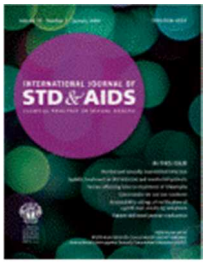

UK Guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE), 2015

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Title:

UK Guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE), 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

New in the 2015 guidelines:

1. PEPSE is not routinely recommended after any type of sex with HIV-positive source on antiretroviral therapy (ART) with a **confirmed** and **sustained** (>6 months) undetectable plasma HIV viral load (<200c/ml).

2. Initiation of PEPSE is recommended as soon as possible after exposure, preferably within 24 hours of exposure but can be offered up to 72 hours.

3. The first-line regimen is Truvada and raltegravir.

4. Routine blood test monitoring is not recommended for raltegravir-based 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.

8. If further risk occurs during the last two days of the PEPSE course, then PEPSE should be continued for 48 hours 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 hours 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 viral load, resistance profile and treatment history (1D).
- PEPSE is no longer recommended if the source is on antiretroviral therapy (ART) with a confirmed and sustained (>6 months) undetectable plasma HIV viral load (<200c/ml) (1B). However, if there are any doubts about the HIV viral load 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 viral load (GPP).
- If drug resistance is suspected in the source the regimen should be tailored accordingly following discussion with an HIV physician (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 hours, but can be considered up to 72 hours (1D).

We do not recommend giving PEPSE beyond 72 hours (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 counselling 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 2 weeks post-exposure (2C).

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

We recommend using a 4th 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 counselled 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 hours 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 counselling individuals at risk of acquiring HIV infection as well as those already diagnosed with HIV infection (2D).

Contents:

1. 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 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.

2. 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. 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
COMPARISON: no intervention, ART treatment as prevention (TasP), condoms, pre-exposure prophylaxis (PrEP)
OUTCOME: HIV infection, seroconversion, toxicity, completion, sexual behavior, cost-effectiveness

2.1 Search strategy:

Current British Association for Sexual Health and HIV (3), USA Centers for Disease Control and Prevention (4), World Health Organisation (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 (ICAAC), HIV Drug Therapy from January 2012 to November 2014 were reviewed.

Restrictions: English language papers.

2.2 Stakeholder involvement, piloting and feedback:

The guideline-working group included representatives from the British Association for Sexual Health and HIV (BASHH), British HIV Association (BHIVA), EAGA, Society of Sexual Health Advisers (SSHA), HIV Pharmacy Association (HIVPA), 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.

3. 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 hours 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 antiretroviral therapy (ART) has been shown to reduce dissemination and replication of virus in all tissues if initiated early after inoculation in an animal model (9).

4. 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 hours 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 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 = risk that source is HIV positive x risk per exposure

For example, if a man 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 x 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:

5. Data supporting the use of PEP against HIV:

5.1 Animal studies

Animal studies suggest that PEP can be potentially effective and that time to initiation and duration are important. Animal studies are not standardised 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 PMPA (tenofovir) in macaque models following intravenous SIV (46) or intravaginal HIV-2 inoculation (47); efficacy was highest if PEP was administered within 24-36 hours 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).

More recent animal studies have demonstrated effectiveness of intermittent pre-exposure

prophylaxis (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).

5.2 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% confidence interval (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 (ACTG) 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 hours 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 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).

6. 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 amongst heterosexuals (6.0% in 2013). No baseline integrase resistance has been detected in the national database but the data is 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 physician (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).

7. Possible risks of PEPSE:

7.1 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.

7.2 Behavioural 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 behaviour: a Brazilian MSM cohort (54) 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 capitalising on ‘close calls’ to motivate and sustain risk reduction in individuals who have engaged in risk behavior (70).

7.3 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).

8. 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 and as such PEPSE should not be considered or encouraged as a first line method of HIV prevention (1C). Alternative methods of HIV prevention and their respective effectiveness are summarized in the BHIVA/BASHH position statement on HIV Pre-exposure Prophylaxis and should be used to aid discussion of the options available to service users (71): 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 is 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 pre-exposure prophylaxis (PrEP); individuals presenting for PEPSE may be candidates for PrEP when it becomes available.

9. 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 viral load in the source, if known. The recommendations are summarised 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).

9.1 Source individual is of unknown HIV status

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

Proactive attempts should be made to establish the HIV status of the source as early as possible (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.

9.2 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)

If source individual is known to be HIV-positive attempts should be made at the earliest opportunity to determine the HIV viral load, resistance profile and treatment history.

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).

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)

The dates and results of the source's last viral load tests should be confirmed with their clinic for a minimum of the last 6 months and recorded in the PEP assessment. If there is any doubt about the source's viral load 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 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 (14, 15, 19) (2C). Again, presence of additional factors in Box 1 should be reviewed and clinician discretion applied.

