIV may also occur through heterosexual sex or non-occupational needlestick injuries.

## Assessment of effectiveness

Tables 5–9 present the results of the included cohort study<sup>21</sup> in terms of seroincidence of HIV within the cohort, PEP use, non-completion of PEP, adverse events and reports of risky behaviours.

### Seroconversion to HIV

The HIV seroincidence is presented in Table 5. One incidence of seroconversion to HIV was reported in the group of participants that took PEP, compared with 10 from the ‘no PEP’ group. No *p*-value was reported. Over the course of the study the overall incidence of HIV was 2.9 per 100 person-years (95% CI 1.4–5.1). The authors report that, based on the risk profile of the participants and experience from a previous study, the expected number of new HIV infections overall was 11.8 ( $p > 0.97$  compared with the observed 11 infections) and the expected seroincidence was 3.1 per 100 person-years ( $p > 0.97$  compared with the seroincidence of 2.9 found in this study).

**TABLE 5** HIV seroincidence

	PEP (n = 68)	No PEP (n = 132)	<i>p</i> -value
Seroconversion to HIV	1	10	Not reported



**TABLE 6** PEP use (28-day course)

	PEP (n = 68)	No PEP (n = 132)
Prescribed once, n (%)	49 (72.1)	–
Prescribed twice, n (%)	14 (20.6)	–
Prescribed three times, n (%)	2 (2.9)	–
Prescribed four times, n (%)	2 (2.9)	–
Prescribed nine times, n (%)	1 (1.5)	–

### PEP use

The PEP use in the cohort is presented in *Table 6*. In the majority of cases the full 28-day course was prescribed once per participant (72.1%). In total, 100 out of 109 exposures for which PEP was initiated by participants were considered eligible and received the 4-week course. The authors report that the most common reasons for not initiating PEP ( $\geq$ one possible response per participant) were sex with a steady partner ( $n = 150$ ), the participant did not consider the exposure to be of sufficiently high risk to warrant PEP ( $n = 94$ ) and concerns about side effects ( $n = 23$ ).

### Adverse events and adherence

The number of non-completed PEP courses is shown in *Table 7*. The authors report that the full 28-day regimen of PEP was completed for 89 (89%) of the eligible exposures, including the participant who seroconverted, and that the 11 discontinuations correspond to nine participants.

Two of the participants did not come back to the study site to complete their visits at 28 days.

There were seven discontinuations of PEP because of adverse events. At least one side effect was reported in 82% of episodes of PEP use. Nausea was the most commonly reported side effect: six of the discontinuations for adverse events were due to this. Apart from one patient with a history of

pancreatitis who had to stop taking PEP because of an asymptomatic increase in pancreatic enzymes, it is reported that there were no clinically significant laboratory abnormalities among those receiving PEP.

### Risk behaviours and PEP use

The median numbers of male partners reported by participants are presented in *Table 8*. These remained the same from the baseline visit to the last visit at 24 months for both groups, although the range was increased in both groups at the last visit.

*Table 9* shows the types of risk behaviours that participants were asked to report and the changes from the 6 months previous to the baseline visit to the 6 months previous to the last follow-up visit at 24 months. Reported unprotected anal intercourse decreased in both groups; in the no PEP group this decrease was statistically significant. Reported unprotected oral intercourse decreased significantly in both the PEP and the no PEP groups. Unprotected vaginal intercourse increased; this was not statistically significant.

Self-reported results should be viewed with some caution where there is the possibility that high-risk behaviour has been under-reported or where reports may be inconsistent.

**TABLE 7** Non-completed PEP courses

	PEP (n = 68)	No PEP (n = 132)
Did not return to complete course	2	–
Discontinued because of adverse events	7	–

**TABLE 8** Numbers of male partners and PEP use

	PEP (n = 68)	No PEP (n = 132)
Median number of male partners 6 months before baseline (range)	4 (0–50) <sup>a</sup>	2 (0–40) <sup>b</sup>
Median number of male partners 6 months before last visit (range)	4 (0–180) <sup>a</sup>	2 (0–100) <sup>b</sup>
a $p = 0.43$ .		
b $p = 0.46$ .		

**TABLE 9** Risk behaviours and PEP use

	PEP (n = 68)			No PEP (n = 132)		
	6 months before baseline	6 months before last visit	p-value	6 months before baseline	6 months before last visit	p-value
Unprotected anal intercourse, n (%)	32 (47.1)	27 (39.7)	$p = 0.35$	48 (36.4)	32 (24.2)	$p = 0.008$
Unprotected oral intercourse, n (%)	16 (23.5)	8 (11.8)	$p = 0.06$	32 (24.4)	16 (12.2)	$p = 0.002$
Unprotected vaginal intercourse	1.6%	4.7%	$p = 0.16$	6.1%	8.3%	$p = 0.26$

## Summary of clinical effectiveness of PEP for non-occupational exposure to HIV

- One cohort study of PEP in a high-risk HIV-negative homosexual male cohort in Brazil met the inclusion criteria of the review. The methodological quality and the quality of the reporting of the study were generally weak.
- The seroconversion to HIV rate in this study was one in the PEP group and 10 in the non-PEP group.
- The results suggest that PEP made no difference to the expected seroconversion to HIV for this cohort.
- Over the course of the study the overall seroincidence (combining the PEP and non-PEP groups) was 2.9 per 100 person-years (95% CI 1.4–5.1). This was compared with the authors expected seroincidence of 3.1 per 100 person-years ( $p > 0.97$  compared with the observed seroincidence of 2.9).
- PEP was rarely prescribed on more than two occasions per participant, with the majority (72.1%) receiving just one course.
- The number of non-completed courses appears to be low, with only 2 out of 68 not returning to complete the course and 7 out of 68 discontinuing because of adverse events.
- The authors report that, on average, high-risk sexual activities declined over time for both PEP and non-PEP users. This does not appear to be related to the decision to initiate PEP; both groups had access to interventions designed to prevent/reduce risk behaviour, including at each visit pre- and post-test counselling, provision of condoms and safer sex workshops.
- The authors conclude that the results from their study 'argue against establishing a public health PEP programme in our population with the aim of having a major impact on HIV transmission' because of the observed overall seroincidence of 2.9% being so similar to that expected for this population.

## Chapter 5

# Cost-effectiveness

The aim of this chapter is to evaluate the cost-effectiveness of non-occupational PEP for HIV. A systematic review of the literature was conducted to identify economic evaluations of the use of PEP in people with non-occupational exposure to HIV. The feasibility of developing an economic model was also considered.

The methods used for the systematic review are described in Chapter 3. The details of the inclusion and exclusion criteria are shown in Appendix 1 and the search strategies are shown in Appendix 2.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two reviewers. The full text of relevant papers was obtained and inclusion criteria were applied to each study independently by two reviewers. Differences in opinion were resolved through discussion or by arbitration by a third reviewer if necessary.

Economic evaluations were eligible for inclusion if they reported on the cost or cost-effectiveness of any antiviral drug regimen administered as PEP in people with non-occupational exposure to HIV (unprotected sexual exposure or needle contamination) compared with another PEP regimen or a group of people not receiving PEP (Appendix 1).

### Quantity and quality of research available

Four economic evaluations<sup>22–25</sup> met the inclusion criteria for the review and are shown in *Table 10* (details in *Figure 2* in Appendix 2 and Appendix 5).

A summary of the methodological quality of reporting in the four included studies is shown in *Table 11*. Each of the cost-effectiveness studies outlined a well-defined question: to assess the cost-effectiveness of PEP for HIV following a non-occupational exposure.<sup>22–25</sup> The patient group was clearly stated in three of the four studies.<sup>23–25</sup> In the study by Pinkerton and colleagues<sup>22</sup> the patient group is less clear as the authors have referred to

a hypothetical cohort of 10,000 ‘patients’ (a cohort that includes women) but have used this term interchangeably with 10,000 ‘men who have sex with men’.

All of the studies clearly stated that their perspective was societal, with the analysis including all identifiable costs, regardless of who bore them. However, Pinkerton and colleagues<sup>22</sup> stated only the monetary costs of PEP drugs and of treating a patient with HIV/AIDS. Herida and colleagues<sup>25</sup> referred only to health sector costs in their study, despite employing a societal perspective.

Two of the studies<sup>23,25</sup> gave a clear description of the interventions considered. One study<sup>24</sup> does not describe the PEP programme employed, whereas in the other<sup>22</sup> the intervention applied to a hypothetical cohort was assumed to be zidovudine, lamivudine and indinavir, or zidovudine and lamivudine only, but no further details are given. Three of the four studies<sup>22,24,25</sup> employed the comparator of ‘no PEP’ whereas in the fourth study<sup>23</sup> the comparator used is unclear.

The study types used were appropriate for economic analysis in each case; three of the four studies included both cost-effectiveness and cost-utility analyses<sup>22,23,25</sup> and one employed a cost-utility analysis alone.<sup>24</sup>

Each of the four studies is limited as the effectiveness of the intervention, PEP in non-occupational exposure to HIV, has not been established. The effectiveness parameter in each of the papers is based on the results of a case-control study undertaken in health-care workers who were prescribed zidovudine monotherapy. The dual or triple drug regimens considered in these cost-effectiveness studies are assumed to be as effective as zidovudine alone in this study of occupational exposure. Pinkerton and colleagues<sup>22</sup> have taken their effectiveness parameter, the probability that PEP is effective, from the original study,<sup>26</sup> set at 79%. The remaining three studies<sup>23–25</sup> have taken their effectiveness parameter from the update of that study,<sup>27</sup> in which effectiveness is set at 81%, although one of these studies<sup>25</sup> reports that an effectiveness of 80% is used.

**TABLE 10** Study characteristics of economic evaluations

	<b>Pinkerton et al. 1998<sup>22</sup></b>	<b>Pinkerton et al. 2004<sup>23</sup></b>	<b>Pinkerton et al. 2004<sup>24</sup></b>	<b>Herida et al. 2006<sup>25</sup></b>
Country of origin	US	US	US	France
Base year prices	1996 US\$	2000 US\$	2000 US\$	2002 Euros
Intervention	PEP following potential HIV exposure through sexual contact with a partner who may or may not be infected vs a 'no programme option'. PEP was assumed to consist of a 4-week regimen of triple combination therapy with ZDV, 3TC and the protease inhibitor indinavir	Initial 7-day PEP with additional 21 days supplied at follow-up visit. Also medical evaluation, HIV risk assessment, risk-reduction counselling. Response to medication of HIV-infected sources was obtained if possible to tailor PEP to that most appropriate	Hypothetical PEP programme in 96 US metropolitan statistical areas (MSA), based on San Francisco PEP programme	PEP programme vs 'no PEP' alternative. Clinicians prescribe drugs of their choice (usually tri-therapy containing protease inhibitor). Antiretroviral drugs and counselling provided at each visit
Study type	Cost-utility analysis; decision-analytical model to evaluate cost-effectiveness	Cost-effectiveness and cost-utility study	Cost-utility analysis	Cost-effectiveness analysis based on decision trees and cost-utility study
Study group	A hypothetical cohort of 10,000 patients who reported sexual intercourse with a partner of unknown HIV status	401 participants with possible non-occupational exposure to HIV (sexual, needle sharing, non-occupational needlestick injury, other (bite or assault))	Information on PEP clients taken from the San Francisco PEP programme, which was used to estimate the number of potential PEP clients in each group in each MSA	12,551 individuals who sought PEP between July 1999 and December 2003; 8958 (71%) were prescribed PEP and included in a national hospital-based voluntary surveillance of PEP programme for both occupational and non-occupational exposure
Perspective	Societal	Societal	Societal	Societal
Industry role	None stated	None stated (one of the authors has received honorariums from GlaxoSmithKline, Bristol-Myers Squibb and Agouron Pharmaceuticals)	Not stated	Not stated

3TC, lamivudine; ZDV, zidovudine.

The effectiveness of PEP and its effects on the cost-utility ratios presented in the studies, along with other parameters, are clearly explored in sensitivity analyses in each of the studies.<sup>22-25</sup> Authors of two of the studies reported multivariate and threshold analyses in addition to the univariate sensitivity analysis.<sup>22,23</sup>

Costs and consequences were judged to have been valued credibly in three of the four included studies.<sup>22,23,25</sup> Pinkerton and colleagues<sup>24</sup> have

calculated the costs of providing PEP from a previously published cost analysis.

Three of the four studies have used a lifetime horizon for analysis.<sup>22,24,25</sup> A shorter time horizon of 10 years has been employed for estimating long-term infection, but no justification has been given.<sup>23</sup> Discount rates are clearly reported in three studies. In two studies<sup>23,25</sup> an annual rate of 3% was used to discount both costs and benefits, such as future savings in averted HIV-related

**TABLE 11** Summary of the methodological quality of reporting of the cost-effectiveness studies

Quality criteria	Pinkerton et al. 1998 <sup>22</sup>	Pinkerton et al. 2004 <sup>23</sup>	Pinkerton et al. 2004 <sup>24</sup>	Herida et al. 2006 <sup>25</sup>
Is there a well-defined question?	Yes	Yes	Yes	Yes
Is there a clear description of alternatives (i.e. who did what to whom, where and how often)?	Unclear	Yes	No	Yes
Has the correct patient group/population of interest been clearly stated?	No	Yes	Yes	Yes
Is the correct comparator used?	Yes	Unclear	Yes	Yes
Is the study type reasonable?	Yes	Yes	Yes	Yes
Is the perspective of the analysis clearly stated?	Yes	Yes	Yes	Yes
Is the perspective employed appropriate?	Unclear	Yes	Yes	Unclear
Is the effectiveness of the intervention established?	No	No	No	No
Has a lifetime horizon been used for analysis? If not, has a shorter time horizon been justified?	Yes	No	Yes	Yes
Are the costs and consequences valued credibly?	Yes	Yes	Unclear	Yes
Is differential timing considered?	Yes	Yes	Unclear	Yes
Is incremental analysis performed?	Yes	No	No	No
Is sensitivity analysis undertaken and presented clearly?	Yes	Yes	Yes	Yes

medical costs. Pinkerton and colleagues<sup>22</sup> used a 3% annual rate (applied to both costs and benefits) and altered this to 0% (undiscounted) and 5% in the sensitivity analysis. It is unclear if discounting has been applied in one of the 2004 Pinkerton and colleagues studies.<sup>24</sup>

Incremental analysis was reported by only one of the studies.<sup>22</sup> The remaining three papers report cost-utility ratios but no incremental ratios. Pinkerton and colleagues<sup>23</sup> compare their results with previously published papers.

