

STANDARDS RELATED DOCUMENT

AJMedP-4-6

**UK GUIDELINE FOR THE USE OF HIV
POST-EXPOSURE PROPHYLAXIS
FOLLOWING
SEXUAL EXPOSURE, 2015**

Edition A Version 1

JULY 2018



NORTH ATLANTIC TREATY ORGANIZATION

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Zoltán GULYÁS
Brigadier General, HUNAF
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UK guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure, 2015

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Abstract

We present the updated British Association for Sexual Health and HIV guidelines for HIV post-exposure prophylaxis following sexual exposure (PEPSE). This document includes a review of the current data to support the use of PEPSE, considers how to calculate the risks of infection after a potential exposure, and provides recommendations on when PEPSE should and should not be considered. We also review which medications to use for PEPSE, provide a checklist for initial assessment, and make recommendations for monitoring individuals receiving PEPSE. Special scenarios, cost-effectiveness of PEPSE, and issues relating to service provision are also discussed. Throughout the document, the place of PEPSE within the broader context of other HIV prevention strategies is considered.

Keywords

Post-exposure prophylaxis (PEP), sexual exposure, HIV prevention, BASHH guidelines, antiretroviral therapy

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New in the 2015 guidelines

1. Post-exposure prophylaxis following sexual exposure (PEPSE) is not routinely recommended after any type of sex with HIV-positive source on anti-retroviral therapy (ART) with a **confirmed** and **sustained** (>6 months) undetectable plasma HIV viral load (VL) (<200 c/mL).
2. Initiation of PEPSE is recommended as soon as possible after exposure, preferably within 24 h of exposure but can be offered up to 72 h.
3. The first-line regimen is Truvada and raltegravir.
4. Routine blood test monitoring is not recommended for raltegravir-based post-exposure prophylaxis (PEP) with normal baseline blood tests, unless clinically indicated.
5. Follow-up HIV testing is recommended 8–12 weeks after exposure.
6. It is acceptable to provide the full 28-day course of PEPSE on first visit to a specialist clinic provided the recipient has met with a Sexual Health

Adviser, source testing is not possible and there are no clinical or adherence concerns.

7. PEPSE is an emergency method of HIV prevention and should not be considered or encouraged as a method of first resort. Other evidence-based HIV prevention methods should be discussed.

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NICE has accredited the process used by BASHH to produce its European guideline for the use of HIV post-exposure prophylaxis following sexual exposure. Accreditation is valid for 5 years from 2011. More information on accreditation can be viewed at www.nice.org.uk/accreditation

8. If further risk occurs during the last two days of the PEPSE course, then PEPSE should be continued for 48 h after the last high-risk sexual exposure.
9. In the event of a new HIV diagnosis after initiation of PEP, PEP should be continued pending discussion with an HIV specialist. Long-term ART may be beneficial in the setting of primary HIV infection.
10. If the recipient has missed more than 48 h of PEPSE, then the course should be discontinued.

Summary of recommendations

When to use PEPSE?

- We recommend the use of PEPSE where there is a significant risk of HIV transmission (risk > 1/1000), see Table 3 (1C).

If the source is of unknown status:

- We suggest proactive attempts are made to establish the HIV status of the source (2C).

Source individual known to be HIV-positive:

- Attempts should be made at the earliest opportunity to determine the HIV VL, resistance profile and treatment history (1D).
- PEPSE is no longer recommended if the source is on ART with a **confirmed** and **sustained** (>6 months) undetectable plasma HIV VL (<200 c/mL) (1B). However, if there are any doubts about the HIV VL history or the source's adherence to ART, then PEP should be given following unprotected receptive anal intercourse.
- Individuals should be encouraged to attend for formal PEP assessment and verification of source's HIV details even when they believe the source has an undetectable HIV VL (GPP).
- If drug resistance is suspected in the source, the regimen should be tailored accordingly following discussion with an HIV specialist (1D).

What to use for PEPSE?

- We recommend the use of Truvada and raltegravir as the regimen of choice for PEPSE (1B). See Table 4 for alternatives regimens and Appendix A for interactions.

- We recommend that an accurate medication history should be taken, including the use of over the counter medication, vitamins/minerals, herbal remedies, and recreational drugs before PEPSE is prescribed (1D).

How to use PEPSE?

- We recommend PEPSE should be initiated as soon as possible after exposure, preferably within 24 h, but can be considered up to 72 h (1D).
- We do not recommend giving PEPSE beyond 72 h (1D).
- We recommend that the duration of PEPSE should be 28 days (1D).
- PEPSE should not be considered or encouraged as a first-line method of HIV prevention. Other more evidence-based methods should be discussed (1C).
- We recommended that all individuals attending for PEP be strongly encouraged to meet with an appropriate health-care professional competent in sexual health advising to discuss risk reduction. Provision of PEPSE should be fully integrated into counseling around safer sex strategies (1C).
- We suggest individuals seeking PEPSE should be encouraged to attend for future regular sexual health check-ups (2C).
- We recommend that an accurate medication history should be obtained, including use of over the counter medications, vitamins/minerals, herbal remedies, and recreational drugs before PEPSE is prescribed (1D).
- We suggest routine blood test monitoring after initiation of raltegravir-based PEPSE is not necessary unless clinically indicated or if baseline blood tests are abnormal (2C).
- We suggest performing an STI screen at baseline as indicated, as well as at two weeks post-exposure (2C).
- We recommend follow-up HIV testing at 8–12 weeks after exposure (1C).
- We recommend using a fourth generation laboratory venous blood HIV test at baseline and for follow-up testing (1D).
- We suggest offering an ultra-rapid course of hepatitis B vaccination if clinically indicated and the individual has no immunity at baseline (GPP).
- We recommend pregnancy testing in women considering PEPSE (1D). We suggest pregnancy should not alter the decision to start PEPSE (2D). Women must be counseled that antiretroviral agents used for PEPSE are unlicensed in pregnancy and risks/benefits must be carefully discussed (1D).

- In the event of a further high-risk sexual exposure in the last two days of the PEPSE course, the PEP should be continued for 48 h after the last high-risk exposure (2B).
- Individuals experiencing a skin rash or flu-like illness during or after taking PEPSE should be advised to attend for urgent review to exclude an HIV seroconversion illness (2D).
- If the HIV test is positive after PEPSE has already been initiated, we recommend continuing PEPSE pending review by an HIV specialist (GPP).
- For PEPSE to be maximally effective, 24-hour availability is recommended (1C). This should include out of hours expert advice if required (1D).
- Information about PEPSE should be included when counseling individuals at risk of acquiring HIV infection as well as those already diagnosed with HIV infection (2D).

Objectives

We aim to provide evidence-based recommendations for the most appropriate use of HIV post-exposure prophylaxis following sexual exposure (PEPSE). The aim of PEPSE is to prevent HIV transmission. Risk of transmission, timing of post-exposure prophylaxis (PEP), preferred regimen, drug–drug interactions, follow-up, risk reduction, and special scenarios are discussed. Consideration is given to the role of PEPSE within the broader context of HIV prevention and sexual health.

The guideline is intended to be complementary to existing Department of Health and Expert Advisory Group on AIDS (EAGA) guidance on PEP.¹ It is aimed primarily at clinicians and policy-makers in sexual health, sexual assault referral centres (SARCs), and primary and emergency care providers within the UK who should consider the development of appropriate local pathways. It is likely that this guideline will also be used for information provision by voluntary sector agencies to provide information for individuals.

The recommendations are aimed primarily at individuals aged 16 or older and may not be appropriate for use in all situations, including occupational exposures. Decisions to follow these recommendations must be based on the professional judgment of the clinician and consideration of individual patient circumstances and available resources.

Methods

The multidisciplinary guideline-working group developed the guidelines based on processes outlined in the BASHH Framework for Guideline

Development.² The guideline is based on a comprehensive literature review on PEPSE and HIV transmission. All members underwent GRADE training, see Appendix C for more information on the GRADE system. The recommendations are the result of a series of face-to-face and virtual meetings of the Writing Committee and will incorporate input from the public consultation process.

PICO questions were set as:

POPULATIONS: sexual, non-occupational, bite exposure to HIV.

INTERVENTION: post-exposure prophylaxis, PEP, PEPSE, antiretroviral therapy (ART).

COMPARISON: no intervention, ART treatment as prevention, condoms, pre-exposure prophylaxis (PrEP)

OUTCOME: HIV infection, seroconversion, toxicity, completion, sexual behavior, cost-effectiveness.