9.3 Needlestick injury in the community

In general, PEP is not recommended following a community needlestick exposure as it is usually not possible to determine: (i) whether the needle has been used and for what purpose; (ii) the HIV status of the source and; (iii) 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 hours (80).

9.4 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 viral load, 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

9.5 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).

9.6 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).

10. 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 following 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 HIV (68) 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 Pre-Exposure Prophylaxis when this becomes available (2C).

11. Timing of PEPSE:

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

We do not recommend giving PEPSE beyond 72 hours (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-hour 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 3-5 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).

12. 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 suggests 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 5-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.

13. Which medication regimen to use for PEPSE:

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

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 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).

13.1 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 hours 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.

13.2 Integrase inhibitors (INI)

Integrase inhibitors 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 (RAL) 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 then Truvada plus Kaletra (101).

Many clinics across the UK have already switched to using raltegravir in favour of Kaletra in PEP regimens since an EAGA statement was released in April 2015: https://www.gov.uk/government/publications/eaga-guidance-on-hiv-post-exposure-prophylaxis

13.3 Non-nucleoside reverse transcriptase inhibitors (NNRTI)

Nevirapine-based PEP is not recommended; almost 10% of individuals experience grade 3 or 4 hepatotoxicity (102) 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 is 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).

13.4 Protease Inhibitors (PI)

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 antiretrovirals. One study reports high levels of recreational drug use among MSM genitourinary 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 disturbances (106) 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).

13.5 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).

An RCT concluded that a PEP regimen of Truvada plus maraviroc is better tolerated than Truvada plus Kaletra (101). A study of maraviroc-based PEP in the UK came to similar conclusions (110).

13.6 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 raltegravir 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 be 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 raltegravir (112) 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)

13.7 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.

14. 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 protease inhibitors (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).

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 2 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 2 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).

15. Special Scenarios:

15.1 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 counselled 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 infection. A thorough risk assessment should be undertaken and expert advice should be sought.

The antiretroviral pregnancy registry (http://www.apregistry.com) demonstrates no increase in birth defects in women exposed to tenofoviremtricitibine during pregnancy, including 1st trimester exposures (APR category B).

There are insufficient reports of raltegravir exposure during pregnancy for it to be catergorised in the APR and its use in pregnancy is currently not advised in the SPC (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 characterised on the APR may be preferred by clinician or the patient.

15.2 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).

15.3 Discontinuation or missed doses of PEPSE

Individuals missing doses of PEPSE should be counselled 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 hours) such that predicted levels of this agent will be sub-therapeutic 18 hours after a missed dose and largely undetectable by 45 hours. Truvada plasma half-life is 12-18 hours according to the Summary of Product Characteristics (119) but were longer in a recent study: 31 and 37 hours for tenofovir and emtricitabine, respectively (120). Tenofovir and emtricitabine are activated intracellularly and the median intracellular half-lives are approximately 150-160 hours (120, 121); and 39 hours (120), respectively. Recommendations on whether and when 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 hours since the last missed dose) is related to intolerance to one or more ART agents, continue PEP with an alternative agent(s) (see Table 4).

15.4 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 48hours 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 hours 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).

15.5 Management of individuals who repeatedly present for PEPSE or with ongoing high-risk behaviour.

We recommended that repeat attenders meet with a health Sexual Health Adviser and/or psychologist and provision of PEPSE is fully integrated into counselling 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 behaviour 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 counselling 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 behaviour change theory which can address factors that can help reduce risk-taking and improve self-efficacy and motivation.

15.6 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 4th 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)

If the 4th-generation HIV test is positive after PEP has already been initiated we recommend continuing PEP pending review by an HIV specialist. 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).

16. PEPSE Service Provision:

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

For PEPSE to be maximally effective 24-hour access should be available. 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 genitourinary (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 or team is essential. It is recommended that local policies should include 24-hour access to advice from an experienced HIV clinician, particularly for complex cases (1D).

17. 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) and 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, see Appendix B. Community based

organisations will have a large part to play in providing this information. Consideration should be given to provision of 24-hour helpline access to enable individuals to establish whether presentation to hospital services for PEPSE is appropriate (2D). SARCs 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 if in a serodifferent relationship, reporting frequent partner change or condomless sexual intercourse (GPP).

18. 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 modelling utilising data from several USA cities (134) and Australia (135) suggests 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.

19. 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. Despite this HIV incidence has risen in MSM over the same time period and other evidence-based strategies must be advocated.

20. 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 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.

21. Applicability:

The provision of PEPSE requires consideration of appropriate pathways of care between Sexual health/HIV clinicians and those providing emergency/primary care, including SARCs, 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 pro-vision of additional resources.