Table 12 presents a summary of the external validity of the included cost-effectiveness studies. Three of the four studies are set in the US<sup>22-24</sup> and the fourth in France,<sup>25</sup> where the institutional health-care arrangements and resource costs, and access to them, are not comparable to those in England and Wales. It is unclear whether the patient groups are similar to those of interest in England and Wales as these studies are set in differing health-care systems but are conducted among the relevant population: those taking PEP after a non-occupational exposure.

Either the intervention in each of the four studies was not sufficiently clear for a judgement to be made of treatment comparability<sup>24,25</sup> or the research protocol included such elements as counselling and adherence counselling that may not be a feature of clinical management.<sup>23</sup> Pinkerton and colleagues<sup>22</sup> have assumed that the PEP in their study consists of triple combination therapy, which is comparable to that recommended in the UK, but no further details are given.

## Assessment of cost-effectiveness

Summaries of the results of the four published economic evaluations in terms of cost-utility ratios for different population subgroups are shown in Tables 13-15.

Herida and colleagues<sup>25</sup> found that the French PEP programme did not appear to be cost-effective overall, with a cost-effectiveness ratio of €996,104 per infection averted and €88,692 per quality-adjusted life-year (QALY) saved.

**TABLE 12** Summary of the external validity of the cost-effectiveness studies

Quality criteria	Pinkerton et al. 1998 <sup>22</sup>	Pinkerton et al. 2004 <sup>23</sup>	Pinkerton et al. 2004 <sup>24</sup>	Herida et al. 2006 <sup>25</sup>
Patient group – are the patients in the study similar to those of interest in England and Wales?	Unclear	Unclear	Unclear	Unclear
Health-care system/setting – comparability to England and Wales; comparability of available alternatives; similar levels of resources; institutional arrangements comparable?	No	No	No	No
Treatment – comparability with clinical management?	Unclear	Unclear	Unclear	Unclear
Resource costs – comparability between study and setting/population of interest?	No	No	No	No

**TABLE 13** Base-case cost–utility ratios for men who have sex with men

Type of exposure	Probability PEP effective	HIV transmission probability	Probability source is HIV positive	Estimated or actual PEP compliance	Cost per QALY	Study
Unprotected receptive anal intercourse	0.80	0.02	1.00	0.83	–€22,141	Herida et al. 2006 <sup>25</sup>
	0.80	0.02	0.14	0.74	€31,862	Herida et al. 2006 <sup>25</sup>
	0.81	0.02	0.293	1.00 <sup>a</sup>	Cost saving (actual cost per QALY not reported)	Pinkerton et al. 2004 <sup>23</sup>
	0.81	0.02	Not reported	0.778	US\$ < 0 (actual figure not reported)	Pinkerton et al. 2004 <sup>24</sup>
	0.79	0.02	0.18	0.69	US\$6354	Pinkerton et al. 1998 <sup>22</sup>
Unprotected insertive anal intercourse	0.80	0.0006	1.00	0.83	€241,716	Herida et al. 2006 <sup>25</sup>
	0.80	0.0006	0.14	0.80	€1,952,497	Herida et al. 2006 <sup>25</sup>
	0.81	0.0006	0.293	1.00 <sup>a</sup>	US\$686,525	Pinkerton et al. 2004 <sup>23</sup>
	0.81	0.0006	Not reported	0.778	US\$554,814	Pinkerton et al. 2004 <sup>24</sup>
	0.79	0.0006	0.18	0.69	US\$773,785	Pinkerton et al. 1998 <sup>22</sup>
All exposures combined <sup>b</sup>					US\$8607	Pinkerton et al. 2004 <sup>23</sup>
					US\$4907	Pinkerton et al. 2004 <sup>24</sup>

QALY, quality-adjusted life-year.

a PEP was assumed to be effective only if the patient was known to have completed the regimen; otherwise effectiveness was set to 0.

b Receptive or insertive anal intercourse, receptive oral sex and ‘other’. References for sources of data can be found in the individual papers.<sup>22–25</sup>

**TABLE 14** Base-case cost–utility ratios for heterosexuals

Type of exposure	Probability PEP effective	HIV transmission probability	Probability source is HIV positive	Estimated or actual PEP compliance	Cost per QALY	Study
Unprotected receptive anal intercourse	0.80	0.02	1.00	0.81	–€22,031	Herida <i>et al.</i> 2006 <sup>25</sup>
	0.80	0.02	0.005	0.60	€1,943,685	Herida <i>et al.</i> 2006 <sup>25</sup>
	0.81	0.02	0.041	1.00 <sup>a</sup>	US\$165,289	Pinkerton <i>et al.</i> 2004 <sup>23</sup>
	0.81	0.02	Not reported	0.778	US\$ < 0 (actual figure not reported)	Pinkerton <i>et al.</i> 2004 <sup>24</sup>
	0.79	0.02	0.18	0.69	US\$6354	Pinkerton <i>et al.</i> 1998 <sup>22</sup>
Unprotected receptive vaginal intercourse	0.80	0.001	1.00	0.81	€135,111	Herida <i>et al.</i> 2006 <sup>25</sup>
	0.80	0.001	0.005	0.62	€38,653,452	Herida <i>et al.</i> 2006 <sup>25</sup>
	0.81	0.001	0.041	1.00 <sup>a</sup>	US\$262,562	Pinkerton <i>et al.</i> 2004 <sup>23</sup>
	0.81	0.001	Not reported	0.778	US\$380,891	Pinkerton <i>et al.</i> 2004 <sup>24</sup>
	0.79	0.001	0.02	0.69	US\$4,254,916	Pinkerton <i>et al.</i> 1998 <sup>22</sup>
All exposures combined: heterosexual females <sup>b</sup>					US\$161,114	Pinkerton <i>et al.</i> 2004 <sup>24</sup>
All exposures combined: heterosexual males <sup>c</sup>					US\$685,560	Pinkerton <i>et al.</i> 2004 <sup>24</sup>

QALY, quality-adjusted life-year.  
a PEP was assumed to be effective only if the patient was known to have completed the regimen; otherwise effectiveness was set to 0.  
b Male–female receptive anal intercourse, male–female receptive vaginal intercourse.  
c Male–female insertive anal intercourse, male–female insertive vaginal intercourse, male–female other sexual exposure.

**TABLE 15** Base-case cost–utility ratios for intravenous drug users (IDUs)

Type of exposure	Probability PEP effective	HIV transmission probability	Probability source is HIV positive	Estimated or actual PEP compliance	Cost per QALY	Study
IDU	0.80	0.0067	1.00	0.61	–€1141	Herida <i>et al.</i> 2006 <sup>25</sup>
	0.81	0.003	0.214	1.00	US\$86,462	Pinkerton <i>et al.</i> 2004 <sup>23</sup>
	0.81	0.003	Not reported	0.778	US\$97,867	Pinkerton <i>et al.</i> 2004 <sup>24</sup>

QALY, quality-adjusted life-year.



However, the authors report major differences in the cost-effectiveness ratio according to the type of exposure. PEP after receptive anal intercourse with an HIV-infected individual (men –€22,141, women –€22,031 per QALY saved) and PEP to an intravenous drug user (IDU) after sharing a needle with an HIV-infected person (–€1141 per QALY saved) were cost saving. PEP was cost-effective for MSM having receptive anal intercourse with a partner of unknown status (€31,862 per QALY saved). PEP was not considered cost-effective (cost per QALY €50,000) for all other exposures considered in the analysis.

One-way sensitivity analyses were performed on the compliance and life expectancy of HIV-infected individuals in this study.<sup>25</sup> PEP after receptive anal intercourse with an HIV-infected individual remained cost saving (–€17,778 and –€18,860 per QALY saved for MSM and heterosexual women respectively). PEP to an IDU after needle sharing with an HIV-infected person remained cost-effective but was no longer cost saving (€18,445 per QALY saved). Further sensitivity analyses incorporating higher lifetime HIV costs resulting from longer survival resulted in the three exposure risks with negative ratios in the base case remaining cost saving but with higher cost ratios.

Herida and colleagues<sup>25</sup> also performed threshold analyses for exposures with cost-effectiveness ratios under €200,000 per QALY saved, using minimum values of prevalence, per-contact HIV transmission or compliance required to achieve the cost-saving threshold (€0 per QALY saved) or the cost-effective threshold (€50,000 per QALY saved). The authors reported that PEP for MSM after receptive anal intercourse with a partner of unknown HIV status was cost saving for a per-contact transmission risk of at least equal to 0.0411 or an HIV prevalence of at least 0.208. For needle sharing with an individual of unknown serostatus the authors reported that cost-effectiveness occurred with a compliance of  $\geq 0.92$  with both the highest values of prevalence (0.21) and of the per-contact transmission risk (0.0092). The cost-effectiveness ratio was reached for a per-contact transmission risk equal to 0.0208 for receptive vaginal intercourse with an HIV-infected partner.

Pinkerton and colleagues<sup>23</sup> cost-utility analysis of a PEP programme for 401 participants with possible non-occupational exposure to HIV found that the use of PEP prevented an estimated 1.59 HIV infections (1.26 infections after adjusting for continuing risk behaviours over the subsequent

10 years), with an overall cost-utility ratio of US\$14,449 per QALY saved. In total, 96% of averted infections were among men who reported exposure through receptive anal intercourse with other men.

The authors report that the PEP programme was cost saving amongst men who have receptive anal intercourse with other men, and when the partner was known to be HIV positive.<sup>23</sup> The overall cost-utility ratio for men reporting exposure through male-male sex (receptive or insertive anal intercourse, receptive oral intercourse or 'other') was US\$8607 per QALY saved, whereas the cost-utility ratio for all other exposures combined was US\$258,667 per QALY saved. The cost per QALY saved for exposure by injecting drugs and male-female receptive anal sex was US\$86,462 and US\$165,289 respectively.

The results of the sensitivity analyses reported by the authors suggest that the PEP programme remained cost-effective when the effectiveness of PEP was set as low as 48% (base case 81%) and as long as PEP completion rates were greater than 29%.<sup>23</sup> The programme also remained cost-effective regardless of the percentage of partners known to be infected with HIV or the prevalence of infection among partners whose HIV status was unknown.

The cost-utility ratio was most sensitive to the receptive anal intercourse transmission probability.<sup>23</sup> The authors report that the PEP programme would be cost saving overall if this probability exceeded 0.033 and would be cost-effective (defined by the authors as a cost-utility ratio of US\$60,000 per QALY saved) for probabilities as small as 0.009 (the base case was set at 0.02).

The Pinkerton and colleagues study<sup>24</sup> of PEP in 96 metropolitan statistical areas in the US estimated the respective mean and median cost-utility ratios to be US\$15,728 and US\$15,367 per QALY saved, with 63.9 HIV infections averted. PEP was cost saving for male-male and male-female receptive anal intercourse exposures (see *Tables 13–15*). Cost-utility ratios for needle sharing and needlestick exposures were US\$97,867 and \$159,686 per QALY saved respectively. The cost-utility ratio exceeded \$380,000 per QALY saved for all other types of exposure.

The authors report<sup>24</sup> that the sensitivity analysis suggests that the results are moderately sensitive to PEP effectiveness and somewhat sensitive to the



proportion of people completing the PEP regimen, the proportion of PEP clients with known infected source partners and the lifetime costs of medical care and lost QALYs associated with a case of HIV infection.

The authors<sup>24</sup> conclude that PEP is only cost-effective in limited circumstances such as following receptive anal intercourse with a partner at high risk of infection and possibly following other high-risk exposures with a partner known to be infected. The authors state that PEP was highly cost-effective for MSM, less cost-effective for IDUs and high-risk women, and probably not cost-effective for general population exposures or heterosexual men.<sup>24</sup>

The study by Pinkerton and colleagues<sup>22</sup> evaluating the cost-effectiveness of PEP for a hypothetical cohort of 10,000 patients reporting sexual intercourse with a partner of unknown HIV status estimated that 19.62 HIV infections would be averted following receptive anal intercourse, 0.59 following insertive anal intercourse, 0.11 following receptive vaginal intercourse and 0.07 following insertive vaginal intercourse.

In this study<sup>22</sup> the base-case analysis suggested that PEP is only cost-effective for receptive anal intercourse (all other cost-utility ratios exceeded US\$750,000 per QALY saved). The cost-utility ratio following receptive anal intercourse among MSM was US\$6354 per QALY saved. This became cost saving if the probability that the source partner was HIV positive was greater than 0.25 (see *Tables 13–15*).

