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

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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 regime 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, hepatitis and syphilis testing is recommended 4-6 weeks after completion of PEP.

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 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 must be considered as a last resort alongside other evidence-based HIV prevention methods.

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.
- 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 (1A). 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 be considered as a last measure where conventional, and proven, methods of HIV prevention have failed (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 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, hepatitis and syphilis testing at 4-6 weeks after completion of PEPSE (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). Women should be informed that antiretroviral agents used for PEPSE are unlicensed in pregnancy and risks / benefits should be carefully discussed (1D).

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).

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 (2A).

For maximal effectiveness 24-hour availability is an important element of PEPSE provision. 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).
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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 (SARC), 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 Centre for Disease Control (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.

The risk of an individual acquiring HIV following an exposure is dependent upon the risk that the source is HIV-positive where their status is unknown (Table 1), whether the HIV-positive individual is on suppressive ART if the status is known and the nature of the exposure (Table 2). 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.

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

<table>
<thead>
<tr>
<th>Population group (aged 15-59 years)†</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men (MSM)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>5.9</td>
<td>–</td>
</tr>
<tr>
<td>London</td>
<td>12.5</td>
<td>–</td>
</tr>
<tr>
<td>Brighton</td>
<td>13.7</td>
<td>–</td>
</tr>
<tr>
<td>Manchester</td>
<td>8.6</td>
<td>–</td>
</tr>
<tr>
<td>Elsewhere in the UK</td>
<td>3.8</td>
<td>–</td>
</tr>
<tr>
<td>Heterosexuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black African Ethnicity</td>
<td>4.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Non Black African Ethnicity</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Injecting drug users (IDU)</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>
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.\textsuperscript{6,7}


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

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

**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 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).

**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 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 be considered as a last measure where conventional, and proven, methods of HIV prevention have failed (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. As such, PEPSE should be considered as a last measure where conventional, and proven, methods of HIV prevention have failed (1C). Other methods of HIV prevention and their respective effectiveness are summarized in Table 2 of the British HIV Association / BASHH position statement on HIV Pre-exposure Prophylaxis (71):

http://www.bashh.org/documents/PreP_BHIVA_BASHH_Update_14June15_for consultation.pdf

and should be used to aid discussion of the options available to their service users. The data in support of condoms (12) and treatment of HIV-positive partners are also robust (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 recommends that PEPSE is indicated when the estimated transmission risk is 1 in 1000 or greater (2D). Where the estimated 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). Where the estimated 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 (72, 73). 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 group or area of high HIV prevalence then PEPSE is routinely recommended following receptive anal sex only. Where the source is not from a group or area of high HIV prevalence then PEPSE is not recommended.

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 (74-76). 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 (77). 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) (78). 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). Clinician discretion should be exercised if other factors exist (as per Box 1) which might increase the likelihood of transmission.

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. 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 (2C) (25). Case reports of oral transmission exist and modeling studies have estimated a risk of 4/10,000 (12) so PEP can be considered in extreme circumstances at clinician discretion. PEPSE is 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 should be 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 (79).

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 - lscenario:1

9.5 Sexual assault
It is believed that transmission of HIV is likely to be increased 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 (80). 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).
### Table 3: Summary table of PEPSE prescribing recommendations

<table>
<thead>
<tr>
<th>Source HIV status</th>
<th>HIV positive</th>
<th>Unknown HIV status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV VL detectable (&gt;200copies/ml)</td>
<td>HIV VL undetectable (&lt;200copies/ml)</td>
<td>From high prevalence group / area *</td>
</tr>
<tr>
<td>Receptive anal sex</td>
<td>Recommend</td>
<td>Not recommended †</td>
<td>Recommend</td>
</tr>
<tr>
<td>Insertive anal sex</td>
<td>Recommend</td>
<td>Not recommended</td>
<td>Consider †</td>
</tr>
<tr>
<td>Receptive vaginal sex</td>
<td>Recommend</td>
<td>Not recommended</td>
<td>Consider †</td>
</tr>
<tr>
<td>Insertive vaginal sex</td>
<td>Consider</td>
<td>Not recommended</td>
<td>Consider †</td>
</tr>
<tr>
<td>Fellatio with ejaculation ‡</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Fellatio without ejaculation ‡</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Splash of semen into eye</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Cunnilingus</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Sharing of injecting equipment **</td>
<td>Recommended</td>
<td>Not recommended</td>
<td>Consider</td>
</tr>
<tr>
<td>Human bite §</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Needlestick from a discarded needle in the community</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

* 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

† High prevalence groups within this recommendation 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 men who have sex with men and individuals who have immigrated to the UK from areas of high HIV prevalence (particularly sub-Saharan Africa)

‡ 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

‡ PEP is not recommended for individuals receiving fellatio i.e. inserting their penis into another’s oral cavity. For individuals giving fellatio PEP is generally not-recommended unless other co-factors in Box 1 are present, see notes in guideline above.