Search strategy

Current British Association for Sexual Health and HIV (BASHH),³ USA Centers for Disease Control and Prevention,⁴ World Health Organization,⁵ and Australian Society of HIV Medicine guidelines were reviewed.⁶

Medline, Embase, Cochrane Library were searched from January 1990 to November 2014 for all articles relating to HIV post-exposure prophylaxis (985 abstracts reviewed). Search terms were HIV AND post-exposure prophylaxis, PEP, PEPSE, non-occupational, sexual, antiretroviral, chemoprophylaxis. A second search from 2008 to November 2014 was conducted for HIV transmission (2493 abstracts reviewed). Search terms were HIV AND transmission AND risk/risk reduction. Conference abstracts from Conference on Retroviruses and Opportunistic Infection, World AIDS, Interscience Conference on Antimicrobial Agents and Chemotherapy, HIV Drug Therapy from January 2012 to November 2014 were reviewed.

Restrictions: English language papers.

Stakeholder involvement, piloting, and feedback

The guideline-working group included representatives from the BASHH, British HIV Association (BHIVA), EAGA, Society of Sexual Health Advisers, HIV Pharmacy Association, the Terrence Higgins Trust (THT), and the National AIDS Trust (NAT). Patients' perspectives were considered by involvement of THT and NAT, reviewing the literature for information from patient surveys and the public consultation

process. The guideline underwent a peer-review process whereby comments were received by others working in the field and considered at the guideline working group meeting.

Background

Pathogenesis studies indicate that there may be a window of opportunity to avert HIV infection by inhibiting viral replication following an exposure. Once HIV crosses a mucosal barrier, it may take up to 48–72 h before HIV can be detected within regional lymph nodes and up to five days before HIV can be detected in blood.^{7,8} Initiation of ART has been shown to reduce dissemination and replication of virus in all tissues if initiated early after inoculation in an animal model.⁹

Risk of HIV transmission

The probability of HIV transmission depends upon the exposure characteristics, the infectivity of the source, and host susceptibility. Where individuals have multiple exposures within 72 h, a cumulative risk should be considered.

Table 1 shows the estimated HIV prevalence (including both diagnosed and undiagnosed infection) in adults aged over 15–59 years in the UK in 2014. HIV

Table 1. Estimated HIV prevalence (diagnosed and undiagnosed infection) in adults aged 15–59 years in the UK in 2014.

| Population group (aged 15–59 years) ^a | HIV prevalence (%) | |
|--|--------------------|----------|
| | Men | Women |
| Men who have sex with men (MSM)^b | | |
| UK | 5.9 | – |
| London | 12.5 | – |
| Brighton | 13.7 | – |
| Manchester | 8.6 | – |
| Elsewhere in the UK | 3.8 | – |
| Heterosexuals | | |
| Black African ethnicity | 4.1 | 7.1 |
| Non Black African ethnicity | 0.06 | 0.06 |
| Injecting drug users (IDU) | 0.67–1.1 | 0.67–1.1 |

^aThese data are for England and Wales only.

^bThe prevalence of HIV among MSM varies across the UK and is higher in metropolitan areas with large MSM populations.^{6,7}

Prevalence estimates were obtained at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/475712/Shooting_Up_2015_FINAL.pdf

prevalence in other countries can be found in the UNAIDS 2014 Gap report:

<http://www.unaids.org/en/resources/campaigns/2014/2014gapreport/gapreport>

The risk of HIV transmission per exposure from a known HIV-positive individual not on ART is summarized in Table 2. These figures are estimates that have been deduced from cohort and modeling studies.

The risk of an individual acquiring HIV following an exposure can be calculated by multiplying the risk that the source is HIV-positive (Table 1) and the risk per exposure (Table 2):

Risk of HIV transmission

$$= \text{risk that source is HIV positive} \\ \times \text{risk per exposure}$$

For example, if a male presents for PEPSE following unprotected receptive anal intercourse with ejaculation with male partner of unknown HIV status in London:

Risk of HIV transmission

$$= 12.5/100 \times 1/65 = 12.5/6500 = 1/520$$

However, certain factors may increase the risk of HIV transmission and must be considered and discussed in a PEP consultation, see Box 1.

Data supporting the use of PEP against HIV

Animal studies

Animal studies suggest that PEP can be potentially effective and that time to initiation and duration are important. Animal studies are not standardized and use different retroviruses, size of inocula, and modes of administration; this may, at least in part, explain their differing results.

Two studies demonstrated effectiveness of subcutaneous tenofovir in macaque models following intravenous simian immunodeficiency virus (SIV)⁴⁶ or intravaginal HIV-2 inoculation;⁴⁷ efficacy was highest if PEP was administered within 24–36 h and continued for 28 days. In another macaque study, oral zidovudine, lamivudine, and indinavir offered no protection following intravenous exposure,⁴⁸ though this may have been due to inoculation mode and/or size. The same group demonstrated that higher dose oral PEP was effective following intravaginal exposure highlighting the importance of achieving adequate drug concentrations.⁴⁹

Table 2. Risk of HIV transmission per exposure from a known HIV-positive individual not on ART.

| Type of exposure | Estimated risk of HIV transmission per exposure from a known HIV-positive individual not on ART | References |
|--|---|-------------|
| Receptive anal intercourse | 1 in 90 | 10-16 |
| Receptive anal intercourse with ejaculation | 1 in 65 | 10-17 |
| Receptive anal intercourse no ejaculation | 1 in 170 | 17 |
| Insertive anal intercourse | 1 in 666 | 10,12,13,18 |
| Insertive anal intercourse not circumcised | 1 in 161 | 17 |
| Insertive anal intercourse and circumcised | 1 in 909 | 17 |
| Receptive vaginal intercourse | 1 in 1000 | 10,15,19-15 |
| Insertive vaginal intercourse | 1 in 1219 | 14,15,19-25 |
| Semen splash to eye | <1 in 10,000 | 26 |
| Receptive oral sex (giving fellatio) | <1 in 10,000 | 13,20,25,27 |
| Insertive oral sex (receiving fellatio) | <1 in 10,000 | 12,25 |
| Blood transfusion (one unit) | 1 in 1 | 28 |
| Needlestick injury | 1 in 333 | 27,29,30 |
| Sharing injecting equipment (includes chemsex) | 1 in 149 | 26 |
| Human bite | <1 in 10,000 | 31,32 |

ART: antiretroviral therapy.

More recent animal studies have demonstrated effectiveness of intermittent PrEP and PEP using oral Truvada (tenofovir and emtricitabine) in macaques following rectal inoculation. The highest level of protection was achieved with a first dose 22 hours to seven days prior to the exposure and a second dose two hours after the exposure.⁵⁰

Human studies

Prospective randomized controlled trials (RCTs) to determine the efficacy of PEPSE have not been performed and are not feasible due to the ethics of withholding a potentially efficacious treatment and the difficulty in recruiting a sufficient sample size.

(a) Occupational exposure to HIV

A retrospective case-controlled study among health-care workers occupationally exposed to HIV infection demonstrated that a 28-day course of zidovudine was protective, odds ratio (OR) 0.19 [95% CI 0.06–0.52%].²⁹ However there are also instances where PEP has failed to prevent HIV infection following occupational exposure.⁵¹

(b) Vertical transmission

In a subset of women in the AIDS Clinical Trials Group 076 study who did not receive zidovudine

prior to delivery but where the neonate was given a six-week course of zidovudine, initiated within 48 h of delivery, a protective effect was observed.^{52,53}

(c) Sexual exposure to HIV

No prospective RCTs to determine the efficacy of PEPSE were identified. Two observational PEPSE studies undertaken in Brazil, one among men who have sex with men (MSM) and another in women following sexual assault, demonstrated that fewer HIV seroconversions in individuals receiving PEPSE compared with those who did not. However, neither study was powered to detect a difference in HIV incidence.⁵⁴

Factors influencing the efficacy of PEP

PEP is not considered 100% effective, as there have been cases of HIV acquisition whilst on PEP. These may be related to:

- Delayed initiation^{29,46}
- Transmission of resistant virus
- Variable genital tract drug penetration
- Poor/non-adherence
- Further high-risk sexual exposures

Baseline HIV resistance recorded on the UK HIV Drug Resistance Database is declining amongst MSM in the UK (7.2%, in 2013) but is stable

Box 1. Factors increasing the risk of HIV transmission:

1. **A high plasma HIV viral load (VL) in the source**—with each \log_{10} increase in plasma HIV RNA, the per-act risk of transmission is increased 2.9 fold [95% CI 2.2–3.8].³³ This may be particularly relevant during primary HIV infection.²⁰
2. **Breaches in the mucosal barrier** such as mouth or genital ulcer disease and anal or vaginal trauma following sexual assault or first intercourse.^{34,35}
3. **Menstruation or other bleeding**—theoretical risk only.
4. **Sexually transmitted infections** in HIV-positive individuals not on ART^{36,37} or HIV-negative individuals with genital ulcer disease.³⁸
5. **Ejaculation**—Among a community cohort of men who have sex with men (MSM), the risk of HIV acquisition per episode of unprotected receptive anal intercourse with and without ejaculation was estimated to be 1.43% [95% CI 0.48–2.85] and 0.65% [95% CI 0.15–1.53], respectively.¹⁷
6. **Non-circumcision**—circumcision has been shown to significantly reduce HIV acquisition among heterosexual men in high prevalence countries.^{39–42} In 2008, a meta-analysis of observational studies in MSM suggests circumcision has little impact upon HIV acquisition.⁴³ However, since then the risk of HIV acquisition per episode of unprotected insertive anal intercourse in circumcised men was estimated to be 0.11% [95% CI 0.02–0.24] versus 0.62% [95% CI 0.07–1.68] in uncircumcised men in a community cohort of MSM in Australia.¹⁷
7. **Discordant HIV VL in the genital tract**—In general, the genital tract VL is undetectable when the plasma VL is undetectable. When this is not the case, the VL in the genital tract is usually low.^{44,45}

amongst heterosexuals (6.0% in 2013). No baseline integrase resistance has been detected in the national database but the data are limited (120 tests 2010–2012). Integrase-experienced patients demonstrate stable levels of resistance at 15% of those tested, though rates may be higher in other countries.⁵⁵ If drug resistance is suspected in the source, the regimen should be tailored accordingly following discussion with an HIV specialist (1C).