The sensitivity analysis reported by Pinkerton and colleagues<sup>22</sup> showed that PEP following receptive anal intercourse was always cost-effective across a range of values. PEP following receptive vaginal intercourse became cost-effective when the probability that the source partner was HIV positive was at least 0.73. The authors report that triple therapy was unlikely to be cost-effective relative to double therapy as the additional drug costs were not offset by treatment savings. The results did not appear to be sensitive to repeated exposure to HIV and PEP.<sup>22</sup>

## Economic evaluation

One of the aims of the current report was to draw together the best available evidence to estimate the cost-effectiveness of non-occupational PEP for HIV in a UK setting. The current authors

explored the feasibility of developing a de novo economic model, either by adapting an existing cost-effectiveness model or by constructing a new one. However, the available data to inform any cost-effectiveness analysis are very sparse, making it inappropriate to model the cost-effectiveness of non-occupational PEP for HIV at the present time. The limitation in the extent of the evidence for the clinical effectiveness of non-occupational PEP for HIV is the main reason for arriving at this conclusion, that is, the effectiveness of non-occupational PEP is unknown. Only one study met the systematic review criteria for assessing the clinical effectiveness of non-occupational PEP, and the authors state that the study design and relatively small number of seroconversions do not allow conclusions about the effectiveness of PEP in preventing infection. In addition, there were limited data for other model parameters, such as per-exposure transmission probabilities, prevalence of HIV among different population groups and treatment compliance. Any modelling using such data inputs will be of limited value.

However, should better quality and more relevant data become available, the modelling frameworks presented by Pinkerton and colleagues<sup>23</sup> and Herida and colleagues<sup>25</sup> may be useful starting points for cost-effectiveness analysis. Although these studies should be viewed with caution, because the clinical effectiveness was informed from one study of the use of PEP in an occupational setting and was based on assumptions that the same conditions exist in a non-occupational setting, they have been conducted in an appropriate way and appear to have internal validity in terms of model structure. Any model should incorporate PEP adverse events and completion rates as these have important economic consequences.

## Summary of cost-effectiveness of PEP for non-occupational exposure to HIV

- Four economic evaluations met the inclusion criteria of the review.
- The methodological quality of the four studies is mixed. Each had a well-defined question, stated a reasonable study type and perspective and undertook a clear sensitivity analysis. However, each of the studies is constrained by a lack of published data on the clinical effectiveness of PEP after non-occupational

- exposure, the per-exposure transmission risk, the compliance with medication and the prevalence of HIV infection amongst different population subgroups.
- In addition, external validity appears to be poor. None of the studies was clearly generalisable to the UK. Lack of detailed information on the PEP regimes used in all of the studies prevented comparison with UK clinical management, as did the lack of information on study participants.
  - Results from the included studies suggest that PEP following non-occupational exposure to HIV is cost saving for:
    - men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not
    - heterosexuals after unprotected receptive anal intercourse
    - intravenous drug users sharing a needle with a known HIV-positive person.
  - PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex and ‘other’).
  - PEP following non-occupational exposure to HIV was possibly cost-effective for intravenous drug users and high-risk women.
  - In general, sensitivity analyses did not greatly alter the base-case findings. Some sensitivity to the following parameters was noted:
    - transmission probability following receptive anal intercourse
    - effectiveness of PEP
    - proportion of clients completing PEP
    - proportion of clients with known HIV-positive partners
    - lifetime costs of treatment and number of lost QALYs
    - receptive vaginal intercourse (which became cost-effective) when the probability of the source partner being HIV positive was  $\geq 0.73$ .
  - In summary, although the results of the studies are consistent and suggest that non-occupational PEP may be cost-effective, the results should be treated with caution. It may not be appropriate to make assumptions that the same conditions exist in a non-occupational setting as in an occupational setting. The generalisability to the UK of studies conducted in the US and France is not clear. Although transmission risks for specific sexual practices are likely to be the same, sexual behaviour and HIV incidence may not be similar and local costs may be different.
  - Because of limited data, especially on the effectiveness of non-occupational PEP for HIV, no de novo economic evaluation was conducted in the present study.

## Chapter 6

# Adverse events

Four additional studies were identified that report data on adverse events and they are presented here to provide further information on this issue. Two comparative studies<sup>28,29</sup> consider different non-occupational PEP interventions and two prospective observational studies<sup>30,31</sup> in relevant populations report data on toxicity and completion of medication. Details of the four studies are shown below (*Table 16*). Study results are presented in *Tables 17* and *18*.

In one prospective comparative study<sup>28</sup> of sexual assault victims who sought treatment within 72 hours of sexual exposure, participants were assigned to either medium or high severity groups according to factors that could influence HIV transmission. Those in the medium severity group ( $n = 141$ ) were given zidovudine plus lamivudine and those in the high severity group ( $n = 137$ ) were given zidovudine plus lamivudine plus protease inhibitor. Follow-up was at 6 months and toxicity and compliance are reported. In the other comparative study<sup>29</sup> PEP was provided within 72 hours to individuals with exposures from partners known to have been or to be at risk for HIV infection through sexual exposure or injecting drug use. In total, 97% of participants were treated exclusively with dual reverse transcriptase inhibitors. Rates of completion of PEP and toxicities after 4 weeks are reported.<sup>29</sup>

In one 18-month prospective observational study<sup>30</sup> sexual assault survivors attending one of 24 Sexual Assault Treatment Centres (SATCs) within 72 hours of the assault were offered PEP if considered to be at high or unknown risk of HIV infection. The primary outcomes in this study were acceptance and completion rate, and adverse events were also reported. All participants were prescribed Combivir (zidovudine + lamivudine) and Kaletra (lopinavir + ritonavir) and received counselling regarding dosing, adherence and adverse events. Follow-up visits were scheduled for days 2–4 and weeks 1, 2, 3 and 4. The second prospective observational study<sup>31</sup> enrolled patients presenting after sexual exposure to HIV from source partners known to be, or suspected of being, infected with HIV. The participants were prescribed zidovudine plus lamivudine if reporting the exposure within 72 hours and also received risk reduction counselling.

Follow-up visits were scheduled for weeks 1, 2, 4, 6, 12 and 26. The primary outcomes for this study were enrolment into concurrent behavioural risk reduction interventions, demand for non-occupational PEP and characteristics of those treated. Completion and adverse events were also reported.

All of the studies have methodological limitations in that, although there were objective criteria for the eligibility of subjects, subjects were self-referring and there was non-blinded assessment of self-reported outcomes. Not all outcomes are reported separately for all treatment groups in the comparative studies and it is not clear whether the different groups within each study are comparable; participants were also allowed to switch between treatment groups. The observational studies are limited by the lack of control groups. Although all of the sexual assault survivors attending SATCs were offered PEP,<sup>30</sup> 25.9% of health-care providers prescribing PEP reported strongly encouraging or encouraging participants to accept and 3.1% reported strongly discouraging or discouraging acceptance, which could affect both acceptance and possibly completion. Selected outcomes were reported separately for the high-risk and unknown-risk groups.<sup>30</sup> The recruitment by Shoptaw and colleagues<sup>31</sup> focused on an underserved area and participants then self-referred to the study, meaning that the generalisability of the study findings is unclear.

### Completion of treatment

Completion of treatment rates in the four studies are shown in *Table 17*. Garcia and colleagues<sup>28</sup> found that participants who received dual therapy were more likely to complete PEP (68%) than those who received three drugs (53%) ( $p = 0.01$ ). In the high severity group 21% interrupted the use of protease inhibitor and completed PEP with two drugs, with the main reason for interruption being toxicity. Compliance at 6 months of follow-up was similar in both the medium and the high severity groups [odds ratio (OR) 1.0, 95% CI 0.8–1.3].<sup>28</sup> In the San Francisco PEP study,<sup>29</sup> over all groups, 78% of participants completed 4 weeks of treatment. Significantly more patients treated

TABLE 16 Studies reporting adverse event/compliance data

Study	Population	Interventions
Garcia et al. 2005 <sup>28</sup>	Sexual assault victims	
Brazil		
Prospective cohort study		
	Medium-risk group ( $n = 141$ ) (vaginal/oral intercourse with ejaculation but without trauma)	ZDV + 3TC
	High-risk group ( $n = 137$ ) [anal penetration; vaginal exposure with genital trauma; exposure to many aggressors; presence of factors that increase risk (inflammation, ulcers, bleeding, trauma, laceration, menstruation); aggressor known to be HIV positive]	ZDV + 3TC + PI
	All patients offered psychological and supportive counselling	
Kahn et al. 2001 <sup>29</sup>	Sexual or injecting drug use exposure	
San Francisco	Source HIV status/ART history unknown ( $n = 351$ )	ZDV + 3TC (combined pill twice daily)
PEP study	As above with source plasma HIV RNA levels on treatment above the limits of detection ( $n = 8$ )	ZDV + 3TC + Nfv (combined pill twice daily + Nfv three times daily)
	Source receiving or participant refused ZDV ( $n = 31$ )	ddl + d4T (two pills twice daily)
	As above with source plasma HIV RNA levels on treatment above the limits of detection ( $n = 5$ )	ddl + d4T + Nfv (two pills twice daily + Nfv three times daily)
	If source was receiving Nfv and had detectable plasma HIV RNA levels, alternative to Nfv given ( $n = 2$ )	Other ART
	All groups received risk reduction counselling and medication adherence counselling	
Loutfy et al. 2008 <sup>30</sup>	Sexual assault survivors ( $n = 798$ ): 69 high risk; 729 unknown risk	Combivir (ZDV + 3TC) (one pill twice daily) and Kaletra (lopinavir/ritonavir) (three capsules orally twice a day) for 28 days
Canada		
Prospective observational study		
	Counselling regarding dosing, the importance of adherence and adverse events was provided	
Shoptaw et al. 2008 <sup>31</sup>	Patients presenting post sexual exposure to persons known or suspected to be infected with HIV ( $n = 100$ )	ZDV + 3TC (twice daily)
US		
Prospective observational study		
	Risk reduction counselling provided	

3TC, lamivudine; ART, antiretroviral therapy; d4T, stavudine; ddl, didanosine; Nfv, nelfinavir; PI, protease inhibitor (indinavir or nelfinavir); RNA, ribonucleic acid; ZDV, zidovudine.

with didanosine plus stavudine completed 4 weeks of therapy than did those receiving zidovudine plus lamivudine (94% versus 76%,  $p = 0.01$ ). However, the higher rates of completion seen in participants using didanosine plus stavudine may have been due to the study protocol. This discouraged participants from changing to zidovudine plus lamivudine if they developed

tolerable adverse events, in an attempt to provide treatment against a possibly resistant strain. In contrast, those taking zidovudine plus lamivudine who experienced adverse events were encouraged to switch to didanosine plus stavudine to complete their treatment course. Among participants who completed 4 weeks of therapy, the percentage of participants reporting complete adherence during

**TABLE 17** Assessment of completion of treatment

Study	Compliance	Intervention			
Garcia et al. 2005 <sup>28</sup>		Medium severity group (dual therapy, n = 141)		High severity group (triple therapy, n = 137)	
	Completed 6 months of follow-up and 28 days of PEP, n (%)	69 (48.9)		53 (38.7)	
	Completed 6 months of follow-up, interruption of PEP, n (%)	11 (7.8)		23 (16.8)	
	Abandoned follow-up but completed 28 days of PEP, n (%)	27 (19.2)		20 (14.6)	
	Abandoned follow-up and 28 days of PEP, n (%)	34 (24.1)		41 (30)	
	Total, n (%)	141 (100)		137 (100)	
Kahn et al. 2001 <sup>29</sup>		ZDV + 3TC (n = 351)	ZDV + 3TC + Nfv (n = 8)	ddl + d4T (n = 31)	ddl + d4T + Nfv (n = 5)
	Completed 4 weeks of assigned PEP, n (%)	267 (76)	6 (75)	29 (94)	5 (100)
	Completed 4 weeks but changed initial PEP, n (%)	3 (1)	0	0	0
	Discontinued PEP, n (%)	47 (13)	0	1 (< 1)	0
	Toxicity, n (%)	27 (8)	–	0	–
	Source not infected, n (%)	10 (3)	–	0	–
	Participant preference, n (%)	6 (2)	–	1 (< 1)	–
	Participant HIV infected, n (%)	4 (1)	–	0	–
Loutfy et al. 2008 <sup>30</sup>	Non-adherent (%)	76.0 high-risk group 66.7 unknown-risk group			
	28-day course completed (%)	23.9 high-risk group 33.2 unknown-risk group			
Shoptaw et al. 2008 <sup>31</sup>	Non-adherent (%)	36			
	28-day course completed (%)	64			
n = 100					

3TC, lamivudine; d4T, stavudine; ddl, didanosine; Nfv, nelfinavir; ZDV, zidovudine.

the 4 days before the clinic visit ranged from 78% to 84%.<sup>29</sup>

The percentage of participants receiving Combivir and Kaletra who completed the course of PEP was 23.9% in the high-risk group and 33.2% in the unknown-risk group in the study of sexual assault survivors by Loutfy and colleagues.<sup>30</sup> This study found that health-care provider-perceived moderate or high participant anxiety at the initial visit, assault by a stranger or an assailant known to the participant less than 24 hours previously or absence of concomitant physical assault were predictors of completion. Reasons for discontinuation included adverse events (81.2%), interference with usual routine (42%), inability

to take time away from work, school or other commitments (21.7%) and reassessment of HIV risk (18.8%). In the study by Shoptaw and colleagues<sup>31</sup> 86% of participants were dispensed the full 28-day supply of PEP and 64% of participants receiving zidovudine plus lamivudine completed treatment.