22. Auditable outcome measures:

1. Proportion of PEPSE patients having a baseline HIV test: aim 100% within 72 hours of presenting for PEPSE
2. Proportion of PEPSE prescriptions that fit within recommended indications: aim 90%
3. Proportion of PEPSE prescriptions administered within 24 hours of risk exposure: aim 90%
4. Proportion of individuals completing 4-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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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)‡	HIV prevalence (%)	
	Men	Women
Men who have sex with men (MSM)†		
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

‡ These data are for England and Wales only
†The 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 (page 8, figure 1)

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

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, 19-25)
Insertive vaginal intercourse	1 in 1,219	(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)

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 in increased 2.9 fold [95% confidence interval (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% confidence interval [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 viral load in the genital tract -** In general, the genital tract viral load is undetectable when the plasma viral load is undetectable. When this is not the case the viral load in the genital tract is usually low (44, 45).

Table 3: Summary table of PEPSE prescribing recommendations

	Source HIV status			
	HIV positive		Unknown HIV status	
	HIV VL unknown / detectable (>200copies/ml)	HIV VL undetectable (<200copies/ml)	From high prevalence country / risk-group (e.g. MSM) *	From low prevalence country / group
Receptive anal sex	Recommend	Not recommended[%] *Provided source has confirmed HIV VL<200c/ml for >6 months*	Recommend	Not recommended
Insertive anal sex	Recommend	Not recommended	Consider[†]	Not recommended
Receptive vaginal sex	Recommend	Not recommended	Consider[†]	Not recommended
Insertive vaginal sex	Consider[&]	Not recommended	Consider[†]	Not recommended
Fellatio with ejaculation[‡]	Not recommended	Not recommended	Not recommended	Not recommended
Fellatio without ejaculation[‡]	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**	Recommended	Not recommended	Consider	Not recommended
Human bite[§]	Not recommended	Not recommended	Not recommended	Not recommended
Needlestick from a discarded needle in the community			Not recommended	Not recommended

[*] High 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 ** below) and individuals who have immigrated to the UK from areas of high HIV prevalence, particularly sub-Saharan Africa (high prevalence is >1%). HIV prevalence Country specific HIV prevalence can be found in UNAIDS Gap Report: http://www.unaids.org/en/resources/campaigns/2014/2014gapreport/gapreport

[%] The source's viral load must be confirmed with the source's clinic as <200c/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

[†] More 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

[&] Co-factors in Box 1 that influence the likelihood of transmission should be considered

[‡] PEP 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

**HIV 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

[§] A bite is assumed to constitute breakage of the skin with passage of blood. See notes in guideline above about extreme circumstances where PEP could be considered after discussion with a specialist

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 health Sexual Health Advisers can offer ongoing risk reduction work or referral to psychology

Table 4. Recommended combinations for PEP

	NRTI Backbone (2 medications)	Third agent
Recommended combination	**Truvada[&] one tablet once daily** (tenofovir disoproxil fumarate 245mg, emtricitabine 200mg)	**Raltegravir 400mg every 12 hours***
Alternative 1[#]	Combivir (Zidovudine 250mg twice daily plus lamivudine 150mg twice daily)	Protease inhibitor Kaletra (lopinavir 200mg, ritonavir 50mg**) Two tablets twice daily OR Darunavir 800mg once daily + ritonavir 100mg** once daily OR Atazanavir 300mg once daily + ritonavir 100mg** once daily OR Dolutegravir 50mg once daily[$]

[&] Truvada is the preferred agent in chronic hepatitis B virus infection

* Antacids 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

[#] Combivir may be preferred to Truvada in patients with abnormal renal function at baseline. Lamivudine may require dose-adjustment depending on renal function.

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

[$]At the time of publication there are no data on the use of dolutegravir as PEP but it is anticipated to be well-tolerated

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 5ml twice daily with food.

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 UPSI has taken place
Creatinine	✔	Only if abnormalities at baseline	
Alanine transaminase (ALT)	✔	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 2 weeks
Pregnancy test	✔	If appropriate	If appropriate
CK		Only if symptomatic of myositis	

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

Scenario	Recommendation	Comments
<24 hours 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 hours elapsed since last dose	Continue PEPSE	Reinforce importance of adherence and re-evaluate motivation to continue PEP
>48 hours since last dose	Recommend stop PEPSE	

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

	2011	2012	2013
Male Heterosexual	677	974	988
MSM	2,386	3,763	4,237
Women heterosexual	723	940	982
Women who have sex with women	20	24	22
Total	**3,975**	**5,862**	**6,410**