Poor adherence was a risk for subsequent seroconversion in a retrospective analysis of PEPSE failures.⁵⁶ A recent case-series of 19 HIV diagnoses after PEPSE initiation found that one was a chemoprophylactic failure related to suboptimal dosing of Kaletra in the first week of treatment; the other 18 had primary HIV at baseline.⁵⁷ Worryingly, PEP completion rates to 28 days have been historically poor in the UK (range 42–82%).^{58–67}

Possible risks of PEPSE

Safety

The possibility of side effects and both short and potential long-term toxicities must be balanced with the potential benefit of PEP. This has been considered when determining risk thresholds for recommending PEPSE.

Behavioral implications

Historically there were concerns that PEPSE availability would reduce commitment to other prevention

strategies. However several studies have demonstrated a reduction in self-reported risk behavior: a Brazilian MSM cohort⁵⁴ and two San Francisco clinics providing PEPSE to MSM.⁶⁸ PEP awareness had no effect on condom use by serodiscordant couples in a cross-sectional survey.⁶⁹

Conversely, some authors have argued that health-related interventions such as PEPSE may actually provide benefit by capitalizing on ‘close calls’ to motivate and sustain risk reduction in individuals who have engaged in risk behavior.⁷⁰

Acute anxiety

The decision to administer PEPSE should be based on the risk of HIV acquisition and not to manage a state of acute anxiety following a sexual exposure. Referral for psychological support for individuals reporting anxiety related to the risk of HIV transmission may be beneficial (2D).

Comparison with other HIV prevention strategies

PEPSE should not be considered or encouraged as a first line method of HIV prevention (1C)

The Writing Committee believes it is crucial to consider PEPSE as only one strategy for preventing HIV infection and must be considered within the broader context of HIV prevention. Other methods of HIV prevention have a more robust evidence base. Alternative methods of HIV prevention and their respective effectiveness are summarized in the

BHIVA/BASHH position statement on HIV pre-exposure prophylaxis (PrEP) and should be used to aid discussion of the options available to service users⁷¹: <http://www.bhiva.org/documents/Publications/PrEP2012.pdf>. Condoms are highly protective, although use is inconsistent.^{12,72} Data in support of treatment of HIV-positive partners as a prevention strategy are strong.^{13,14}

The Writing Committee anticipates that, pending results of discussions at the time of guideline development, the repertoire of prevention tools will expand to include PrEP; individuals presenting for PEPSE may be candidates for PrEP when it becomes available.

Recommendations for prescribing PEPSE

We recommend the use of PEPSE where there is a significant risk of HIV transmission (1C)

A risk-benefit analysis should be undertaken for every individual presenting following an exposure and the decision to initiate PEPSE made on a case-by-case basis. This should consider both the risk of the source being HIV-positive (Table 1), the risk of transmission according to exposure (Table 2), and as well as the VL in the source, if known. The recommendations are summarized in Table 3. Awareness of the local HIV seroprevalence in the potential source should be factored into local protocols.

The Writing Committee suggests using the following threshold to determine if PEPSE is indicated:

- **Transmission risk is greater than 1 in 1000**—PEPSE is recommended (2D).
- **Transmission risk is between 1 in 1000 and 1 in 10,000**—PEPSE may be considered (2D). The Writing Committee feels that when the exposure is classified as 'consider', PEPSE should only be prescribed if there are additional factors that may increase the likelihood of transmission (see Box 1).
- **Transmission risk is less than 1 in 10,000** PEPSE is not recommended (2D).

Source individual is of unknown HIV status

We suggest proactive attempts are made to establish the HIV status of the source (2C)

It has been shown that in presentations following sexual intercourse with a source of unknown HIV status, it was possible to contact and test the source in 43.4% of cases and avoid/discontinue PEPSE in 40.7%; this resulted in a 31% reduction in cost. Importantly, this strategy avoids unnecessary side

effects and toxicity for the individual and facilitates HIV-testing of a high-risk group.^{73,74} It is therefore recommended that appropriate partner notification is undertaken and the source tested for HIV as soon as possible; this should not delay PEPSE initiation.

If the source is from a risk-group or country of high HIV prevalence (prevalence > 1%), then PEPSE is routinely recommended following receptive anal sex, see Table 3.

Source individual known to be HIV-positive

We suggest attempts should be made at the earliest opportunity to determine the plasma HIV viral load, resistance profile, and treatment history of the source (GPP)

PEPSE is no longer recommended if the source is on ART with a confirmed and sustained (>6 months) undetectable plasma HIV viral load (<200copies/mL) (1B)

Observational studies have long demonstrated a protective effect of viral suppression on risk of transmission.^{75–77} Then followed the HPTN 052 study, an RCT primarily in heterosexual serodifferent couples, which demonstrated a 96% reduction in HIV transmission risk with suppressive ART.⁷⁸ Most recently, the PARTNER Study demonstrated no linked transmissions from people with plasma HIV-1 RNA load < 200 copies/mL despite a large number of condomless sex acts with serodifferent partners (>28,000 acts in heterosexuals and >16,000 acts in MSM).⁷⁹

In light of this, the recommendation for receptive anal sex with a HIV-positive partner with an undetectable plasma HIV VL (confirmed VL < 200 copies/mL sustained for > 6 months and high adherence to ART) has been changed from 'recommended' to 'not-recommended', see Table 3 (1B).

The dates and results of the source's last VL tests should be confirmed with their clinic for a minimum of the last six months and recorded in the PEP assessment. If there is any doubt about the source's VL or adherence to ART, then PEPSE should be given as a precaution following unprotected anal intercourse.

Individuals should be encouraged to attend for formal PEP assessment and verification of source's HIV details even when they believe the source has an undetectable HIV viral load (GPP)

PEPSE is 'not-recommended' following fellatio with ejaculation as we believe the risk is <1/10,000 (2C). A cohort study demonstrated that after an estimated total of over 19,000 unprotected orogenital exposures with an HIV-positive partner, no HIV seroconversions occurred.²⁵ Case reports of oral transmission exist and modeling studies have estimated a risk of 4/10,000.¹² In extreme circumstances such as primary HIV infection and oropharyngeal trauma/ulceration, PEP can be considered but in

Table 3. Summary table of PEPSE prescribing recommendations.

| | Source HIV status | | Unknown HIV status | |
|--|---|--|---|---|
| | HIV-positive | | | |
| | HIV VL unknown/ detectable (>200 copies/mL) | HIV VL undetectable (<200 copies/mL) | From high prevalence country/risk-group (e.g. MSM) ^a | From low prevalence country/group |
| Receptive anal sex | Recommend | Not recommended ^b Provided source has confirmed HIV VL < 200 c/mL for- > six months | Recommend | Not recommended |
| Insertive anal sex | Recommend | Not recommended | Consider ^c | Not recommended |
| Receptive vaginal sex | Recommend | Not recommended | Consider ^c | Not recommended |
| Insertive vaginal sex | Consider ^d | Not recommended | Consider ^c | Not recommended |
| Fellatio with ejaculation ^e | Not recommended | Not recommended | Not recommended | Not recommended |
| Fellatio without ejaculation ^e | Not recommended | Not recommended | Not recommended | Not recommended |
| Splash of semen into eye | Not recommended | Not recommended | Not recommended | Not recommended |
| Cunnilingus | Not recommended | Not recommended | Not recommended | Not recommended |
| Sharing of injecting equipment ^f | Recommended | Not recommended | Consider | Not recommended |
| Human bite ^g | Not recommended | Not recommended | Not recommended | Not recommended |
| Needlestick from a dis- carded needle in the community | | | Not recommended | Not recommended |

PEPSE: post-exposure prophylaxis following sexual exposure; MSM: men who have sex with men.