## Assessment of toxicity

Toxicity results are shown in *Table 18*. In one study<sup>28</sup> 93% of the participants receiving three drugs reported at least one side effect, compared with 66% of the participants receiving two drugs ( $p < 0.01$ ). Digestive discomfort was the most common side effect and was statistically more

TABLE 18 Assessment of toxicity

Study	Side effect	Medium severity group (dual therapy, <i>n</i> = 141)	High severity group (triple therapy, <i>n</i> = 137)	<i>p</i> -value
Garcia et al. 2005 <sup>28</sup>	Any referred intolerance, <i>n</i> (%)	76 (66)	106 (93)	<i>p</i> < 0.01
	Digestive intolerance, <i>n</i> (%)	70 (60)	101 (89)	<i>p</i> < 0.01
	Nausea, <i>n</i> (%)	62 (53)	93 (82)	<i>p</i> < 0.01
	Vomiting, <i>n</i> (%)	23 (20)	55 (48)	<i>p</i> < 0.01
	Dyspepsia, <i>n</i> (%)	20 (17)	40 (35)	<i>p</i> < 0.01
	Malaise, <i>n</i> (%)	26 (12)	60 (53)	<i>p</i> < 0.01
	Headache, <i>n</i> (%)	14 (12)	19 (17)	<i>p</i> = 0.35
	Fever, <i>n</i> (%)	–	6 (5)	<i>p</i> = 0.01
	Asthenia, <i>n</i> (%)	4 (3)	13 (11)	<i>p</i> = 0.02
	Dizziness, <i>n</i> (%)	7 (6)	20 (18)	<i>p</i> < 0.01
	Myalgia, <i>n</i> (%)	2 (2)	5 (4)	<i>p</i> = 0.28
	Cutaneous rash, <i>n</i> (%)	3 (3)	16 (14)	<i>p</i> < 0.01
	Nephrolithiasis, <i>n</i> (%)	–	9 (8)	<i>p</i> < 0.01
	Laboratorial abnormalities, <i>n</i> (%)	18 (16)	39 (33)	<i>p</i> < 0.01
	Premature interruption of PEP (all drugs), <i>n</i> (%)	12 (10)	35 (29)	<i>p</i> < 0.01
Kahn et al. 2001 <sup>29</sup>	Adverse events experienced:	Combined treatment groups		
	Nausea	52%		
	Fatigue	44%		
	Headache	24%		
	Diarrhoea	15%		
	Anorexia	12%		
Loutfy et al. 2008 <sup>30</sup>	Adverse events resulting in drug discontinuation, <i>n</i>	3		
	Participants reporting at least one adverse event, any grade, <i>n</i> (%)	265 (96.4)		
	Participants reporting at least one adverse event grade 2–4 (median 3, range 1–8), <i>n</i> (%)	212 (77.1)		
	Adverse events experienced:			
	Fatigue	58.5%		
	Nausea	49.5%		
	Diarrhoea	22.5%		
	Headache	20.7%		
	Mood changes	20.7%		
Vomiting	20.4%			
Stomach problems	16.4%			

common in participants who received three drugs ( $p < 0.01$ ).<sup>28</sup> Severe side effects were seen in patients receiving three drugs and hospitalisation occurred in six cases, as a result of Stevens–Johnson syndrome ( $n = 1$ ), nephrolithiasis ( $n = 2$ ) and severe gastrointestinal symptoms ( $n = 3$ ).<sup>28</sup> In

the San Francisco study<sup>29</sup> subjective toxicity for all study groups included nausea (52%), fatigue (44%), headache (24%), diarrhoea (15%) and anorexia (12%). Toxicity was the main reason for discontinuing treatment ( $n = 27$ , 8%).<sup>29</sup>



**TABLE 18** Assessment of toxicity (continued)

Study	Side effect	
Shoptaw et al. 2008 <sup>31</sup>	Participants reporting at least one adverse event, n (%)	79 (79)
n = 100	Adverse events experienced:	
	Fatigue	48%
	Nausea	45%
	Diarrhoea	7%
	Headache	20%
	Stomach problems	11%
	Malaise	8%
	Insomnia	6%
	Difficulty in concentrating	4%
	Depression	4%

The most common adverse events experienced in both observational studies were also fatigue (58.5%<sup>30</sup> and 48%<sup>31</sup>) and nausea (49.5%<sup>30</sup> and 45%<sup>31</sup>). Loutfy and colleagues<sup>30</sup> report that the majority of sexual assault survivors (77.1%) reported at least one adverse event (median 3, range 1–8) of grade 2–4 severity [adverse events were graded 1–4 using the US National Institute of Allergy and Infectious Diseases standardised toxicity grading system (grade 4 most severe)]. Three participants discontinued PEP because of adverse events, but no further details were given. The authors reported that participants who experienced vomiting were less likely to complete PEP than those who did not (OR 0.27, 95% CI 0.12–0.6,  $p = 0.0007$ ).<sup>30</sup> Shoptaw and colleagues<sup>31</sup> describe one participant requiring hospitalisation for suicide ideation, but this was not thought to be as a result of the study medication.

### Summary of adverse events of PEP for non-occupational exposure to HIV

- There is limited evidence in terms of quantity and quality, with two comparative studies and two prospective observational studies reporting adverse events and/or treatment completion rates for non-occupational PEP for HIV.
- One comparative study reported a significantly higher degree of toxicity and therapy discontinuation among sexual assault victims

taking a three-drug regimen compared with those taking a two-drug therapy. Digestive discomfort was the most common side effect and was significantly higher in participants who received three drugs. PEP therapy was completed by 68% of participants receiving dual therapy and 53% of those receiving triple therapy.

- A second comparative study reported statistically higher completion rates among participants taking didanosine plus stavudine compared with those taking zidovudine plus lamivudine, although this may have been due to the study protocol. Complete adherence at 4 weeks was 78% overall, ranging from 40% to 79% for different drug combinations. Toxicity was the main reason for discontinuation of treatment, with nausea and fatigue being the most common side effects.
- One prospective observational study reported low completion of treatment rates, with 23.9% in the high-risk group and 33.2% in the unknown-risk group completing the course of PEP. The most common adverse events experienced by the participants were fatigue and nausea.
- A second prospective observational study also found that fatigue and nausea were the most commonly experienced adverse events and that the majority of participants experienced adverse events. PEP therapy was completed by 64% of participants.





# Chapter 7

## Discussion

### Statement of principal findings

#### Clinical effectiveness

One cohort study<sup>21</sup> met the inclusion criteria for the review of clinical effectiveness.

This study had methodological limitations and limitations in the quality of the reporting: it was unclear how the sample was selected, whether the sample size was adequate and whether the study is generalisable beyond the specific cohort among which it was conducted. Dropouts are reported but are not included in the analysis and there is no blind assessment of outcomes. The authors do report objective eligibility criteria and the groups are comparable at baseline.

The study reported seroconversion to HIV, drug use and risk behaviours in a group receiving non-occupational PEP for HIV. The participants in the study were a Brazilian cohort of 200 high-risk MSM.

Seroincidence in the cohort as a whole (2.9 per 100 person-years) was very similar to that expected by the study authors in this population (3.1 per 100 person-years,  $p > 0.97$ ), despite the seroconversion to HIV being 1 out of 68 in the PEP group and 10 out of 132 in the group not receiving PEP. The study reported that, on average, high-risk sexual activities declined over time for both PEP and non-PEP users. The study authors concluded that a public health PEP programme would not have a major impact on HIV transmission in this population.

#### Cost-effectiveness

Four studies<sup>22–25</sup> met the inclusion criteria for the review of cost-effectiveness.

The methodological quality of the cost-effectiveness studies was mixed, with each employing well-defined questions, the appropriate perspective, appropriate methods of analysis and clear sensitivity analyses. Each study is, however, limited by the unknown effectiveness of the intervention,

both the dual/triple drug regimen and the use of PEP in a non-occupational exposure patient group.

All four studies evaluated 28 days of PEP post non-occupational exposure to HIV, but full details are not given. Two of the studies considered hypothetical cohorts.<sup>22,24</sup>

Results from the studies suggest that PEP following non-occupational exposure to HIV is cost saving for men who have unprotected receptive anal intercourse with men, whether the source partner is known to be HIV positive or not; heterosexuals after unprotected receptive anal intercourse; and intravenous drug users sharing needles with a known HIV-positive person.

PEP following non-occupational exposure to HIV was cost-effective for all male–male intercourse (unprotected receptive and insertive anal intercourse, unprotected receptive oral sex and ‘other’). PEP following non-occupational exposure to HIV was possibly cost-effective for intravenous drug users and high-risk women.

In general, sensitivity analyses did not greatly alter the base-case findings.

In summary, although the results of the studies are consistent and suggest that non-occupational PEP may be cost-effective, the results should be treated with caution. It may not be appropriate to make assumptions that the same conditions exist in a non-occupational setting as in an occupational setting and the generalisability to the UK of studies conducted in the US and France is questionable as sexual behaviour and HIV incidence may not be similar.

#### Adverse events

Additional studies were sought to supply further information on adverse events. The evidence was limited in terms of quantity and quality, with two comparative studies and two observational studies reporting adverse events and/or treatment completion rates for non-occupational PEP.

One comparative study<sup>28</sup> reported a significantly higher degree of toxicity and therapy discontinuation among rape victims taking a three-drug regimen compared with those taking a two-drug regimen. Completion of PEP therapy was low in both dual and triple therapy. A second comparative study<sup>29</sup> reported statistically higher completion rates among participants taking didanosine plus stavudine compared with those taking zidovudine plus lamivudine, although this may have been due to the study protocol.

One prospective observational study reported low rates of completion of treatment, with 23.9% in the high-risk group and 33.2% in the unknown-risk group completing the course of PEP. The most common adverse events experienced by the participants were fatigue and nausea.<sup>30</sup> A second prospective observational study<sup>31</sup> also found that fatigue and nausea were the most commonly experienced adverse events and that the majority of participants experienced adverse events. PEP therapy was completed by 64% of participants.

## Strengths and limitations of the assessment

The review has certain strengths:

- It is independent of any vested interest.
- The review brings together the evidence for the clinical effectiveness and the cost-effectiveness of non-occupational PEP for HIV and adverse event data by applying consistent methods of critical appraisal, presentation and transparency.
- The review was guided by the principles of undertaking a systematic review. Before undertaking the review the methods were set out in a research protocol (Appendix 1) and this was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations placed upon the review:

- The number and type of studies available for inclusion in the review was limited. No RCTs

were identified and the economic evaluations were not conducted in the UK.

- Synthesis of the included studies was through narrative review. Because of the limitations of the literature, meta-analysis was not possible.
- Time and resource constraints for this short report together with the lack of effectiveness data for the use of non-occupational PEP for HIV prevented the development of an economic evaluation and so the assessment of cost-effectiveness was limited to a systematic review of existing cost-effectiveness studies.

## Other relevant issues

- Only one cohort study met the systematic review inclusion criteria for the assessment of the clinical effectiveness of non-occupational PEP for HIV. The study design and relatively small number of seroconversions do not allow conclusions to be made about the effectiveness of PEP in preventing infection. However, results suggest that PEP made no difference to the expected HIV seroconversion rate for a high-risk HIV-seronegative homosexual male cohort in Rio de Janeiro, Brazil.
- One of the issues of concern is that PEP may be relied upon as a primary form of HIV prevention and will fail to reduce or may actually increase high-risk exposures because it is perceived to fully prevent virus transmission. In the included study PEP was not associated with an increase in reported high-risk behaviour. Reported high-risk behaviour declined slightly for the cohort as a whole but these results should be viewed with caution because of the potential for under-reporting of self-reported high-risk activities.
- Various assumptions were made in the studies considering the cost-effectiveness of non-occupational PEP for HIV. Of most concern is the use of the estimate of effectiveness from the occupational PEP setting, which is based on the assumption that the same conditions exist in the non-occupational setting as in the occupational setting.
- Other assumptions are acknowledged in the studies. For example, in the study conducted in France<sup>25</sup> compliance could only be estimated from the database for 47% of PEP prescriptions and so overall compliance was estimated at 0.75. However, overestimation of compliance would improve the cost-effectiveness ratio. There were no available data for lifetime HIV/AIDS costs in France and so these were

estimated by the authors. The model did not take into account the possibility that some patients seeking PEP may continue at-risk behaviour. The study also did not consider PEP adverse events. The authors state that taking these into account would further reduce the cost-effectiveness ratio of the overall PEP programme. The number of HIV infections predicted by the model was higher than that actually seen; however, HIV serology 6 months after PEP initiation was only available for 18% of patients and so the authors suggest that the true number of PEP failures may be higher.

- Pinkerton and colleagues<sup>24</sup> acknowledge that there are a number of issues of uncertainty in their study of non-occupational PEP in US metropolitan statistical areas. The results were most sensitive to the effectiveness of PEP and the per-exposure transmission probability for receptive anal intercourse. The lack of evidence of effectiveness of PEP for non-occupational exposures to HIV means that the results should be interpreted with caution. With regard to per-exposure transmission probabilities, the probabilities used in this study did not take into account variations in infectiousness over the

course of HIV disease, interpersonal variability or potential reductions from the use of highly active antiretroviral therapy.

- Pinkerton and colleagues conclude from their hypothetical cohort study<sup>22</sup> that, from an economic effectiveness perspective, PEP should be restricted to partners of infected persons (e.g. serodiscordant couples), patients reporting unprotected receptive anal intercourse (including condom breakage) and possibly cases in which there is a substantial likelihood that the partner is infected.
- Various uncertainties, such as HIV prevalence rates, per-exposure transmission rates, completion of treatment and the impact of the number of pills prescribed daily, HIV status of partner and incomplete suppression of virus, some of which may vary in different locales, must be considered when modelling cost-effectiveness. Also, the potential for PEP programmes to incorporate risk counselling and the opportunity for intensive prevention counselling at the time of medication with PEP to influence future exposures must also be considered.