§ 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.

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11. **Assessment and Initial Management:**

We suggest individuals presenting for PEPSE should be encouraged to attend for future 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 must be discussed with the individual:

**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 4-6 weeks post-completion of PEP
8. The need to safer sex for the following two months
9. Coping strategies, assessment of vulnerabilities and social support
10. For patients concerned about sexual risk-taking health advisers can offer ongoing risk reduction work or referral to psychology

Early assessment in a specialist Sexual Health service, including meeting with a counselor / sexual health advisor has been shown to improve rates of adherence and follow-up HIV testing (81, 82). 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 (83). 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 fourth 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 predicted 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 (84). A repeat prescription of two 14-day installments may be preferable so that the second 14-day installment can be dispensed when the individual returns for their 14 day STI screen. In an emergency care setting initiation of PEP with a 5-day started 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 DRUG 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 drug therapy with at least three drugs from two drug
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 (85, 86).

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 (87); 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 (88-91).

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) (92-94). 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 (95-97). In an RCT, a PEP regimen of Truvada plus raltegravir was better tolerated then Truvada plus Kaletra (98).
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 (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 (99) 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 (100, 101).

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 (102).

Kaletra (lopinavir/ritonavir co-formulation) was the previously recommended PI for PEP. Kaletra is associated with hyperlipidaemia and frequently causes gastrointestinal disturbances (103) necessitating the inclusion of anti-diarrhoeal and antiemetic medication in PEP packs. Side-effects are frequently reported and associated with non-adherence / discontinuation (104).

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 (104, 105).

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 (106).

An RCT concluded that a PEP regimen of Truvada plus maraviroc is better tolerated than Truvada plus Kaletra (98). A study of Maraviroc-based PEP is underway in the UK and results are awaited http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=12548.
Table 4. Recommended combinations for PEP

<table>
<thead>
<tr>
<th>Recommended combination</th>
<th>NRTI Backbone (2 drugs)</th>
<th>Third agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternative 1</strong>&lt;sup&gt;#&lt;/sup&gt;</td>
<td>Truvada® (tenofovir disoproxil fumarate 245mg, emtricitabine 200mg)</td>
<td>Raltegravir 400mg every 12 hours*</td>
</tr>
<tr>
<td><strong>Truvada</strong>&lt;sup&gt;α&lt;/sup&gt;</td>
<td>Combivir® (Zidovudine 250mg twice daily plus lamivudine 150mg twice daily)</td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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&lt;sup&gt;$&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* 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

**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

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

α Truvada is the preferred agent in chronic hepatitis B virus infection

$ 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.

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 drug 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 (107).
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 (89).

Myopathy and rhabdomyolysis have been reported with raltegravir (108) 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 carbonate) 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 (89). There have been no reports of proximal renal tubular dysfunction in individuals receiving PEP. The randomized control trial of raltegravir v’s Kaletra PEP (combined with a Truvada backbone) did not report any liver, renal or haematological abnormalities in the raltegravir arm (98).

Raltegravir is less commonly associated with transaminitis and hepatic adverse events than protease inhibitors (109). The most at risk group of liver dysfunction are those co-infected with Hepatitis C (110).
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 (111).

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 should be tested if muscle pain develops on PEP, particularly on raltegravir-based PEP.

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**We suggest performing an STI screen 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 (112). As loss to follow-up is common in PEP-recipients we recommend opportunistic testing at baseline.

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**We recommend follow-up blood-borne virus and syphilis testing at 4-6 weeks after completion of PEPSE (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 4-6 weeks may improve testing rates. The HIV test must be on a fourth generation laboratory assay.

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**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 (113). 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 8-10 weeks post exposure (114).
### Table 5: Recommended monitoring during PEP course and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>14 days</th>
<th>4-6 weeks post-completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Hep A IgG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep B cAb</td>
<td>✓</td>
<td></td>
<td>✓ (only if not immune)</td>
</tr>
<tr>
<td>(if no history of vaccination)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep B sAb</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(if previously vaccinated)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep C IgG</td>
<td>✓</td>
<td></td>
<td>✓ (Hep C Antigen/RNA in those with high-risk exposure)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STI</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>✓ (only if abnormalities at baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>✓ (only if abnormalities at baseline, Hep B/C co-infected or on Kaletra)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis or uPCR</td>
<td>✓ (only if abnormalities at baseline)</td>
<td></td>
<td>if abnormalities at baseline or 2 weeks</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>✓ (if appropriate)</td>
<td></td>
<td>If appropriate</td>
</tr>
<tr>
<td>FBC</td>
<td>Not required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td></td>
<td></td>
<td>Only if symptomatic of myositis</td>
</tr>
</tbody>
</table>

### 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 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 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 tenofovir or emtricitabine during pregnancy, including 1st trimester exposures (APR category B).