^aHigh prevalence countries or risk-groups are those where there is a significant likelihood of the source individual being HIV-positive. Within the UK at present, this is likely to be MSM, IDUs from high-risk countries (see ^f below) and individuals who have immigrated to the UK from areas of high HIV prevalence, particularly sub-Saharan Africa (high prevalence is >1%). Country specific HIV prevalence can be found in UNAIDS Gap Report:<http://www.unaids.org/en/resources/campaigns/2014/2014gapreport/gapreport>

^bThe source's viral load must be confirmed with the source's clinic as <200 c/ml for > 6 months. Where there is any uncertainty about results or adherence to ART then PEP should be given after unprotected anal intercourse with an HIV-positive person

^cMore detailed knowledge of local prevalence of HIV within communities may change these recommendations from consider to recommended in areas of particularly high HIV prevalence. Co-factors in Box 1 that influence the likelihood of transmission should be considered

^dCo-factors in Box 1 that influence the likelihood of transmission should be considered

^ePEP is not recommended for individuals receiving fellatio i.e. inserting their penis into another's oral cavity. For individuals giving fellatio PEP is not recommended unless co-factors 1 & 2 in Box 1 are present e.g HIV seroconversion and oropharyngeal trauma / ulceration, see notes in guideline above
^fHIV prevalence amongst IDUs varies considerably depending on country of origin and is particularly high in IDUs from Eastern Europe and central Asia. Region-specific estimates can be found in the UNAIDS Gap Report http://www.unaids.org/sites/default/files/media_asset/05_Peoplewhoinjectdrugs.pdf

^gA bite is assumed to constitute breakage of the skin with passage of blood. See notes in guideline below about extreme circumstances where PEP could be considered after discussion with a specialist

general PEP is not recommended. PEPSE is also not recommended following semen splash in the eye as there have been no documented HIV transmissions via this route (GPP). Following insertive vaginal intercourse with an HIV-positive partner not on ART, PEPSE should be 'considered' rather than routinely 'recommended' as the risk is <1/1219 (2C).^{14,15,19} Again, presence of additional factors in Box 1 should be reviewed and clinician discretion applied.

Needlestick injury in the community

In general, PEP is not recommended following a community needlestick exposure as it is usually not possible to determine: (a) whether the needle has been used and for what purpose; (b) the HIV status of the source and; (c) the interval between the needle use and the exposure (2D). Once blood has dried, HIV becomes non-viable within a couple of hours. In studies where only small amounts of blood are in the syringe viable HIV cannot be detected after 24 h.⁸⁰

Box 2. Items to discuss with individual initiating PEPSE:

1. The rationale for PEPSE.
2. The lack of conclusive data for the efficacy of PEPSE.
3. The potential risks and side effects of PEPSE.
4. The arrangement for early follow-up with an HIV/GU medicine clinician.
5. Pre-test discussion and HIV test (4th generation laboratory test).
6. The need to continue PEPSE for 28 days if the baseline result is negative.
7. The need to have a follow-up HIV test 8–12 weeks post-exposure.
8. The need for safer sex for the following two months.
9. Emergency contraception should be discussed if relevant.
10. Coping strategies, assessment of vulnerabilities, and social support.
11. For patients concerned about sexual risk-taking Sexual Health Advisers can offer ongoing risk reduction work or referral to psychology.

Human bites

Requests for PEP following human bites have been reported. In general, PEP is not recommended following a bite as, although the risk of transmission is unknown, it is likely to be extremely small (2D). In the few reported cases of HIV-transmission following a bite, the person inflicting the bite had advanced HIV with a high plasma VL, there was blood in the oropharynx from trauma or deep wounds were caused by the bite.^{31,32} In extreme circumstances, PEP could be considered after discussion with a specialist. Further guidance regarding the management of human bites is available at: <http://cks.nice.org.uk/bites-human-and-animal/#!scenario:1>

Sexual assault

It is believed that transmission of HIV is likely to be increased as a result of any trauma following aggravated sexual intercourse (anal or vaginal). Clinicians may therefore consider recommending PEPSE more readily in such situations, particularly if the assailant is from a high prevalence group.⁸¹ It is likely that the uptake will be lower in UK settings if the assailant is from a low prevalence group after the balance of risks and benefits are discussed with the patient (2D).

Commercial sex workers

Historically in Western Europe, HIV prevalence among female sex workers has remained low <1%. Prevalence of HIV is also low in Central Europe (1–2%) but is higher in Eastern Europe ranging between 2.5 and 8%.⁸² HIV prevalence is greatest in sex workers who inject drugs.⁸² HIV prevalence among male sex workers, reported from 27 countries, was 14%.⁸³

Assessment and initial management

We suggest individuals presenting for PEPSE should be encouraged to attend for regular sexual health check-ups and are referred to risk-reduction services if appropriate (2C)

It is essential that an appropriate risk assessment be performed to enable provision of PEPSE according to the recommendations outlined above. A checklist outlining the necessary risk assessment for HIV and hepatitis B/C has been created which may be a useful tool in PEP consultations, see Appendix B. At presentation, and prior to administration of PEPSE, the issues summarized in Box 2 must be discussed with the individual.

Early assessment in a specialist Sexual Health service, including meeting with a counsellor/sexual health advisor has been shown to improve rates of adherence and follow-up HIV testing.^{84,85} Individuals presenting for PEPSE are at higher risk of future acquisition of HIV⁶⁸ and so should be encouraged to attend for future regular sexual health check-ups and considered for referral to risk-reduction services and for HIV PrEP when this becomes available (2C).

Timing of PEPSE

We recommend PEPSE should be initiated as soon as possible after exposure, preferably within 24h, but can be considered up to 72 h (1D)

We do not recommend giving PEPSE beyond 72 h (1D)

In a recent study in rhesus monkeys, ART was initiated on day 3 following an intrarectal inoculum of SIV in rhesus monkeys. This blocked emergence of viral RNA and proviral DNA in peripheral blood, lymph nodes, and gastrointestinal tract but on

discontinuation of ART after 24 weeks, all animals experienced viral rebound.⁸⁶ This supports a maximum 72-h window of opportunity for PEP; every effort should be made to make PEP obtainable as soon as possible after the exposure.

Starter packs are pre-prepared three to five day supplies of antiretrovirals; their use enables timely provision of PEP, especially out of hours or from emergency care facilities. This 'starter' PEPSE regimen can be continued or modified at initial review within five days, depending on further information about the source's HIV status, the source's virus, and the patient's tolerance of the medication (2D).

Duration of PEPSE

We recommend that the duration of PEPSE should be 28 days (1D)

The optimal duration of PEP is unknown. However, animal studies and case-controlled studies of health-care workers suggest effectiveness of PEP declines if less than 28 days is used.⁴⁶ If the source tests negative on a 4th generation laboratory assay, then PEP can be discontinued.

If it is unlikely the source can be contacted for HIV testing, there are no significant comorbidities, no baseline blood/urine test abnormalities are predicted, and Truvada/raltegravir is used then a complete 28 days supply can be prescribed at the first specialist clinic visit.⁸⁷ In an emergency care setting, initiation of PEP with a five-day starter pack remains preferable so that early contact with Sexual Health services can be made and STI screening, testing of the source and risk reduction can be facilitated.

Which medication regimen to use for PEPSE

We recommend the use of Truvada and raltegravir as the regimen of choice for PEPSE (1B)

Antiretroviral prescribing recommendations are summarised in Table 4. In established HIV infection, combination therapy with at least three medications from two medication classes is recommended for initial therapy. It is thus recommended, when the risk of HIV transmission is considered significant, to use a triple agent regimen for PEPSE (1D). Some international guidelines do recommend dual-class regimens in selected situations.^{88,89}

If there is evidence that the source has a current or past history of treatment failure, the PEPSE regimen

should be modified in relation to the drug history and/or resistance testing, if available. Expert advice should be sought (1D).

Nucleoside reverse transcriptase inhibitors (NRTI)

Truvada (a fixed dose combination of tenofovir and emtricitabine) is recommended as the NRTI backbone based on efficacy, tolerability, safety, and convenience. Tenofovir and emtricitabine demonstrate good genital tract and rectal tissue penetration in animal models (reaching peak levels within 24 h of dosing and maintaining high levels for up to seven days)⁴⁸ and good male and female genital tract penetration in human studies;⁹⁰ these characteristics may be advantageous for PrEP and PEP.⁴⁸ Phase 3 PrEP studies have demonstrated high efficacy rates for tenofovir (TDF) and Truvada in high-risk heterosexuals and MSM.⁹¹⁻⁹⁴

Abacavir is not recommended. A hypersensitivity reaction is reported in up to 8% of patients with established infection. Although the risk has not been assessed in HIV-negative individuals, it is recommended that abacavir be used in exceptional circumstances only.