## Chapter 8

# Conclusions

### Non-occupational PEP for HIV

It is not possible to draw conclusions on the clinical effectiveness of non-occupational PEP for HIV because of the limited evidence in terms of the quantity and quality of studies. Only one small cohort study was identified that met the inclusion criteria for the systematic review. Cost-effectiveness has been assessed in four economic evaluations using evidence on effectiveness taken from the use of PEP in the occupational setting. Results are consistent across studies and suggest that non-occupational PEP may be cost-effective, especially in certain population subgroups. Although the studies have been conducted in an appropriate way and have internal validity in terms of the structure of the model and plausible results, the assumptions and data sources mean that the results should be treated with caution. The generalisability to the UK of studies conducted in the US and France is not clear. Although transmission risks for specific sexual practices are likely to be the same, sexual behaviour and HIV incidence may not be similar and local costs may be different.

### Research priorities

The most important research need is a comparative study to establish the effectiveness of using non-occupational PEP compared with not using PEP,

preferably within the UK using the currently recommended intervention. Data are also needed on HIV prevalence, seroconversion rates, per-exposure transmission, adverse events, treatment compliance rates, viral resistance rates, high-risk behaviours and effects of intensive counselling in different population groups. Some of these issues will be addressed by the NONOPEP project, which is an MRC-funded surveillance programme of PEP for non-occupational exposure to HIV. The study aims to describe current PEP prescribing practices and the demographic and exposure characteristics of individuals presenting for PEP; to evaluate the problems associated with taking antiretroviral therapy such as adverse events; to assess whether seroconversion has occurred and within which groups; and to contribute to a wider European study on the efficacy of PEP in the non-occupational setting. Data have been collected on individuals by means of a paper questionnaire, submitted to the Communicable Disease Surveillance Centre at baseline (presentation at clinic) and at three follow-up intervals (4 weeks, 3 months and 6 months). This study is due for submission shortly. Although there are challenges in conducting this research because of factors such as self-referral and follow-up of participants and self-reported outcomes, data generated from this study will be useful for informing any future economic modelling of the cost-effectiveness of non-occupational PEP in the UK.





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### Contribution of authors

Jackie Bryant was responsible for protocol development, the screening of the clinical effectiveness studies for inclusion, analysis and

interpretation of the clinical effectiveness studies, the screening of the cost-effectiveness studies for inclusion, analysis and interpretation of the cost-effectiveness studies, writing the report and project management and report editing. Susan Hird was responsible for protocol development, the screening of the clinical effectiveness studies for inclusion, data extraction and critical appraisal of the clinical effectiveness studies, analysis and interpretation of the clinical effectiveness studies, screening of the cost-effectiveness studies for inclusion, data extraction and critical appraisal of the cost-effectiveness studies, analysis and interpretation of the cost-effectiveness studies and report writing. Louise Baxter was responsible for the screening of the clinical effectiveness studies for inclusion, data extraction and critical appraisal of the clinical effectiveness studies, analysis and interpretation of the clinical effectiveness studies, the screening of the cost-effectiveness studies for inclusion, data extraction and critical appraisal of the cost-effectiveness studies, analysis and interpretation of the cost-effectiveness studies and report writing.







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# Appendix I

## Review methods from the research protocol

The a priori methods used for the review are outlined below. The sources of information used are outlined in Appendix 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 review are as follows.

#### Population

Humans with non-occupational exposure to HIV. This may be by:

- unprotected sexual exposure (oral, vaginal, anal), either voluntary or rape, with an HIV-infected partner or partner of unknown HIV status
- exposure to a needle contaminated by a known or potentially infected substance in a non-occupational setting.

#### Intervention

Any antiretroviral drug regimen administered as PEP 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 PEP regimen.

#### Outcomes

- HIV seroconversion frequency.
- Adverse effects and complications of PEP.

- Adherence to PEP.
- Health-related quality of life.
- Costs or some measure of cost-effectiveness.

#### Design

- RCT, CCT, cohort study or case-control study.
- Cost-effectiveness/utility studies.
- Descriptive studies with no control group will be excluded.

#### Data extraction

The extraction of study findings will be conducted by two reviewers using a predesigned 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.

#### 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 the NHS Centre for Reviews and Dissemination; observational studies will be assessed using criteria developed by Spitzer *et al.*<sup>18</sup> Quality assessment of economic evaluations will be conducted using a checklist adapted from those developed by Drummond and Jefferson<sup>19</sup> and Philips *et al.*<sup>20</sup> 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.

#### 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, for example 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.

### **Economic evaluation**

When 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 taken from the published literature and from NHS sources

when appropriate and available. The perspective of the economic analysis will be that of the NHS and Personal Social Services. Effectiveness data will be taken from published studies and used in conjunction with other relevant data (e.g. 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 QALY. The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

## Appendix 2

### Sources of information, including databases searched and search terms

The following search strategy was used in Ovid MEDLINE(R) from 1950 to November Week 2 2007 and adapted for other databases. Results were obtained for English language and non-English language papers. Bibliographies of related papers were assessed for relevant studies. *Tables 19 and 20* outline the databases and issues/dates searched. *Figures 1 and 2* provide flowcharts of the clinical effectiveness and cost-effectiveness studies respectively.

The search strategy used for non-occupational PEP was as follows:

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>1 exp HIV/ (59429)</li> <li>2 exp hiv-1/ (46463)</li> <li>3 exp hiv-2/ (3192)</li> <li>4 exp HIV Infections/ (169604)</li> <li>5 exp hiv antibodies/ (7992)</li> <li>6 (hiv or human immunodeficiency virus\$.ti,ab. (140649)</li> <li>7 exp Acquired Immunodeficiency Syndrome/ (68119)</li> <li>8 or/1-7 (214277) Population set 1</li> <li>9 (post?exposure prophylax\$or PEP or nPEP or PEPSE).ti,ab. (4037)</li> <li>10 post-exposure prophylax\$.ti,ab. (475)</li> <li>11 post exposure prophylax\$.ti,ab. (475)</li> <li>12 postexposure prophylax\$.ti,ab. (483)</li> <li>13 or/9-12 (4402) Population set 2</li> <li>14 (highly active antiretroviral therapy or haart).ti,ab. (7126)</li> </ul> | <ul style="list-style-type: none"> <li>15 exp antiviral agents/ (210658)</li> <li>16 exp anti-retroviral agents/ (40013)</li> <li>17 exp anti-hiv agents/ (34216)</li> <li>18 exp hiv fusion inhibitors/ (438)</li> <li>19 exp hiv integrase inhibitors/ (470)</li> <li>20 exp hiv protease inhibitors/ (7818)</li> <li>21 (combivir or zidovudine or lamivudine or kaletra or lopinavir or ritonavir).ti,ab. (9741)</li> <li>22 or/14-21 (215377) Intervention 1 set 1</li> <li>23 non?occupational.ti,ab. (506)</li> <li>24 nonoccupational.ti,ab. (506)</li> <li>25 non occupational.ti,ab. (671)</li> <li>26 or/23-25 (1169) Population set 3</li> <li>27 Occupational Exposure/ (28336) Population set 4</li> <li>28 8 and 13 (514) Combined population set 5</li> <li>29 28 and 22 (345) PEP population with intervention</li> <li>30 29 not 27 (212) Non-occupational set</li> <li>31 limit 30 to (humans and english language) (182) Non-occupational set English language download A</li> <li>32 30 not 31 (30) Non-occupational set non-English download B</li> <li>33 29 not 30 (133) Occupational set all languages download C</li> <li>34 from 31 keep 1-182 (182)</li> <li>35 from 32 keep 1-30 (30)</li> <li>36 from 33 keep 1-133 (133)</li> </ul> |
|--|--|

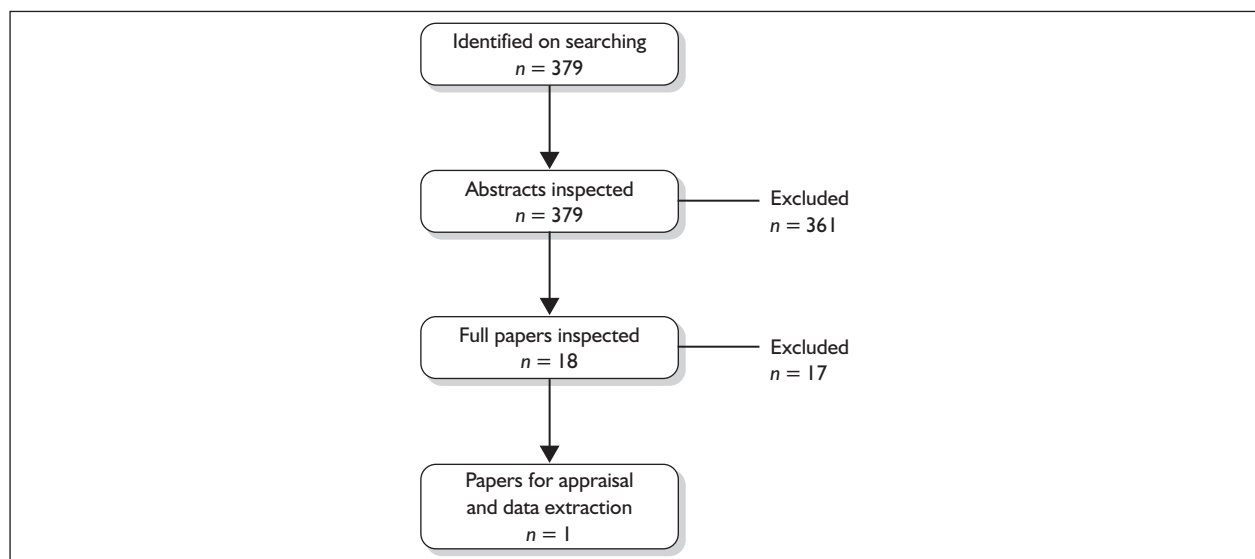
The search strategies were translated to run in the databases listed above. Full search strategies are available upon request.

**TABLE 19** Clinical effectiveness and cost-effectiveness searches

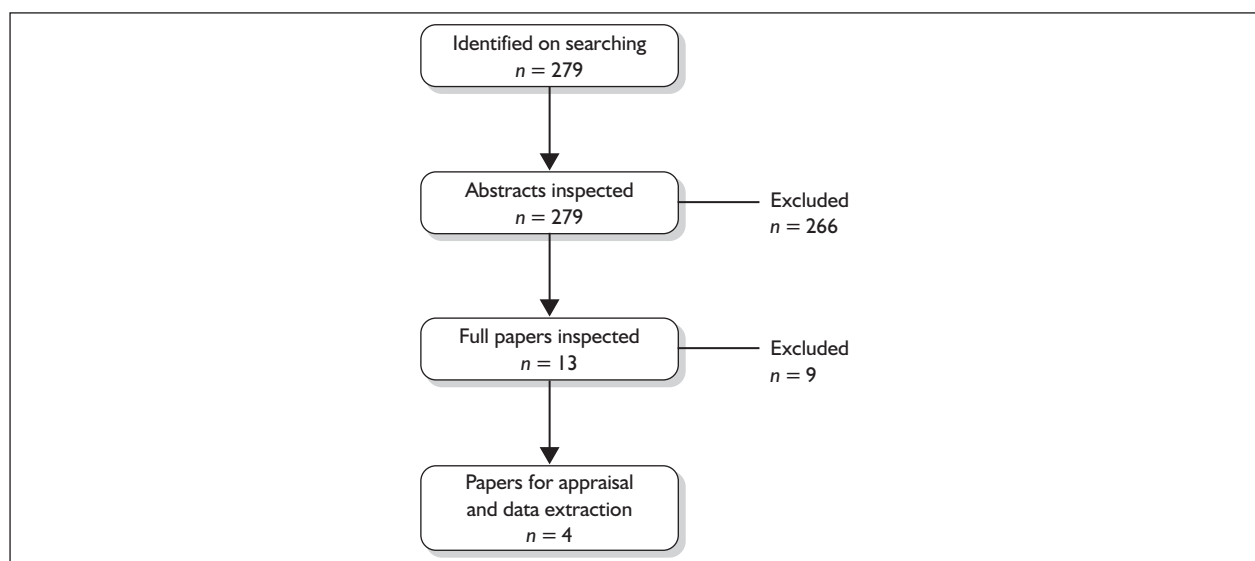
Databases searched	Clinical effectiveness: issues or dates searched	Cost-effectiveness: issues or dates searched
Cochrane Library – CDSR	Issue 4 2007; searched 13 September 2007	
Cochrane Library – CENTRAL	Issue 4 2007	
Ovid MEDLINE(R)	1950–November Week 2 2007	1950–November Week 2 2007
EMBASE	1980–2007 Week 49	1980–2007 Week 49
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	12 December 2007	12 December 2007
DARE (Database of Abstracts of Reviews of Effectiveness)	12 December 2007	
HTA database (on CRD databases)	12 December 2007	
NRR (National Research Register)	12 December 2007	
ClinicalTrials.gov ( <a href="http://clinicaltrials.gov/">http://clinicaltrials.gov/</a> )	12 December 2007	
NHS Economic Evaluations Database 2005–2007		12 December 2007

**TABLE 20** Adverse events searches

Databases	Years/dates searched
Ovid MEDLINE(R)	1996–September Week 3 2007; searched 2 October 2007
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	28 September 2007
EMBASE	1996–2007 Week 38



**FIGURE 1** Flowchart of clinical effectiveness studies.



**FIGURE 2** Flowchart of cost-effectiveness studies.





## Appendix 3

### List of excluded studies

#### Clinical effectiveness studies

Bernasconi E, Jost J, Ledergerber B, Hirschel B, Francioli P, Sudre P. Antiretroviral prophylaxis for community exposure to the human immunodeficiency virus in Switzerland, 1997–2000. *Swiss Med Wkly* 2001;**131**:433–7. (Questionnaire.)