There are insufficient reports of raltegravir exposure during pregnancy for it be categorised in the APR and its use in pregnancy is currently not advised in the SPC (108). Expert opinion from the guideline-working group found raltegravir benefits to outweigh the risks. Kaletra is poorly tolerated in pregnancy and in itself is not without risk. Use of antiretroviral medication already characterized on the APR may be preferred by clinician or the patient.

15.2 Skin rash or flu-like symptoms during or after PEPSE

Individually 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 counseled according to the number of missed doses and the time elapsed from the last administered dose. Persistence of PEP drugs 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 subtherapeutic 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 (115) but were longer in a recent study: 31 and 37 hours for TDF and FTC, respectively (116). TDF and FTC are activated intracellularly and the median intracellular half-lives of TDF and FTC are approximately 150-160 hours (116, 117); and 39 hours (116), 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 5).
Table 6: Guidance on missed doses of PEPSE (2D)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 hours elapsed since last dose</td>
<td>Take missed doses immediately and subsequent doses at usual time</td>
<td>Reinforce importance of adherence and re-evaluate motivation to continue PEP</td>
</tr>
<tr>
<td>24-48 hours elapsed since last dose</td>
<td>Continue PEPSE</td>
<td>Reinforce importance of adherence and re-evaluate motivation to continue PEP</td>
</tr>
<tr>
<td>&gt;48 hours since last dose</td>
<td>Recommend stop PEPSE</td>
<td></td>
</tr>
</tbody>
</table>

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 48 hours after the last high-risk exposure (2B)

Tenoforv and emtricitabine have been shown to prevent acquisition of HIV infection when used as PrEP by MSM (90, 91). 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) (91).

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 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 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) (118). 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 (http://guidance.nice.org.uk/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 fourth generation serological test should be sent urgently and the case discussed with a HIV/GUM Physician 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 (119). Furthermore, stopping ART in the context of acute infection may result in significant viral rebound which could increase the risk of onward transmission (120).

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, 121).

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 (122-124) 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 (125).

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%) (123, 126). 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 (127). However, while the drug 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 (128). 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 (129). Subsequent modelling utilising data from several USA cities (130) and Australia (131) 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 (132). A 28-day course of PEP could be substantially less expensive with the use of generic drugs available now or in the future.

19. SURVEILLANCE ON THE USE OF PEPSE:

Since January 2011 all episodes of PEPSE 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.

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

<table>
<thead>
<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male heterosexual</td>
<td>677</td>
<td>974</td>
<td>988</td>
</tr>
<tr>
<td>MSM</td>
<td>2,386</td>
<td>3,763</td>
<td>4,237</td>
</tr>
<tr>
<td>Women heterosexual</td>
<td>723</td>
<td>940</td>
<td>982</td>
</tr>
<tr>
<td>WSW</td>
<td>20</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>3,975</td>
<td>5,862</td>
<td>6,410</td>
</tr>
</tbody>
</table>

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
guarantee 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.

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 4-6 week post-PEP HIV antibody/antigen test: aim 75%.

23. ACKNOWLEDGEMENTS:
The writing group thanks the following for their valuable contribution to the guideline:
Alison Richards
Beverley Gittins
Sheena McCormack
Sarah Fiddler
Marta Boffito
Sonia Raffe
Goleh Haidari

24. CONFLICTS OF INTEREST:
Martin Fisher – none declared
Eleanor Briggs – none declared
Fiona Cresswell – has received speaker fees from Janssen and conference support from Gilead
Julie Fox – none declared
Justin Harbottle – has received speaker fees from Gilead
David Hawkins – none declared
Martin Murchie – none declared
Keith Radcliffe – none declared
Paul Rafferty – none declared
Alison Rodger – none declared
Laura Waters – has received speaker/advisory board fees or conference support from Bristol Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck Sharpe & Dohme, Janssen Pharmaceuticals and AbbVie.
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 online tools (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 metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Less potent inducers (e.g., efavirenz, nevirapine, etravirine, 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 on line tools such as http://www.hiv-druginteractions.org