Integrase inhibitors (INI)

INI are well tolerated and have all demonstrated at least non-inferior efficacy against non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI).⁹⁵⁻⁹⁷ Raltegravir has been licensed in Europe since 2007. Elvitegravir and dolutegravir are newer agents with less post-marketing experience; both are currently more expensive than raltegravir and elvitegravir has the added complication of requiring co-administration with cobicistat, a pharmacokinetic booster with a similar drug-drug interaction profile as ritonavir. Neither elvitegravir nor dolutegravir has been studied for PEP though both have the advantage of once daily dosing. The Writing Committee believes, based on HIV treatment data, that dolutegravir is an acceptable alternative for individuals who cannot take raltegravir.

Observational studies assessing raltegravir-emtricitabine-tenofovir as PEP in MSM conclude that it is well tolerated, results in high levels of adherence, and avoids potential drug-drug interactions.⁹⁸⁻¹⁰⁰ In an RCT, a PEP regimen of Truvada plus raltegravir was better tolerated than Truvada plus Kaletra.¹⁰¹

Many clinics across the UK have already switched to using raltegravir in favor of Kaletra in PEP regimens

Table 4. Recommended combinations for PEP.

| | NRTI backbone (two medications) | Third agent |
|----------------------------|--|--|
| Recommended combination | Truvada ^a one tablet once daily (tenofovir disoproxil fumarate 245 mg, emtricitabine 200 mg) | Raltegravir 400 mg every 12 h ^b |
| Alternative 1 ^c | Combivir (zidovudine 250 mg twice daily plus lamivudine 150 mg twice daily) | Protease inhibitor Kaletra (lopinavir 200 mg, ritonavir 50 mg ^d) Two tablets twice daily. OR Darunavir 800 mg once daily + ritonavir 100 mg ^d once daily. OR Atazanavir 300 mg once daily + ritonavir 100 mg ^d once daily OR Dolutegravir 50 mg once daily ^e |

NRTI: nucleoside reverse transcriptase inhibitors; PEP: post-exposure prophylaxis.

^aTruvada is the preferred agent in chronic hepatitis B virus infection.

Swallowing difficulty—Truvada can be disintegrated in 100 ml of water or orange juice and taken immediately. Kaletra can be used as an alternative to raltegravir and is commercially available as an oral solution; the recommended dosage is 5 mL twice daily with food.

^bAntacids and multivitamins (products containing metal cations e.g. magnesium/aluminium, which can chelate and reduce the absorption of raltegravir) should be avoided where possible during PEP, see Appendix A. An alternative non-interacting medication may be considered. See Appendix A about co-administration of rifampicin.

^cCombivir may be preferred to Truvada in patients with abnormal renal function at baseline. Lamivudine may require dose-adjustment depending on renal function.

^dSignificant drug–drug interactions can occur with boosted protease inhibitors, seek expert advice from a HIV specialist pharmacist, local medicines and poisons information center, or use the website www.hiv-druginteractions.org

^eAt the time of publication, there are no data on the use of dolutegravir as PEP but it is anticipated to be well tolerated.

since an EAGA statement was released in April 2015: <https://www.gov.uk/government/publications/eaga-guidance-on-hiv-post-exposure-prophylaxis>

Non-nucleoside reverse transcriptase inhibitors

Nevirapine-based PEP is not recommended; almost 10% of individuals experience grade 3 or 4 hepatotoxicity¹⁰² and serious liver toxicity (requiring transplant) and death have been reported. Efavirenz is associated with significant central nervous system side effects, which may be deleterious at a time when levels of anxiety are high; there are no data to support its use in PEP. There is currently also no data to support the use of etravirine or rilpivirine for PEP. Stevens–Johnson syndrome has been reported with etravirine.^{103,104}

Protease Inhibitors

Drug interactions are still of great concern for prescribers experienced in the management of HIV and a

challenge for those not experienced in the use of anti-retrovirals. One study reports high levels of recreational drug use among MSM genitourinary (GU) medicine attendees, an additional interaction concern.¹⁰⁵

Kaletra (lopinavir/ritonavir co-formulation) was the previously recommended PI for PEP. Kaletra is associated with hyperlipidaemia and frequently causes gastrointestinal disturbances¹⁰⁶ necessitating the inclusion of anti-diarrhoeal and antiemetic medication in PEP packs. Side effects are frequently reported and associated with non-adherence/discontinuation.¹⁰⁷

Darunavir/ritonavir and atazanavir/ritonavir have been studied as alternatives to Kaletra and are both once daily formulations; both were comparable to Kaletra in terms of side effects and discontinuations.^{107,108}

CCR5-receptor antagonists

Maraviroc is well tolerated and reaches very high levels in the genital tract so its utility for PEP is being

investigated. One animal study has shown a lack of prophylactic efficacy despite high drug concentrations in rectal tissues.¹⁰⁹

Two RCTs concluded that a PEP regimen of Truvada plus maraviroc is better tolerated than Truvada plus Kaletra.^{101,110}

Side effects

Where an individual reports significant current or previous intolerance to one or more PEP agents, an alternative agent(s) should be considered (2D).

Any antiretroviral medication may have side effects but these are usually mild. When using Truvada and ritonavir, we recommend that the routine inclusion of anti-emetics or anti-diarrhoeals is not necessary. In situations where Kaletra is indicated, routine provision of anti-emetics and anti-diarrhoeals should be considered—this may not be necessary with other PI and is unnecessary with dolutegravir. Where anti-emetics are provided, domperidone should NOT be used with PI due to a significant drug–drug interaction with ritonavir.¹¹¹

Although proximal renal tubular dysfunction and Fanconi's syndrome are well reported in HIV-positive individuals on tenofovir-based ART, these have not been reported in the setting of PEP or PrEP to date.⁹²

Myopathy and rhabdomyolysis have been reported with raltegravir¹¹² and caution should be taken in individuals with a history of these conditions or who are using other medicinal products associated with these conditions, for example statins (www.medicines.org.uk/emc/medicine/20484).

Interactions

We recommend that an accurate medication history should be obtained, including the use of over the counter medication, vitamins/minerals, herbal remedies, and recreational drugs before PEPSE is prescribed (1D)

Although raltegravir (and dolutegravir) poses a low risk in-terms of drug–drug interactions, the concomitant use of metal cation containing antacids (aluminium/magnesium/calcium antacids) and multivitamins should be avoided if possible. Dose-adjustment is required with concomitant rifampicin use. PIs are associated with numerous drug–drug interactions – see Appendix A for details on interactions.

Monitoring and follow-up

We suggest routine blood test monitoring after initiation of raltegravir-based PEPSE is not necessary unless clinically indicated or if baseline blood tests are abnormal (2C)

PrEP studies support the safety of Truvada in HIV uninfected individuals.⁹² There have been no reports of proximal renal tubular dysfunction in individuals receiving PEP. The randomized control trial of raltegravir versus Kaletra PEP (combined with a Truvada backbone) did not report any liver, renal, or haematological abnormalities in the raltegravir arm.¹⁰¹

Raltegravir is less commonly associated with transaminitis and hepatic adverse events than PI.¹¹³ The most at risk-group of liver dysfunction are those co-infected with hepatitis C.¹¹⁴

Full blood count monitoring is no longer deemed relevant as it does not affect the choice of regime and only a single case report of a transient haematological abnormality has been reported on Kaletra-based PEP.¹¹⁵

The recommended monitoring is summarized in Table 5. Closer monitoring is however recommended if new symptoms develop on PEPSE (e.g. rash, jaundice, muscle pain) or if the recipient is pregnant, there is a risk of drug–drug interaction or if significant comorbidities such as hepatitis or renal dysfunction exist or if significant abnormalities are detected on baseline testing. Creatinine kinase (CK) should be tested if muscle pain develops on PEP, particularly on raltegravir-based PEP.

We suggest performing STI testing (based on clinical situation) at baseline as well as at two weeks post-exposure (2C)

Observational studies have found 16.5% of PEP-recipients had an STI at baseline and an additional 4.1% had an incubating STI diagnosed at two weeks.¹¹⁶ As loss to follow-up is common in PEP-recipients, we recommend opportunistic testing at baseline.

We recommend follow-up HIV testing at 8–12 weeks post-exposure (1C)

Several national audits report that the attendance for follow-up HIV testing at 12 weeks is poor (30–67%).^{61–67} Earlier testing at 8–12 weeks post-exposure may improve testing rates. The HIV test must be on a 4th generation laboratory assay.