Braitstein P, Chan K, Beardsell A, McLeod A, Montaner JS, O'Shaughnessy MV, *et al.* Prescribing practices in a population-based HIV postexposure prophylaxis program. *AIDS* 2002;**16**:1067–70. (No comparison group and prescribing practice as outcome.)

Luque A, Hulse S, Wang D, Shahzad U, Tanzman E, Antenozzi S, *et al.* Assessment of adverse events associated with antiretroviral regimens for postexposure prophylaxis for occupational and nonoccupational exposures to prevent transmission of human immunodeficiency virus. *Infect Control Hosp Epidemiol* 2007;**28**:695–701. (Chart review.)

Martin JN, Roland ME, Neilands TB, Krone MR, Bamberger JD, Kohn RP, *et al.* Use of postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior. *AIDS* 2004;**18**:787–92. (No comparison group.)

Meel BL. HIV/AIDS post-exposure prophylaxis (PEP) for victims of sexual assault in South Africa. *Med Sci Law* 2005;**45**:219–24. (No comparison group.)

O'Sullivan BG, Levy MH, Dolan KA, Post JJ, Barton SG, Dwyer DE, *et al.* Hepatitis C transmission and HIV post-exposure prophylaxis after needle- and syringe-sharing in Australian prisons. *Med J Aust* 2003;**178**:546–9. (Study design.)

Poynten IM, Smith DE, Cooper DA, Kaldor JM, Grulich AE. The public health impact of widespread availability of nonoccupational postexposure prophylaxis against HIV. *HIV Med* 2007;**8**:374–81. (No comparison group.)

Puro V, Soldani F, De Carli G, Lazarevic Z, Mattioli F, Ippolito G, *et al.* Drug-induced aminotransferase alterations during antiretroviral HIV post-exposure prophylaxis. *AIDS* 2003;**17**:1988–90. (Occupational exposure.)

Puro V, De Carli G, Orchi N, Palvarini L, Chiodera A, Fantoni M, *et al.* Short-term adverse effects from and discontinuation of antiretroviral post-exposure prophylaxis. *J Biol Regul Homeost Agents* 2001;**15**:238–42. (Includes health-care workers.)

Rabaud C, Bevilacqua S, Beguinot I, Dorvaux V, Schuhmacher H, May T, *et al.* Tolerability of postexposure prophylaxis with zidovudine, lamivudine, and nelfinavir for human immunodeficiency virus infection. *Clin Infect Dis* 2001;**32**:1494–5. (Included occupational exposure.)

Rabaud C, Burty C, Grandidier M, Christian B, Penalba C, Beguinot I, *et al.* Tolerability of postexposure prophylaxis with the combination of zidovudine-lamivudine and lopinavir-ritonavir for HIV infection. *Clin Infect Dis* 2005;**40**:303–5. (No comparator.)

Rey D, Partisani M, Hess-Kempf G, Krantz V, Priester M, Cheneau C, *et al.* Tolerance of a short course of nevirapine, associated with two nucleoside analogues, in postexposure prophylaxis of HIV. *J Acquir Immune Defic Syndr* 2004;**37**:1454–6. (Chart review.)

Roland ME, Neilands TB, Krone MR, Katz MH, Franses K, Grant RM, *et al.* Seroconversion following nonoccupational postexposure prophylaxis against HIV. *Clin Infect Dis* 2005;**41**:1507–13. (No comparison group.)

Schechter M. HIV vaccine evaluation center in Rio de Janeiro, Brazil. *Vaccine* 2002;**20**:1909–11. (Note.)

Sonder G, Regez R, Brinkman K, Prins J, Mulder J, Coutinho R, *et al.* Postexpositiebehandeling tegen HIV buiten het ziekenhuis in Amsterdam, januari-december 2000. *Ned Tijdschr Geneesk* 2002;**146**:629–33. (Non-English.)

Timset F, Maillard A, Spindler E, Taquin Y, Deniaud, Ferchal F, *et al.* Traitement antirétroviral prophylactique après exposition sexuelle au VIH: 93 cas. *Ann Dermatol Venerol* 2002;**129**:866–9. (Non-English.)

Winston A, McAllister J, Amin J, Cooper DA, Carr A. The use of a triple nucleoside–nucleotide regimen for nonoccupational HIV post-exposure prophylaxis. *HIV Med* 2005;**6**:191–7. (Case note review.)

#### Cost-effectiveness studies

Allen UD, Read S, Gafni A. Zidovudine for chemoprophylaxis after occupational exposure to HIV-infected blood: an economic evaluation. *Clin Infect Dis* 1992;**14**:822–30. (Occupational exposure.)

Barham L, Lewis D, Latimer N. One to one interventions to reduce sexually transmitted infections and under the age of 18 conceptions: a systematic review of the

economic evaluations. *Sex Transm Infect* 2007;**83**:441–6. (Not PEP.)

Creese A, Floyd K, Alban A, Guinness L. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence [erratum appears in *Lancet* 2002;**360**:880]. *Lancet* 2002;**359**:1635–43. (Not PEP.)

Forst LS, Fletcher B. HIV prophylaxis for health care workers. *J Occup Environ Med* 1997;**39**:1212–19. (Occupational exposure.)

Greub G, Gallant S, Zurn P, Vannotti M, Burgisser P, Francioli P, *et al*. Spare non-occupational HIV post-exposure prophylaxis by active contacting and testing of the source person. *AIDS* 2002;**16**:1171–6. (Not an economic evaluation.)

Hornberger J. A systematic review of cost–utility analyses in HIV/AIDS: implications for public policy. *Med Decis Making* 2007;**27**:789–821. (Not an economic evaluation of PEP.)

Marin MG, Van LJ, Yee A, Bonner E, Glied S. Cost-effectiveness of a post-exposure HIV chemoprophylaxis program for blood exposures in health care workers. *J Occup Environ Med* 1999;**41**:754–60. (Occupational exposure.)

Pinkerton SD, Holtgrave DR, Pinkerton HJ. Cost-effectiveness of chemoprophylaxis after occupational exposure to HIV. *Arch Intern Med* 1997;**157**:1972–80. (Occupational exposure.)

Scheid DC, Hamm RM, Stevens KW. Cost-effectiveness of human immunodeficiency virus postexposure prophylaxis for healthcare workers. *Pharmacoeconomics* 2000;**18**:355–68. (Occupational exposure.)

## Appendix 4

### Data extraction of clinical effectiveness study

Reference and design	Intervention	Participants	Outcome measures
<p>Author: Schechter <i>et al.</i><sup>21</sup></p> <p>Year: 2004</p> <p>Country: Brazil</p> <p>Study design: cohort study</p> <p>Number of centres: one</p> <p>Funding: GlaxoSmithKline, Conselho Nacional de Desenvolvimento Científico e Tecnológico, National Institute of Allergy and Infectious Diseases (research career award), Fogarty International Center (grant)</p>	<p>Intervention: postexposure prophylaxis (PEP): zidovudine 300 mg and lamivudine 150 mg orally, fixed dose combination tablet, twice daily for 28 days</p> <p>Initial 4-day supply of zidovudine and lamivudine to be taken post eligible exposure; additional 24-day supply provided for exposures deemed eligible by study personnel</p> <p>Subjects were instructed to begin taking the study regimen immediately after eligible exposures and in no circumstances &gt; 48 hours after the exposure</p> <p>Control: no PEP</p>	<p>Number of participants: 200 enrolled in the study</p> <p>Intervention: 68 took PEP at least once; control: 132</p> <p>Sample attrition/dropout: 94% (<math>n = 187</math>) followed up for 24 months or until seroconversion; two excluded immediately because they had no follow-up data; seven (53.9%) had last interview at 6 months; two (15.4%) had last interview at 12 months; four (30.8%) had last interview at 18 months</p> <p>Inclusion criteria for study entry: male gender, confirmed HIV seronegativity, reported homosexual or bisexual behaviour, sexually active, defined as anticipated sexual activity in the next 6 months, willingness to use PEP after high-risk exposures, age 18–35 years</p> <p>Exclusion criteria for study entry: high-risk exposures for HIV in the previous 48 hours, anaemia, leukopenia or hepatic enzyme abnormalities at baseline, history of allergy or intolerance to any of the study medications</p> <p>Characteristics of participants: the cohort was recruited from former participants of an HIV seroconversion study conducted among high-risk men who have sex with men</p> <p>Intervention: see baseline characteristics table below</p> <p>Control: 132 did not take PEP – 86 did not take PEP despite reporting at least one instance of high-risk behaviour, 46 denied any high-risk behaviours during the study period</p> <p>Study participants were recruited from a well-characterised HIV incidence study cohort. The authors took the relationships between follow-up time, previously identified risk factors for new HIV infection and HIV incidence and applied them to the current cohort to produce an expected number of incident HIV cases in the absence of PEP</p> <p>Participants who did not start PEP were instructed to return every 6 months for an evaluation</p>	<p>Outcomes: reported behaviour, PEP utilisation, adverse events, incident HIV infection</p> <p>Observed and expected incidences were compared</p> <p>Method of assessing outcomes: detailed history taken at each visit, physical examination with focus on the presence of sexually transmitted diseases. Laboratory evaluation to assess for potential medication toxicity at baseline, 12- and 24-month visits. Participants to report symptoms consistent with severe toxicity. For participants who seroconverted during the study and who previously used PEP, polymerase chain reaction was performed on blood samples at the beginning and end of the PEP course to ensure that the seroconversion was unrelated to that exposure. Additional laboratory evaluations were undertaken for persons who took PEP based on symptoms that could have been caused by the study medications or if there were other medical reasons to suspect an increased likelihood of PEP-related side effects</p> <p>HIV seroconversion was defined as HIV enzyme-linked immunoabsorbent assay (ELISA) seronegativity at the baseline visit with a subsequent positive ELISA and western blot during a follow-up visit</p> <p>Drug-resistant HIV was assessed for the one participant in whom PEP failed</p> <p>Recruitment dates: July 1995–June 1998</p> <p>Follow up: median 24.2 months</p>

*continued*

<b>Baseline characteristics</b>	<b>PEP (n = 68)</b>	<b>No PEP (n = 132)</b>	<b>Total (n = 200)</b>	<b>p-value</b>
Age (years), median	28	28	28	$p = 0.83$
Race, n (%):				
White	34 (50)	60 (45)	94 (47)	$p = 0.69$
Black	15 (22)	26 (20)	41 (21)	
Mixed	3 (4)	11 (8)	14 (7)	
Other	16 (24)	35 (27)	51 (26)	
Completed high school, n (%)	55 (81)	93 (70)	148 (74)	$p = 0.11$
Income per month (Brazilian reais), median	445	480	465	$p = 0.57$
Receptive anal sex last 6 months, n (%)	48 (71)	84 (64)	132 (66)	$p = 0.33$
Unprotected receptive anal sex last 6 months, n (%)	23 (34)	34 (26)	57 (29)	$p = 0.23$
Insertive anal sex last 6 months, n (%)	46 (68)	93 (70)	139 (70)	$p = 0.68$
Unprotected insertive anal sex last 6 months, n (%)	20 (29)	39 (30)	59 (30)	$p = 0.98$
History of gonorrhoea last 6 months, n (%)	7 (10)	32 (24)	39 (20)	$p = 0.02$
Illicit drug use, n (%)	8 (12)	17 (13)	25 (13)	$p = 0.82$
Hepatitis B core antibody positive, n (%)	23 (34)	34 (26)	57 (29)	$p = 0.22$
Comments: The two groups were comparable on age, race, education, income, risk behaviours at enrolment, illicit drug use and hepatitis B seroprevalence				
<b>Outcomes: HIV incidence</b>	<b>PEP (n = 68)</b>	<b>No PEP (n = 132)</b>		<b>p-value</b>
Seroconversion to HIV	1	10		Not reported
Comments: 11 subjects had new HIV infections during the course of the study, for an overall seroincidence of 2.9 per 100 person-years (95% CI 1.4–5.1). Based on the risk profile of the study participants and the experience of the authors' previous cohort study the expected number of new HIV infections was 11.8 ( $p > 0.97$ compared with the observed 11 infections), for an expected seroincidence of 3.1 per 100 person-years ( $p > 0.97$ compared with the observed seroincidence of 2.9)				
<b>Outcomes: PEP use (28-day course)</b>	<b>PEP (n = 68)</b>	<b>No PEP (n = 132)</b>		<b>p-value</b>
Prescribed once, n (%)	49 (72.1)	–		–
Prescribed twice, n (%)	14 (20.6)	–		–
Prescribed three times, n (%)	2 (2.9)	–		–
Prescribed four times, n (%)	2 (2.9)	–		–
Prescribed nine times, n (%)	1 (1.5)	–		–
PEP utilisation: PEP was initiated a total of 109 times by 68 participants. A total of 100 were considered eligible exposures, for which a 4-week course was prescribed (see above). The most common reasons for not initiating PEP ( $\geq$ one possible response per participant) were sex with a steady partner ( $n = 150$ ), participant did not consider the exposure to be of sufficiently high risk to warrant PEP ( $n = 94$ ) and concerns about side effects ( $n = 23$ )				

<b>Outcomes: non-completed PEP courses</b>	<b>PEP (n = 68)</b>	<b>No PEP (n = 132)</b>	<b>p-value</b>
Did not return to complete course, n	2	–	–
Discontinued because of adverse events, n	7	–	–

Adverse events: At least one side effect was reported in 82% of episodes of PEP use; nausea was the most commonly reported side effect and six discontinuations (of those for adverse events) were due to this. One patient with a history of pancreatitis was instructed to stop taking PEP because of an asymptomatic increase in pancreatic enzymes. Apart from this there were no clinically significant laboratory abnormalities among participants who took PEP.