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

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 (At least 4 hours after or 6 hours 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 hours after or 6 hours before).
Multi-vitamins		
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 hours after or 6 hours before). Or ideally avoid if possible.
Anticonvulsants		
Carbamazepine	Coadministration 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	Coadministration of raltegravir (400 mg twice daily) and rifabutin (300 mg once daily) increased raltegravir AUC (19%) and Cmax (39%), but decreased Ctrough (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 800mg every 12 hours** 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 C12 hr ↑ 24 % raltegravir Cmax ↑ 51 %	No dose adjustment required for raltegravir
Famotidine	raltegravir AUC ↑ 44 % raltegravir C12 hr ↑ 6 % raltegravir Cmax ↑ 60 %	No dose adjustment required for raltegravir
HCV ANTIVIRALS		
Boceprevir	Coadministration of raltegravir (400 mg every 12 hours) and boceprevir (800 mg three times daily) increased raltegravir AUC and Cmax by 4% and 11%, but decreased C12h by 25%. Boceprevir AUC, Cmax and C8h decreased by 2%, 4% and 26% respectively	Increased clinical and laboratory monitoring for HCV suppression is recommended
Daclatasavir	Coadministration 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
Ledipasvir/Sofosbuvir	Coadministration of raltegravir and ledipasvir decreased raltegravir AUC and Cmax by 15% and 18%, whereas coadministration of raltegravir and	No dose adjustment of ledipasvir/sofosbuvir or raltegravir is required

	sofosbuvir decreased raltegravir AUC and Cmax by 27% and 43%. When raltegravir is given with ledipasvir/sofosbuvir it is not known whether the decrease in raltegravir will be greater.	
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	Coadministration of raltegravir (400 mg twice daily for 7 days) and simeprevir (150 mg once daily for 7 days) was studied in 24 subjects. Simeprevir Cmax, AUC and Cmin decreased by 7%, 11% and 14%, respectively. Raltegravir Cmax, AUC and Cmin increased by 3%, 8% and 14%, respectively.	No dose adjustment is required.
Sofosbuvir	Coadministration of sofosbuvir and raltegravir (400 mg once daily) decreased raltegravir Cmax, AUC and Cmin by 43%, 27% and 5%, respectively. Sofosbuvir Cmax and AUC decreased by 13% and 5%, whereas GS-331007 Cmax 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).

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 contra-indicated with all PI; we advise use of The Liverpool Drug Interactions website to check interactions with all concomitant medication.

APPENDIX B

PEPSE CHECKLIST *For further information see complete 2015 BASHH HIV Post-Exposure Prophylaxis guideline* *This checklist is an aid to clinical practice only and does not replace local expert advice where indicated*		
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 ☐			no ☐	
Condom	used ☐	not used ☐		broke ☐	fell off ☐
Receptive anal sex	☐	ejaculation ☐		withdrawal ☐	
Insertive anal sex	☐	circumcised ☐	uncircumcised ☐		
Receptive vaginal sex	☐				
Insertive vaginal sex	☐	circumcised ☐	uncircumcised ☐		
Fellatio (giving)	☐	ejaculation ☐		withdrawal ☐	
Semen splash in eye	☐				
Sharing injecting equipment	☐				
Human bite	☐				

CHARACTERISTICS OF SOURCE				
Source details	Source risk factor	HIV status	HIV details	BBV details
No. of partners …	MSM ☐	Positive ☐	No / Unknown ART ☐	Hep B + ☐
Male ☐	High prev. country ☐	Suspected ☐	On ART ☐	Hep C + ☐
Female ☐	Specify……	Unknown ☐	HIV viral load c/ml	Date
Transgender ☐	Injecting drug use ☐		HIV viral load c/ml	Date

PEP ASSESSMENT Date	Time	Location	
Comorbidities		PEP recommended?	yes ☐ no ☐
Medication history (including over the counter and herbal)		Hep B vaccine required?	yes ☐ no ☐
Drug allergies		Contraception required?	yes ☐ no ☐
Adherence concerns		Sexual Health Adviser	yes ☐ no ☐

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
1 Strong recommendation **For patients** – most people in this stuation would want the recommended course of action and only a small proportion would not **For clinicians** – Most people should receive the intervention	**A. High quality evidence** Benefits clearly outweigh the risk and burdens or vice versa Consistent evidence from well performed randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit or risk.
	B. Moderate quality evidence Benefits clearly outweigh risk and burdens or vice versa Evidence from randomised controlled trials with moderate limitatons (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.
2. Weak recommendation **For patients –** Most people in this situation would want the suggested course of action, but many would not. **For clinicians** – Examine the evidence or a summary of the evidence yourself ans be prepared to discuss that evidence with patients, as well as theor values and preferemces	**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.
	D. Very low quality evidence Benefits appear to outweigh the risk and burdens or vice versa Evidence limited to case studies
	GPP. Good practice point **Recommended best practice based on the experience of the guideline working group**