We suggest offering an ultra-rapid course of hepatitis B vaccination if clinically indicated and the individual has no immunity at baseline (GPP)

In those who do not have immunity to hepatitis B, we suggest offering an ultra-rapid course of hepatitis B vaccination (or hepatitis B Immunoglobulin if clinically indicated) as per BASHH guidelines.¹¹⁷ Individual clinic policies on screening tests for hepatitis C vary; where there has been significant risk, a hepatitis C core-antigen or hepatitis C RNA will have greater sensitivity at the time of follow-up tests 8–12 weeks post-exposure.¹¹⁸

Table 5. Recommended monitoring during PEP course and follow-up.

| | Baseline | 14 days | 8–12 weeks post-exposure |
|--|--|---|---|
| HIV | ✓ | | ✓ |
| Hep B sAg (if no history of vaccination) | ✓ | | ✓ Only if not immune |
| Syphilis, Hep C, Hep B immunity | As per local clinic policy or BASHH guidelines http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx | | |
| STI testing (as appropriate per local clinic policy) | ✓ | ✓ | If further unprotected sexual intercourse has taken place |
| Creatinine | ✓ | Only if abnormalities at baseline | |
| Alanine transaminase | ✓ | Only if abnormalities at baseline, Hep B/C co-infected, or on Kaletra | |
| Urinalysis or uPCR | ✓ | Only if abnormalities at baseline | If abnormalities at baseline or 14 days |
| Pregnancy test | ✓ | If appropriate | If appropriate |
| CK | | Only if symptomatic of myositis | |

PEP: post-exposure prophylaxis; uPCR: urine protein creatinine ratio; CK: creatine kinase.

Special scenarios

Pregnancy

We recommend pregnancy testing in women considering PEPSE (1D)

We suggest pregnancy should not alter the decision to start PEPSE (2D)

Women must be counseled that antiretrovirals used for PEPSE are unlicensed in pregnancy and risks/benefits must be carefully discussed (1D)

Pregnancy is not a contraindication for PEPSE. Indeed if there is a significant risk of infection, and this is not prevented, the high viraemia associated with primary infection would lead to a high likelihood of intrauterine transmission. A thorough risk assessment should be undertaken and expert advice should be sought.

The antiretroviral pregnancy registry (APR, <http://www.apregistry.com>) demonstrates no increase in birth defects in women exposed to tenofovir/emtricitabine during pregnancy, including first trimester exposures (APR category B).

There are insufficient reports of raltegravir exposure during pregnancy for it to be categorized in the APR and its use in pregnancy is currently not advised in the Summary of Product Characteristics (SPC) for raltegravir.¹¹² Expert opinion from the guideline-working group found raltegravir benefits to outweigh the risks. Kaletra is poorly tolerated in pregnancy and is itself not

without risk. Use of antiretroviral medication already characterized on the APR may be preferred by clinician or the patient.

Skin rash or flu-like symptoms during or after PEPSE

Individuals experiencing a skin rash or flu-like illness while or after taking PEPSE should be advised to attend for urgent review to exclude an HIV seroconversion (2D).

Discontinuation or missed doses of PEPSE

Individuals missing doses of PEPSE should be counseled according to the number of missed doses and the time elapsed from the last administered dose. Persistence of PEP medications at therapeutic levels will depend on the pharmacokinetic properties of the individual agents used.

The half-life of raltegravir is relatively short (9 h) such that predicted levels of this agent will be sub-therapeutic 18 h after a missed dose and largely undetectable by 45 h. Truvada plasma half-life is 12–18 h according to the SPC¹¹⁹ but were longer in a recent study: 31 and 37 h for tenofovir and emtricitabine, respectively.¹²⁰ Tenofovir and emtricitabine are activated intracellularly and the median intracellular half-lives are approximately 150–160 h^{120,121}; and 39 h,¹²⁰ respectively. Recommendations on whether and when

Table 6. Guidance on missed doses of PEPSE (2D).

| Scenario | Recommendation | Comments |
|---------------------------------|--|--|
| <24 h elapsed since last dose | Take missed doses immediately and subsequent doses at usual time | Reinforce importance of adherence and re-evaluate motivation to continue PEP |
| 24–48 h elapsed since last dose | Continue PEPSE | Reinforce importance of adherence and re-evaluate motivation to continue PEP |
| >48 h since last dose | Recommend stop PEPSE | |

PEPSE: post-exposure prophylaxis following sexual exposure.

to discontinue PEP after missed doses is largely empirical, based on biological and pharmacological rationales as well as expert opinion (see Table 6).

If discontinuation of PEP (for less than 48 h since the last missed dose) is related to intolerance to one or more ART agents, continue PEP with an alternative agent(s) (see Table 6).

Further high-risk sexual exposures while on PEPSE

In the event of a further high-risk sexual exposure on the last two days of the PEPSE course, PEP should be continued for 48 h after the last high-risk exposure (2B)

Tenofovir and emtricitabine have been shown to prevent acquisition of HIV infection when used as PrEP by MSM.^{93,94} Individuals reporting further high-risk sexual exposures while receiving PEPSE do not need to extend the course of PEP beyond the initial 28 days. However, should this exposure be on the last two days of the course then extending the treatment for 48 h after the last exposure should be advised, as this appears to have been highly effective in the IPERGAY study with treatment before and after exposure (2B).⁹⁴

Management of individuals who repeatedly present for PEPSE or with ongoing high-risk behavior

We recommended that repeat attenders meet with a health Sexual Health Adviser and/or psychologist and provision of PEPSE is fully integrated into counseling around safer sex strategies (1C)

There had been little evidence of repeated PEPSE use^{59,68} perhaps due to historically poor tolerability of prescribed regimens. However, in the PROUD study some particularly high-risk subpopulations had high repeat PEPSE usage and, despite this, a high incidence of HIV acquisition (likely due to ongoing risk behavior which may or may not be covered by PEPSE).

Attending for PEP could be an ideal opportunity to refer individuals for PrEP, if it becomes routinely

available (under consideration by specialist commissioners at the time of guideline preparation).¹²² Until then, it is recommended that repeated attenders be considered for repeat courses of PEPSE on each occasion according to their risk of HIV acquisition. Provision of PEPSE should be fully integrated with advice and counseling around safer sex strategies (1C). It is recommended that in light of the NICE (2007) recommendations (<https://www.nice.org.uk/guidance/ph3>), these repeat attenders are offered one-to-one structured discussions around a model of behavior change theory which can address factors that can help reduce risk-taking and improve self-efficacy and motivation.

Management of those with a positive HIV test at baseline or shortly after initiating PEPSE

HIV testing is mandatory prior to, or shortly after, commencing PEPSE (1A) since undiagnosed HIV infection would significantly alter the risk–benefit balance of short-course ART.

Service providers may obtain rapid results through point-of-care tests (POCTs), although caution must be given to the higher possibility of both false–positive results, and, in early infection, false–negative. If a POCT is reactive, a fourth generation serological test should be sent urgently and expert advice sought prior to initiating PEP.

If the HIV test is positive after PEPSE has already been initiated, we recommend continuing PEPSE pending review by an HIV specialist (GPP)

Acute HIV diagnosis after PEPSE initiation represents a unique opportunity for very early ART and the potential benefits that entails.¹²³ Furthermore, stopping ART in the context of acute infection may result in significant viral rebound which could increase the risk of onward transmission.¹²⁴

PEPSE service provision

For PEPSE to be maximally effective, 24-h availability is recommended (1C)

Local policies and pathways must be established to enable this within a geographical network. Emergency medicine and urgent care providers will therefore be expected to assume significant responsibility for PEPSE provision. Necessary support and training should be provided by local departments with expertise, such as GU medicine, HIV medicine, infectious diseases, or virology/microbiology departments. The training issues are essentially those outlined comprehensively in the DH/EAGA guidance on HIV PEP.^{1,125}

Individuals receiving PEPSE from an emergency or urgent care service should be seen as early as possible by a clinic experienced in the management of ART and HIV testing. PEPSE should not be withheld until such expertise is available. In situations where early referral to an experienced team is not feasible, access to advice from an experienced HIV clinician is essential. It is recommended that local policies should include 24-h access to advice from an experienced HIV clinician, particularly for complex cases (1D).

Awareness of PEPSE

It is important that individuals at risk of acquiring HIV are aware of PEPSE, such as those in serodifferent couples or MSM. Levels of awareness of PEPSE are low amongst MSM in London.^{126–128} In a cohort of MSM in Australia, those who were PEP-aware sought PEPSE only for a minority of high-risk exposures.⁶⁸ Whether or not an individual seeks PEP may be related to whether the episode was ‘unusual’ or a ‘one off’ and influenced by factors such as characteristics of the sexual partner(s), venue, and the use of alcohol and/or recreational drugs.¹²⁹

Individuals at risk of HIV should be provided with information regarding indications for, and timing of, PEPSE as well as other proven risk-reduction strategies. Community-based organizations will have a large part to play in providing this information. Consideration should be given to provision of 24-h helpline access to enable individuals to establish whether presentation to hospital services for PEPSE is appropriate (2D). SARCAs should ensure that clients and police officers are aware of PEP, and the need for a risk assessment of HIV transmission in each case.