Adherence: The full 28-day regimen of PEP was completed for 89 (89%) of the eligible exposures, including the participant who seroconverted.

<b>Outcomes: risk behaviours</b>	<b>PEP (n = 68)</b>	<b>No PEP (n = 132)</b>	<b>p-value</b>
Median number of male partners 6 months before baseline (range)	4 (0–50)	2 (0–40)	PEP: $p = 0.43$ ; no PEP: $p = 0.46$
Median number of male partners 6 months before last visit (range)	4 (0–180)	2 (0–100)	PEP: $p = 0.43$ ; no PEP: $p = 0.46$

Authors state that, on average, reported high-risk sexual activities declined over time for both PEP and non-PEP users

<b>Risk behaviours</b>	<b>PEP (n = 68)</b>			<b>No PEP (n = 132)</b>		
	<b>6 months before baseline</b>	<b>6 months before last visit</b>	<b>p-value</b>	<b>6 months before baseline</b>	<b>6 months before last visit</b>	<b>p-value</b>
Unprotected anal intercourse, n (%)	32 (47.1)	27 (39.7)	$p = 0.35$	48 (36.4)	32 (24.2)	$p = 0.008$
Unprotected oral intercourse, n (%)	16 (23.5)	8 (11.8)	$p = 0.06$	32 (24.4)	16 (12.2)	$p = 0.002$
Unprotected vaginal intercourse (%)	1.6	4.7	$p = 0.16$	6.1	8.3	$p = 0.26$

#### **Additional comments**

- The study regimen was chosen because, at the time of the study, a two-drug regimen was recommended for most HIV exposures that warrant PEP
- PEP failure was defined as a documented HIV seroconversion that occurred within 2 months after the exposure for which PEP was taken. Seroconversions that occurred  $\geq 2$  months after the exposure for which PEP was taken were not considered as PEP failures

#### **Methodological comments**

- Allocation to treatment groups: Participants decided whether to initiate PEP after a high-risk exposure. For seroconversion to HIV PEP users were compared with non-users
- Blinding: No blinding of assessors at follow-up visits
- Comparability of treatment groups: The groups that were compared within this study for seroconversions, PEP vs no PEP, were comparable at baseline

*continued*

- Method of data analysis: Data analysis was performed using SAS version 6.12. Comparisons between groups were analysed using chi-squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Comparisons of numbers of male partners at 6 months before baseline and at last interview were analysed using the signed rank test. Behaviour practices over time were examined using the McNemar test. Authors used the final interview that individuals participated in for those participants who did not have a 24-month interview. Incidence rates are expressed as the incidence of seroconversions per 100 person-years of follow-up and exact 95% confidence limits were calculated.
- The 'control' was modelled by fitting a binomial regression model to the first cohort data with a complementary log (-log) link function that accounts for previously identified risk factors for incidence of HIV in that cohort. The coefficients from that model were applied to the covariate and follow-up patterns of current participants to calculate the expected number of HIV seroconversions and expected HIV seroincidence
- Sample size/power calculation: No power calculation was performed
- Attrition/dropout: A cohort of 200 was enrolled; of these 68 took the study drug 109 times

**General comments**

- Generalisability: The cohort was recruited from former participants of an HIV seroincidence study conducted among high-risk men who have sex with men aged 18–35 years
- Outcome measures: The outcome measures were relevant to the study area
- Intercentre variability: N/A
- Conflicts of interest: Study was funded by GlaxoSmithKline, Conselho Nacional de Desenvolvimento Científico e Tecnológico, National Institute of Allergy and Infectious Diseases (research career award), Fogarty International Center (grant)

## Appendix 5

### Data extraction of cost-effectiveness studies

<b>Study characteristics</b>	
Study	Pinkerton <i>et al.</i> 1998 <sup>22</sup>
Country of origin	US
Base year prices	1996 US\$
Intervention	Postexposure prophylaxis (PEP) following potential HIV exposure through sexual contact with a partner who may or may not be infected, compared with a 'no programme option'. PEP was assumed to consist of a 4-week regimen of triple combination therapy with zidovudine (ZDV), lamivudine (3TC) and the protease inhibitor indinavir and was assumed to be as effective as ZDV monotherapy in the occupational setting
Study type	Cost-utility analysis; decision-analytical model to evaluate cost-effectiveness
Study group	A hypothetical cohort of 10,000 patients who reported sexual intercourse with a partner of unknown HIV status
Perspective	Societal
Industry role	None stated
Effectiveness parameter	Probability PEP effective 0.79 from occupational study <sup>26</sup>
Costs assessment	Primary cost of PEP is drug therapy: cost of PEP triple therapy per patient: US\$619. Obtained from published literature (references given)
Utilities assessment	Quality-adjusted life-years (QALYs) saved per infection prevented: 11.23. Obtained from published literature (references given)
Ranges for sensitivity analyses	Effectiveness: 0.43–0.94 Costs: US\$400–955 QALYs saved: 13.18–9.34
Study base case 'headline' predictions/findings	PEP should be restricted to partners of infected persons, to patients reporting unprotected receptive anal intercourse and possibly to cases where there is substantial likelihood that the partner is infected
<b>Results</b>	
Base case	<p>Authors use predetermined threshold of US\$50,000 per QALY saved</p> <p>The base-case analysis for a cohort of 10,000 patients receiving PEP reported: 19.62 HIV infections averted following receptive anal intercourse; 0.59 HIV infections averted following insertive anal intercourse; 0.11 HIV infections averted following receptive vaginal intercourse; and 0.07 HIV infections averted following insertive vaginal intercourse</p> <p>Authors report that prophylaxis is not cost-effective for sex act/role combinations other than receptive anal intercourse (all cost-utility ratios exceed US\$750,000 per QALY saved)</p> <p>They also report that PEP following receptive vaginal intercourse appears to be cost-effective if certain that the partner is infected [HIV prevalence (probability of HIV infection) has to be &gt; 0.73]</p> <p>PEP following insertive exposures is reported to be marginally cost-effective at best (the cost-utility ratio is &gt; US\$100,000 per QALY saved regardless of the probability of HIV infection)</p> <p>The cost-utility ratio for ZDV/3TC PEP following receptive anal intercourse among men who have sex with men is US\$6354 per QALY saved</p>

continued

**Study characteristics****Sensitivity analysis**

The sensitivity analyses indicated that the results for the receptive anal case were not sensitive to changes in the parameter values and PEP was always cost-effective across a range of values

Both the insertive anal and insertive vaginal cases were not sensitive and were not cost-effective across a (plausible) range of values. The receptive vaginal case was sensitive to the probability of the sexual partner of the patient being HIV infected. In this case, if the probability of infection is  $> 0.73$  then PEP may be cost-effective

PEP is cost saving for receptive anal intercourse if the probability that the partner is infected is  $> 0.25$

Triple PEP therapy was unlikely to be cost-effective relative to dual combination PEP (the additional drug costs will not be offset by treatment savings)

The results did not appear to be sensitive to repeated exposure and PEP

**Conclusions**

PEP following suspected sexual exposure to HIV is only cost-effective for receptive anal intercourse or receptive vaginal intercourse with a partner who is likely to be infected

If the probability that the partner is infected is very small then PEP may not be cost-effective following receptive anal intercourse

PEP after insertive vaginal intercourse or insertive anal intercourse is probably not cost-effective, regardless of the partner's risk status

The authors report that from a purely economic standpoint PEP should be restricted to partners of infected persons (e.g. serodiscordant couples), to patients reporting unprotected receptive anal intercourse (including condom breakage) and possibly to cases in which there is a substantial likelihood that the partner is infected. Providing PEP to all who request it does not appear to be an economically efficient use of limited HIV prevention and treatment resources

**Caveats**

Uncertainty in the effectiveness of PEP has implications for its cost-effectiveness

Authors have assumed that PEP is completely ineffective when the antiretroviral regimen is discontinued prematurely

Analysis assumes that all individuals receiving PEP are uninfected and that PEP therefore can prevent an infection. Therefore, the above results may disproportionately overstate the cost-effectiveness of PEP in high prevalence communities

PEP for receptive anal intercourse may not be cost-effective (authors state US\$100,000 per QALY) if the probability that the partner is infected is quite small

There are limitations with the per-contact probabilities: they are not known with certainty and the probable ranges may overlap. Stage of disease, viral load, genetics and facilitation by sexually transmitted diseases are believed to also affect the risk of transmission; even greater uncertainty surrounds the probability of transmission for oral sex



Study characteristics	
Study	Pinkerton <i>et al.</i> 2004 <sup>23</sup>
Country of origin	US
Base year prices	2000 US\$
Intervention	An initial 7-day supply of antiretroviral medication; additional 21 days supplied at follow-up visit 7 days later
Study type	Cost–utility study
Study group	401 participants with possible non-occupational exposure to HIV [sexual, needle sharing, non-occupational needlestick injury, other (bite or assault)]. Distribution of patients was by exposure type, percentage of patients who completed PEP in each exposure group and proportion of completers with a known HIV-infected source. Patients who reported multiple exposures were classified according to the highest risk exposure. In total, 312 patients (78%) were known to have completed the PEP regimen; 46% reported that they knew that their source was infected with HIV
Perspective	Societal: included all identifiable costs, regardless of who bore these
Industry role	None stated (one of the authors has received honorariums from GlaxoSmithKline, Bristol-Myers Squibb and Agouron Pharmaceuticals)
Effectiveness parameter	Probability PEP effective 0.81 from occupational study <sup>27</sup>
Costs assessment	Five drug costs (for the five different drugs): US\$312, US\$267, US\$222, US\$280 and US\$679 from published literature (reference given)  Itemised laboratory and clinic costs from published literature (reference given)
Utilities assessment	Wages and travel costs from financial records kept by study investigators Quality-adjusted life-years (QALYs) lost per HIV infection: 9.31. Obtained from published literature (reference given)
Ranges for sensitivity analyses	Effectiveness: 0.48–1.0 Costs: least expensive regimen US\$502 and most expensive regimen US\$1258 QALYS saved: 4.28–18.23
Study base case 'headline' predictions/findings	For this study population, HIV PEP was cost-effective by conventional standards and cost saving for persons seeking PEP after male–male receptive intercourse

*continued*

**Study characteristics****Results****Base case**

Use of PEP reduced the expected number of infections to 0.77 and therefore prevented an estimated 1.59 infections (expected infections in the absence of PEP in the exposures reported by the 401 patients would be 2.36). The authors have adjusted for continuing risk behaviours over the subsequent 10 years and report that PEP in this case would have averted 1.26 infections and saved US\$281,323 medical care costs and 11.74 associated QALYs

PEP effectiveness was set at 81%

The overall cost–utility ratio was US\$14,449 per QALY saved

The authors used thresholds of US\$40,000–\$60,000 per QALY for cost-effectiveness and US\$200,000 for non-cost-effectiveness

In total, 96% of averted infections were among men who reported exposure through receptive anal intercourse (RAI) with other men. When restricted to this subgroup the PEP programme was cost saving

Exposure through injection drugs: US\$86,462 per QALY saved; male–female RAI: US\$165,289 per QALY saved

Overall cost–utility ratio for men reporting exposure through male–male sex (receptive or insertive anal sex, receptive oral sex or ‘other’) was US\$8607 per QALY saved. Cost–utility ratio for all other exposures combined was US\$258,667 per QALY saved

The PEP programme was cost saving for patients who reported that their partner was HIV positive. The cost–utility ratio was US\$58,025 when the HIV status of the partner was unknown. The authors state that these results are mainly driven by the men with exposures through RAI as these were cost-saving; the cost–utility ratio for the 93 patients who were exposed through other routes was US\$278,671

Authors assumed that patients remained at risk of infection for 10 years after participating in the PEP programme, with an annual risk equal to the incidence of infection in the associated exposure group

**Sensitivity analysis**

The programme remained cost-effective when the PEP effectiveness parameter was set to 48%

The programme would not be cost saving even if the antiretroviral regimen was 100% effective

The programme was cost-effective for PEP completion rates > 29%

The programme remained cost-effective regardless of the percentage of partners known to be infected with HIV or the prevalence of infection among partners whose HIV status was unknown

The results were not sensitive to the HIV-related treatment cost and QALYs saved parameters

The programme was cost-effective provided that at least 2.24 QALYs were saved per averted infection and was cost-effective regardless of the cost of treating HIV and AIDS

**Study characteristics****Sensitivity analysis**

The programme was still cost-effective if a 5% discount rate was used. When a 0% discount rate was used the cost–utility ratio decreased to US\$2385 per QALY saved

The cost–utility ratio was most sensitive to RAI transmission probability. The threshold analysis indicated that the PEP programme would be cost saving overall if this probability exceeded 0.033 and would be cost-effective (cost–utility ratio of US\$60,000 per QALY saved) for probabilities as small as 0.009 (base case was 0.02)

The programme would not be cost-effective (cost–utility ratio > US\$200,000 per QALY saved) if the per-exposure transmission probability for RAI was less than 0.003

Using alternative published HIV incidence and prevalence rates for San Francisco: US\$11,081 per QALY saved, lower than the base-case value

Cost–utility ratio increased to US\$71,381 when the transmission probabilities were set to their smallest values and decreased to less than zero (cost saving) when they were set to their largest values

**Conclusions**

HIV PEP was cost-effective by conventional standards (here defined as between US\$40,000 and US\$60,000) and cost saving for men seeking PEP after male–male RAI. It is possibly cost-effective for injection drug exposures and women reporting RAI but probably not cost-effective for other exposures. Although fewer than half of the patients reported male–male RAI, the PEP programme was cost-effective overall and authors suggest an economically sound use of societal health promotion resources

**Caveats**

The effectiveness of PEP after sexual exposures is unknown: authors assumed that dual and triple drug PEP was as effective as zidovudine PEP in a case–control study of occupational exposures

Differences in the transmission dynamics of sexual (mucosal) and occupational (percutaneous) exposures may also impact on PEP effectiveness

<b>Study characteristics</b>	
Study	Pinkerton <i>et al.</i> 2004 <sup>24</sup>
Country of origin	US
Base year prices	2000 US\$
Intervention	Hypothetical PEP programme in 96 US metropolitan statistical areas (MSAs), based on San Francisco PEP programme (no further detail provided in this paper)
Study type	Cost-effectiveness analysis
Study group	Information on PEP clients was taken from the San Francisco PEP programme. Potential PEP clients were divided into four risk groups based on exposure type: men who have sex with men (MSM), intravenous drug users (IDUs), male/female heterosexuals and other non-occupational exposures (bites, assaults involving mucosal exposure). It was assumed that the same proportion of each group would access PEP in each MSA as they had in the San Francisco PEP study. This was then used to estimate the number of potential PEP clients in each group in each MSA. Previously published estimates of HIV prevalence in the 96 MSAs for each risk group were used. It was assumed that the distribution of PEP-prompting exposures (e.g. receptive anal intercourse, injection-related exposure, etc.) in each MSAs would mimic the distribution observed in San Francisco. It was also assumed that risk group exposure could be inferred from exposure type (e.g. man reporting vaginal intercourse is in heterosexual group and source partner belongs to same group; one exception: non-occupational needlestick injuries usually come from discarded needles and so the HIV prevalence in IDUs was used to estimate the prevalence of infection among needlestick exposure sources)
Perspective	Societal
Industry role	Not stated
Effectiveness parameter	Probability PEP effective 0.81 from occupational study <sup>27</sup>
Costs assessment	Total cost of PEP programme in a particular MSA was calculated using a formula (given) including: drug costs for completers US\$597 (non-completers US\$454); laboratory work completers US\$26 (non-completers US\$14); other clinical services completers US\$523 (non-completers US\$240). Obtained from published literature (references given) and data from San Francisco PEP programme data
Utilities assessment	Quality-adjusted life-years (QALYs) saved per infection prevented: 9.31. Obtained from published literature (references given)
Ranges for sensitivity analyses	Effectiveness: 0.48–0.94  Costs: not used  QALYs lost: 10.29–8.37
Study base case 'headline' predictions/findings	Proportion of clients completing therapy was set at 77.8% (based on San Francisco PEP study). The effectiveness of PEP in preventing HIV infection was assumed to be 81%, based on the findings of a case-control study in health-care workers (HCWs) exposed occupationally. Across the 96 MSAs the hypothetical PEP programmes would serve 19,154 clients at a total cost of US\$21.7m, averting 63.9 HIV infections (primarily MSM – 96.1% of the averted infections, constituting 75.9% of PEP clients)
<b>Results</b>	
Base case	The combined cost-utility ratio (CUR) for the 96 MSA was US\$12,567 per QALY saved. This ranged from US\$4137 (San Francisco) to US\$39,101 (Stockton-Lodi MSA) per QALY saved. Only two MSAs had CUR greater than US\$30,000. The mean and median CUR were US\$15,728 and US\$15,367 respectively  PEP was cost saving (CUR < US\$0) for male-male and male-female receptive anal intercourse exposures  The CUR for needle-sharing exposures and needlestick exposures was US\$97,867 and US\$159,686 respectively  CUR exceeded \$380,000 per QALY saved for all other types of exposure

**Study characteristics****Sensitivity analysis**

Key parameters were varied one at a time in univariate sensitivity analyses. Only one of the parameter manipulations (reducing the per-exposure transmission probability for receptive anal intercourse from 0.02 to 0.008) resulted in a CUR > US\$60,000 per QALY saved.

Individually varying the other transmission probabilities within plausible ranges produced < 4% deviation from the base CUR

Several prevalence-related measures were moderately to strongly correlated with the inverse of the CUR values for individual MSAs (although overall the CUR across the 96 MSAs was not especially sensitive to the prevalence of infection)

The authors report that the results were moderately sensitive to the effectiveness of PEP and somewhat sensitive to the proportions of persons who completed the PEP regimen, the proportion of PEP clients with known infected source partners and the lifetime costs of medical care and lost QALYs associated with a case of HIV infection

In particular, the proportion of the 'high-risk' MSM, IDUs, heterosexual subpopulation classified as HIV-infected MSM was strongly correlated with the inverse CUR

**Conclusions**

PEP for HIV could be a cost-effective adjunct to existing HIV prevention efforts

Overall across the 96 MSAs, PEP was cost saving for receptive anal intercourse and possibly cost-effective for needle sharing and non-occupational needlestick injuries, but of questionable economic value for all other types of exposure

PEP was highly cost-effective for MSM, less so for IDUs and high-risk women, and probably not cost-effective for general population exposures or heterosexual men

**Caveats**

The effectiveness of PEP in preventing infection and the per-exposure transmission probability are not established. HIV prevalence and population size estimates were based on a study published in 1996 (therefore reflecting HIV epidemiology in the early 1990s). Analysis did not take into account the ages of clients (which would affect the number of QALYs lost to infection) or whether or not a particular client completed the PEP regimen or was known to have been exposed to HIV by an HIV-positive partner. The analysis assumed that the distribution of client exposure groups in each MSA would mimic that observed in the San Francisco study. Implementation of PEP services in a given locale is likely to differ from the San Francisco experience

<b>Study characteristics</b>	
Study	Herida et al. 2006 <sup>25</sup>
Country of origin	France
Base year prices	2002 Euros
Intervention	Comparison of PEP programme with 'no PEP' alternative. For patients in PEP programme clinicians prescribe drugs of their choice (usually tri-therapy containing protease inhibitor). HIV/hepatitis B/hepatitis C serology tests, a pregnancy test and 'other' laboratory tests carried out at the baseline visit. Three follow-up visits scheduled at days 15, 30 and 90 after exposure. Laboratory tests scheduled at day 15. HIV and hepatitis serology is repeated at day 30 (end of treatment), 120 and 180. PEP physician provides patient with 4-week supply of antiretroviral drugs and counselling at each visit. Information on patients' characteristics, risk of exposure, treatments prescribed, serology and potential adverse effects were recorded by clinicians during follow-up visits and entered in an anonymous database. A total of 15 drugs were used in various two-drug (9%), three-drug (90%) and four-drug (1%) combinations
Study type	Cost-effectiveness analysis based on decision tree. As parameters vary according to exposure risks, a separate decision tree was built for each type of exposure event
Study group	12,551 individuals sought PEP between July 1999 and December 2003. Of these, 8958 (71%) were prescribed PEP and included in a national hospital-based voluntary surveillance of PEP programme for both occupational and non-occupational exposure (set up in 1999); 6812 (76%) of those prescribed PEP had a sexual exposure event, 2092 (23.4%) had an occupational exposure event (68.9% of these were HCWs) and 54 (0.6%) were exposed through sharing drug injection equipment. In the sexual exposure group, 2546 (28.4%) were men who have sex with men (MSM) and 4266 (47.6%) were heterosexual. The source was known to be HIV infected for 2413 individuals (27.1%)
Perspective	Societal
Industry role	Not stated
Effectiveness parameter	Probability PEP effective 0.80 from occupational study <sup>27</sup> (in fact, 0.81 from reference)
Costs assessment	Total cost: €988; cost of PEP therapy per patient: €745; physician visits: €80; laboratory costs: €163. Obtained from PEP treatment prescribed between 1999 and 2003 using published prices (reference given)
Utilities assessment	Quality-adjusted life-years (QALYs) saved per infection prevented: 8.34. Obtained from published literature (references given)
Ranges for sensitivity analyses	Effectiveness: 0.48–0.94 Costs: not used QALYs saved: 11.58–4.31
Study base case 'headline' predictions/findings	Number of infections averted and number of QALYs saved during 1999–2003. On the basis of the model it was estimated that among 8958 treated individuals, 12 cases of HIV infection would have occurred if none had received PEP and 4.3 cases would have occurred if all had received PEP
<b>Results</b>	
Base case	Five individuals became infected during follow-up – two were considered PEP failures (receptive anal intercourse in a gay man and a women); the three remaining patients (all MSM) were considered by physicians to have seroconversions resulting from high-risk sexual behaviour after the PEP treatment  Cost of the PEP programme (providing PEP to 8958 individuals) was estimated at €7,670,002 and the cost-effectiveness ratio (CER) at €996,104 per infection averted  The total cost of the programme (including the cost of caring for the estimated 4.3 cases of HIV infection that occurred among the 8958 treated individuals) was €3,035,075  The cost of caring for the estimated 12 cases of HIV infection that would have occurred without the PEP programme was €8,752,150  The estimated marginal cost was €5,717,075 and the CER was €88,692 per QALY saved

**Study characteristics****Sensitivity analysis**

There were major differences in the CER according to the type of exposure. PEP after receptive anal intercourse with an HIV-infected individual was cost saving in men and women (negative ratio of €22,141 and €22,031 per QALY saved respectively). PEP after an intravenous drug user (IDU) sharing needle with an HIV-infected person was cost saving (€1141 per QALY saved). PEP is cost-effective (< €50,000 per QALY saved) for HCW after percutaneous exposure to material from an HIV-infected patient, and for MSM having receptive anal intercourse with a partner of unknown status. These five exposures accounted for 15.7% of prescriptions. In other exposures PEP was not considered cost-effective: 72% of exposures had CER > €200,000 per QALY saved and 52% of cases had CER > €2m per QALY saved

One-way sensitivity analyses were performed on compliance according to the low estimation of the compliance, and on life expectancy of HIV-infected individuals according to the higher lifetime HIV cost resulting from longer survival (other parameters were kept fixed at base-case values)

Patients with missing follow-up information were considered as compliant as those known to have attended the 1-month follow-up (this compliance was used in the base case); patients with missing follow-up information were considered as lost to follow-up with a compliance = 0 (this estimated compliance was used in the sensitivity analysis). In this case the programme would prevent 3.8 infections and save 31.7 QALYs at a marginal cost of €5,087,998, resulting in a CER of €160,382 per QALY saved. As before, PEP after receptive anal intercourse with an HIV-infected individual remains cost saving (−€17,778 and −€18,860 per QALY saved for MSM and heterosexual women respectively). PEP to an IDU after needle sharing with an HIV-infected person remains cost-effective but is no longer cost saving (€18,445 per QALY saved)

One-way sensitivity analyses were performed on the life expectancy of HIV-infected individuals according to the higher value of life expectancy and higher lifetime HIV cost resulting from longer survival (16.82 QALYs compared to base case of 12.79, and €331,869 lifetime HIV/AIDS care costs compared to base case of €252,768; both costs and QALYs are discounted at 3%). According to this scenario the programme is less cost-effective than the base case (33.3 QALYs prevented at marginal cost of €5,105,998; CER = €153,241 per QALY saved). The three exposure risks with negative ratios in the base-case analysis remain cost saving but with higher cost ratios

Threshold analyses were performed for exposures with CER under €200,000 per QALY saved, using minimum values of prevalence, per-contact HIV transmission or compliance required to achieve the cost-saving threshold (€0 per QALY saved) or the cost-effective threshold (€50,000 per QALY saved). PEP for MSM after receptive anal intercourse with a partner of unknown HIV status would be cost saving for a per-contact transmission risk of at least equal to 0.0411 or an HIV prevalence of at least 0.208. After needle sharing with an individual of unknown serostatus, to achieve cost-effectiveness (€50,000 per QALY saved) the compliance should be ≥ 0.92 with both the highest values of prevalence (0.21) and of the per-contact transmission risk (0.0092). For receptive vaginal intercourse with an HIV-infected partner, a per-contact transmission risk equal to 0.0208 would allow the CER to be reached

**Conclusions**

According to international standards that use US\$50,000 per QALY saved as a threshold, the French PEP programme appears not to be a cost-effective intervention; only 15.7% of PEP courses in the French programme can be considered cost-effective

The PEP programme is less cost-effective than other French prevention or screening programmes

*continued*

### Study characteristics

#### Caveats

The authors list several limitations. They had to make several initial assumptions (and used sensitivity analyses to overcome this). Compliance could only be estimated for 47% of PEP prescriptions and so overall compliance was estimated at 0.75. Any overestimation of compliance would improve the CER (demonstrated in the sensitivity analysis by using low estimate of compliance)

There are no available data for lifetime HIV/AIDS costs in France and so the authors estimated these

The model did not take into account the possibility that some patients seeking PEP may continue at-risk behaviour

The study did not consider PEP adverse events. The authors state that taking these into account would further reduce the CER of the overall PEP programme: 65% of 2138 treated patients in the French PEP programme had clinical adverse events and 8% presented with biological abnormalities

The number of HIV infections predicted by the model was higher than that seen; however, HIV serology 6 months after PEP initiation was only available for 18% of patients and so the true number of PEP failures may be higher





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***We look forward to hearing from you.***