In a UK cohort of people living with HIV, overall fewer than half were aware of PEPSE (MSM 65.8% vs. heterosexual 39.1%).^{127,130} PEPSE should be proactively discussed with individuals diagnosed with HIV infection, particularly with those in a serodifferent relationship, reporting frequent partner change or condomless sexual intercourse (GPP).

Cost-effectiveness

There are no conclusive data regarding the cost-effectiveness of PEPSE. It has been argued that the cost of providing PEP may be effectively spent on other prevention initiatives.¹³¹ However, while the medication cost of a full 28-day course of PEP (with Truvada and raltegravir) is approximately £800.14 (BNF price May 2015), the lifetime costs of treatment for an HIV-positive individual are estimated to be approximately £360,000.¹³² A retrospective cost analysis of the San Francisco PEPSE programme showed it to be cost-effective for high-risk exposures and potentially cost-saving after receptive anal intercourse in MSM.¹³³ Subsequent modeling utilizing data from several USA cities¹³⁴ and Australia¹³⁵ suggest similar cost-effectiveness if PEPSE is targeted to high-risk exposures consistent with these guidelines. This is in general accordance with a review by the Health Technology Assessment.¹³⁶ A 28-day course of PEP could be substantially less expensive with the use of generic medications available now or in the future.

Surveillance on the use of PEPSE

Since January 2011, all episodes of PEPSE in England have been reported through the GUMCAD system (<https://www.gov.uk/government/statistics/sexually-transmitted-infections-stis-annual-data-tables>). Reported PEPSE use has risen annually, particularly amongst MSM, as summarized in Table 7. Despite this HIV incidence has risen in MSM over the same time period and other evidence-based strategies must be advocated.

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgment of the clinician and consideration of individual patient circumstances and wishes. It should be acknowledged that use of any

Table 7. Reported use of PEPSE via GUMCAD 2011–2013.

| | 2011 | 2012 | 2013 |
|-------------------------------|-------------|-------------|-------------|
| Male heterosexual | 677 | 974 | 988 |
| MSM | 2386 | 3763 | 4237 |
| Women heterosexual | 723 | 940 | 982 |
| Women who have sex with women | 20 | 24 | 22 |
| Total | 3975 | 5862 | 6410 |

PEPSE: post-exposure prophylaxis following sexual exposure; MSM: men who have sex with men.

antiretroviral agent in this setting is an unlicensed indication. All possible care has been undertaken to ensure the publication of the correct dosage and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Applicability

The provision of PEPSE requires consideration of appropriate pathways of care between Sexual health/HIV clinicians and those providing emergency/primary care, including SARC's, in order to ensure PEPSE is administered in a timely and appropriate fashion. This will require local interpretation of this guideline and will most likely involve a degree of organizational change and provision of additional resources.

Auditable outcome measures

1. Proportion of PEPSE patients having a baseline HIV test: aim 100% within 72 h of presenting for PEPSE
2. Proportion of PEPSE prescriptions that fit within recommended indications: aim 90%
3. Proportion of PEPSE prescriptions administered within 24 h of risk exposure: aim 90%
4. Proportion of individuals completing four-week course of PEPSE: aim 75%
5. Proportion of individuals seeking PEPSE undergoing testing for STIs: aim 90%
6. Proportion of individuals completing 8–12 week post-exposure HIV antibody/antigen test: aim 75%.

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Appendix A

Potential for drug–drug interactions

When prescribing PEP, it is essential to ensure that the potential for drug–drug interactions is considered, therefore an accurate patient medication history should be reconciled. Clinicians are advised to liaise with a HIV specialist pharmacist and/or use Liverpool Drug Interaction website (<http://www.hiv-druginteractions.org>) for this purpose. Examples of relevant drug–drug interactions between raltegravir and other medications are shown in Appendix A. Consideration should be given to the use of over-the-counter and recreational drugs.

Drug–drug interactions with truvada

There are no significant drug–drug interactions although caution should be applied when Truvada is co-administered with other potentially nephrotoxic agents. Enhanced renal monitoring may be warranted in this situation.

Drug–drug interactions with raltegravir

In vitro studies indicate that raltegravir is not a substrate of cytochrome P450 (CYP) enzymes, does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A, does not induce CYP3A4, and does not inhibit P-glycoprotein-mediated transport. Based on these data, raltegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or P-glycoprotein.

Co-administration of raltegravir with aluminium and magnesium antacids resulted in reduced raltegravir plasma levels. Cationic complexation results in reduced absorption of raltegravir therefore co-administration of raltegravir with **antacids and multivitamins should be avoided where possible during PEP**. Caution and appropriate advice as outlined in Appendix A should be given if the patient is taking calcium or iron preparations.

Raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway. Given that raltegravir is metabolized primarily via UGT1A1, caution should be used when co-administering raltegravir with strong inducers of UGT1A1 (e.g. rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults. The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Less potent inducers (e.g. efavirenz, nevirapine, etravirine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with the recommended dose of raltegravir.

The table below outlines the potential drug–drug interactions with raltegravir and commonly used medication, or where interactions are significant. Please

| Medication | Problem | Advice |
|---|---|--|
| Metal cations | | |
| Aluminium/magnesium hydroxide and calcium carbonate antacids. | Co-administration of raltegravir with antacids resulted in reduced raltegravir plasma levels. | Co-administration of raltegravir with antacids is NOT recommended. Stop antacid and prescribe PPI/H2 antagonist if required. |
| Calcium supplements. | Caution is recommended as raltegravir concentrations may be reduced. | No dose adjustment is required but should be taken well separated in time from the administration of raltegravir (st least 4 h after or 6 h before). |
| Iron supplements. | The effect of cationic complexation resulting in reduced absorption cannot be excluded. | Iron supplements should be taken well separated in time from the administration of raltegravir (at least 4 h after or 6 h before). |

(continued)

Continued.

| Medication | Problem | Advice |
|---|---|---|
| Multivitamins | | |
| Multivitamin preparations may contain polyvalent cations. The effect of cationic complexation resulting in reduced absorption cannot be excluded. | Caution is recommended as raltegravir concentrations may be reduced. | Multivitamins should be taken well separated in time from the administration of raltegravir (at least 4 h after or 6 h before). Or ideally avoid if possible. |
| Anticonvulsants | | |
| Carbamazepine | Co-administration has not been studied but could potentially decrease raltegravir concentrations as it is mainly glucuronidated by UGT1A1 and in vitro data suggest that carbamazepine induces UGT1A1. | No dose adjustment recommended. |
| Phenobarbitone/phenytoin. | The impact of phenobarbital on UGT1A1 is unknown. | No dose adjustment recommended. |
| Antimicrobials | | |
| Rifabutin | Co-administration of raltegravir (400 mg twice daily) and rifabutin (300 mg once daily) increased raltegravir AUC (19%) and C _{max} (39%), but decreased C _{trough} (20%). | These changes were not deemed clinically significant and no dose adjustment is required. |
| Rifampicin | Raltegravir AUC ↓ 40% Raltegravir C _{12hr} ↓ 61% Raltegravir C _{max} ↓ 38% (UGT1A1 induction) | Rifampicin reduces plasma levels of raltegravir. If co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir to 800 mg every 12 h can be considered. NB additional quantities of raltegravir will be required to cover until next review. |
| H2 blockers and proton pump inhibitors | | |
| Omeprazole | Raltegravir AUC ↑ 37% Raltegravir C _{12 hr} ↑ 24% Raltegravir C _{max} ↑ 51% | No dose adjustment required for raltegravir |
| Famotidine | Raltegravir AUC ↑ 44% Raltegravir C _{12 h} ↑ 6% Raltegravir C _{max} ↑ 60% | No dose adjustment required for raltegravir |
| HCV antivirals | | |
| Boceprevir | Co-administration of raltegravir (400 mg every 12 h) and boceprevir (800 mg three times daily) increased raltegravir AUC and C _{max} by 4% and 11%, but decreased C _{12h} by 25%. Boceprevir AUC, C _{max} , and C _{8h} decreased by 2, 4, and 26% respectively. | Increased clinical and laboratory monitoring for HCV suppression is recommended. |
| Daclatasavir | Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. | No dose adjustment of daclatasvir or raltegravir is required. |

(continued)

Continued.

| Medication | Problem | Advice |
|---|---|---|
| Ledipasvir/Sofosbuvir | Co-administration of raltegravir and ledipasvir decreased raltegravir AUC and C _{max} by 15% and 18%, whereas co-administration of raltegravir and sofosbuvir decreased raltegravir AUC and C _{max} by 27 and 43%. When raltegravir is given with ledipasvir/sofosbuvir, it is not known whether the decrease in raltegravir will be greater. | No dose adjustment of ledipasvir/sofosbuvir or raltegravir is required. |
| Ombitasvir/paritaprevir/ritonavir | | Raltegravir can be administered with ombitasvir/paritaprevir/ritonavir and no dose alteration is required. |
| Ombitasvir/paritaprevir/ritonavir + dasabuvir | | Raltegravir can be administered with ombitasvir/paritaprevir/ritonavir + dasabuvir and no dose alteration is required |
| Simeprevir | Co-administration of raltegravir (400 mg twice daily for seven days) and simeprevir (150 mg once daily for seven days) was studied in 24 subjects. Simeprevir C _{max} , AUC, and C _{min} decreased by 7, 11, and 14%, respectively. Raltegravir C _{max} , AUC, and C _{min} increased by 3, 8, and 14%, respectively. | No dose adjustment is required. |
| Sofosbuvir | Co-administration of sofosbuvir and raltegravir (400 mg once daily) decreased raltegravir C _{max} , AUC, and C _{min} by 43, 27, and 5%, respectively. Sofosbuvir C _{max} and AUC decreased by 13 and 5%, whereas GS-331007 C _{max} and AUC increased by 9 and 3%. | No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly. |
| Telaprevir | Based on preliminary data, the combination of telaprevir and raltegravir did not result in a clinically significant interaction. | If co-administered, no dose adjustment is required. |
| Miscellaneous | | |
| Antidepressants (including St John's Wort) | | Clinically significant interactions unlikely |
| Antipsychotics/neuroleptics: | | Clinically significant interactions unlikely |
| Gemfibrozil | Could potentially increase raltegravir levels | Monitor for side effects |
| Methadone | | No dose adjustment required for raltegravir or methadone |
| Midazolam | Midazolam AUC ↓ 8% Midazolam C _{max} ↑ 3% | No dose adjustment required for raltegravir or midazolam |
| Oral/emergency contraceptives and contraceptive patch | Ethinyl Estradiol AUC ↓ 2% Ethinyl Estradiol C _{max} ↑ 6% Norelgestromin AUC ↑ 14% Norelgestromin C _{max} ↑ 29% | No dosage adjustment required for raltegravir or hormonal contraceptives (estrogen- and/or progesterone-based). |

seek advice from a specialist HIV pharmacist and/or use Liverpool Drug Interaction website <http://www.hiv-druginteractions.org>

Drug–drug interactions with dolutegravir

Since dolutegravir is an alternative agent, detailed discussion of pharmacokinetics and drug–drug interactions is not included here. Like raltegravir, dolutegravir interacts with magnesium/aluminium-containing antacids—these should be taken well separated in time from the administration of dolutegravir. Other significant interactions include enzyme-inducing anti-

epileptics and metformin; we advise use of The Liverpool Drug Interactions website to check interactions with all concomitant medication.

Drug–drug interactions with protease inhibitors

As these are alternatives for PEP, detailed discussion of pharmacokinetics and drug–drug interactions is not included here. Ritonavir is associated with numerous drug–drug interactions and St John’s Wort is contraindicated with all PI; we advise use of The Liverpool Drug Interactions website to check interactions with all concomitant medication.

APPENDIX B

| PEPSE CHECKLIST <i>For further information see complete 2015 BASHH HIV Post-Exposure Prophylaxis guideline</i> <i>This checklist is an aid to clinical practice only and does not replace local expert advice where indicated</i> | | | | | |
|---|-------------------------------|--------------------------|--|------------------------------|---|
| CLINIC ID | | DOB | | DATE | |
| PREVIOUS TESTING | | | | | |
| Test | Result | Date | Test | Result | Date |
| HIV | | | HBcAb | | |
| Syphilis | | | HBsAg | | |
| Hepatitis A IgG | | | HBsAb | | |
| Hepatitis C | | | | | |
| BASELINE TESTING | | | | | |
| Test | Result | Date | Test | Result | Date |
| HIV | | | STI screen | | |
| Syphilis | | | Renal | | |
| Hep A IgG (MSM non-immune) | | | Liver | | |
| HBcAb (no history of vaccination) | | | Urinalysis / uPCR | | |
| HBsAb (history of vaccination) | | | Pregnancy test (if indicated) | | |
| Hep C IgG | | | | | |
| CHARACTERISTICS OF EXPOSURE | | | | | |
| Date of exposure | | Time of exposure | | Hours since exposure | |
| Sexual Assault | yes <input type="checkbox"/> | | | no | <input type="checkbox"/> |
| Condom | used <input type="checkbox"/> | not used | <input type="checkbox"/> | broke | <input type="checkbox"/> |
| | | | | fell off | <input type="checkbox"/> |
| Receptive anal sex | <input type="checkbox"/> | ejaculation | <input type="checkbox"/> | withdrawal | <input type="checkbox"/> |
| Insertive anal sex | <input type="checkbox"/> | circumcised | <input type="checkbox"/> | uncircumcised | <input type="checkbox"/> |
| Receptive vaginal sex | <input type="checkbox"/> | | | | |
| Insertive vaginal sex | <input type="checkbox"/> | circumcised | <input type="checkbox"/> | uncircumcised | <input type="checkbox"/> |
| Fellatio (giving) | <input type="checkbox"/> | ejaculation | <input type="checkbox"/> | withdrawal | <input type="checkbox"/> |
| Semen splash in eye | <input type="checkbox"/> | | | | |
| Sharing injecting equipment | <input type="checkbox"/> | | | | |
| Human bite | <input type="checkbox"/> | | | | |
| CHARACTERISTICS OF SOURCE | | | | | |
| Source details | | Source risk factor | HIV status | HIV details | BBV details |
| No. of partners ... | MSM | <input type="checkbox"/> | Positive | <input type="checkbox"/> | No / Unknown ART <input type="checkbox"/> |
| Male <input type="checkbox"/> | High prev. country | <input type="checkbox"/> | Suspected | <input type="checkbox"/> | On ART <input type="checkbox"/> |
| Female <input type="checkbox"/> | Specify..... | | Unknown | <input type="checkbox"/> | HIV viral load c/ml |
| Transgender <input type="checkbox"/> | Injecting drug use | <input type="checkbox"/> | | | Date |
| | | | | HIV viral load | c/ml |
| | | | | | Date |
| PEP ASSESSMENT | | | | | |
| Date | | Time | | Location | |
| Comorbidities | | | PEP recommended? | yes <input type="checkbox"/> | no <input type="checkbox"/> |
| Medication history (including over the counter and herbal) | | | Hep B vaccine required? | yes <input type="checkbox"/> | no <input type="checkbox"/> |
| Drug allergies | | | Contraception required? | yes <input type="checkbox"/> | no <input type="checkbox"/> |
| Adherence concerns | | | Sexual Health Adviser | yes <input type="checkbox"/> | no <input type="checkbox"/> |
| PEP regimen prescribed | Dose | | Frequency | Duration | |
| | | | | | |
| | | | | | |
| DISCUSSION POINTS WITH PATIENT | | | | | |
| The ART is unlicensed for use as PEP | | | Side-effects | | |
| PEP is not 100% effective | | | Emergency contact details | | |
| Possible risks and benefits | | | Safe sex | | |
| Adherence and missed doses rules | | | Risk reduction around alcohol and drugs (if indicated) | | |
| Follow up location | | | Follow up time and date | | |
| Clinician name | | | Signature | | |

APPENDIX C

LEVELS AND GRADING OF EVIDENCE

| Strength of recommendation | Grading of evidence |
|--|---|
| <p>1. Strong recommendation</p> <p>For patients – most people in this situation would want the recommended course of action and only a small proportion would not</p> <p>For clinicians – Most people should receive the intervention</p> | <p>A. High-quality evidence Benefits clearly outweigh the risk and burdens or vice versa Consistent evidence from well performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit or risk.</p> <p>B. Moderate-quality evidence Benefits clearly outweigh risk and burdens or vice versa Evidence from randomized controlled trials with moderate limitations (inconsistent results, methodological flaws, indirect or imprecise) or very strong evidence from some other research design. Further research may impact on our confidence in the estimate of benefit or risk.</p> |
| <p>2. Weak recommendation</p> <p>For patients – Most people in this situation would want the suggested course of action, but many would not.</p> <p>For clinicians – Examine the evidence or a summary of the evidence yourself and be prepared to discuss that evidence with patients, as well as their values and preferences</p> | <p>C. Low-quality evidence Benefits appear to outweigh the risk and burdens or vice versa Evidence from observational studies, unsystematic clinical experience or from RCTs with serious flaws. Any estimate of effect is uncertain.</p> <p>D. Very low quality evidence Benefits appear to outweigh the risk and burdens or vice versa Evidence limited to case studies</p> <p>GPP. Good practice point Recommended best practice based on the experience of the guideline working group</p> |