<table>
<thead>
<tr>
<th>Drug</th>
<th>Problem</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal Cation Antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminium and magnesium</td>
<td>Co-administration of raltegravir with aluminium and magnesium antacids</td>
<td>Co-administration of raltegravir with aluminium and magnesium antacids is NOT recommended. Stop antacid and prescribe PPI/H2 antagonist if required</td>
</tr>
<tr>
<td>hydroxide antacids</td>
<td>resulting in reduced raltegravin plasma levels.</td>
<td></td>
</tr>
<tr>
<td>Calcium carbonate antacid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No dose adjustment is required but should be taken well separated in time from the administration of raltegravin (At least 4 hours after or 6 hours before). Or ideally avoid if possible.</td>
<td></td>
</tr>
<tr>
<td>Multi-vitamins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivitamin preparations may contain polyvalent cations. The effect of cationic complexation resulting in reduced absorption cannot be excluded.</td>
<td>Caution is recommended as raltegravin concentrations may be reduced. Multivitamins should be taken well separated in time from the administration of raltegravin (At least 4 hours after or 6 hours before). Or ideally avoid if possible.</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Coadministration has not been studied but could potentially decrease raltegravin concentrations as it is mainly glucuronidated by UGT1A1 and in vitro data suggest that carbamazepine induces UGT1A1</td>
<td>No dose adjustment recommended</td>
</tr>
<tr>
<td>Phenobarbital/phenytoin</td>
<td>The impact of phenobarbital on UGT1A1 is unknown.</td>
<td>No dose adjustment recommended</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Coadministration of raltegravin (400 mg twice daily) and rifabutin (300 mg once daily) increased raltegravin AUC (19%) and Cmax (39%), but decreased Cthrough (20%).</td>
<td>These changes were not deemed clinically significant and no dose adjustment is required.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>raltegravin AUC ↓ 40 %</td>
<td>Rifampicin reduces plasma levels of raltegravin. If co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravin to 800mg every 12 hours can be considered. NB additional quantities of raltegravin will be required to cover until next review.</td>
</tr>
<tr>
<td></td>
<td>raltegravin C12h ↓ 61 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravin Cmax ↓ 38 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(UGT1A1 induction)</td>
<td></td>
</tr>
<tr>
<td>H2 Blockers and Proton pump inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>raltegravin AUC ↑ 37 %</td>
<td>No dose adjustment required for raltegravir</td>
</tr>
<tr>
<td></td>
<td>raltegravin C12 h ↑ 24 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravin Cmax ↑ 51 %</td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td>raltegravin AUC ↑ 44 %</td>
<td>No dose adjustment required for raltegravir</td>
</tr>
<tr>
<td></td>
<td>raltegravin C12 h ↑ 6 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravin Cmax ↑ 60 %</td>
<td></td>
</tr>
<tr>
<td>HCV ANTIVIRALS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bocepravir</td>
<td>Coadministration of raltegravin (400 mg every 12 hours) and boceprevir (800 mg three times daily) increased raltegravin AUC and Cmax by 4% and 11%, but decreased C12h by 25%. Boceprevir AUC, Cmax and C8h decreased by 2%, 4% and 26% respectively</td>
<td>Increased clinical and laboratory monitoring for HCV suppression is recommended</td>
</tr>
<tr>
<td>Daclatasavir</td>
<td>Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.</td>
<td>No dose adjustment of daclatasvir or raltegravir is required</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>Coadministration of raltegravin and ledipasvir decreased raltegravin AUC and Cmax by 15% and 18%, whereas coadministration of raltegravin and sofosbuvir decreased raltegravin AUC and Cmax by 27% and 43%. When raltegravir is given with</td>
<td>No dose adjustment of ledipasvir/sofosbuvir or raltegravir is required</td>
</tr>
</tbody>
</table>
ledipasvir/sofosbuvir it is not known whether the decrease in raltegravir will be greater.

Raltegravir can be administered with ombitasvir/paritaprevir/ritonavir and no dose alteration is required.

Raltegravir can be administered with ombitasvir/paritaprevir/ritonavir + dasabuvir and no dose alteration is required.

No dose adjustment is required.

No dose adjustment of sofosbuvir or raltegravir is required when sofosbuvir and raltegravir are used concomitantly.

No dose adjustment is required.

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

<table>
<thead>
<tr>
<th>CLINIC ID</th>
<th>DOB</th>
<th>DATE</th>
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PREVIOUS TESTING

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Date</th>
<th>Test</th>
<th>Result</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td>HIV</td>
<td></td>
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</tr>
<tr>
<td>Syphilis</td>
<td></td>
<td></td>
<td>HBcAb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A IgG</td>
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<td></td>
<td>HBsAg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td></td>
<td></td>
<td>HBsAb</td>
<td></td>
<td></td>
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</table>

BASELINE TESTING

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<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Date</th>
<th>Test</th>
<th>Result</th>
<th>Date</th>
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<tbody>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td>STI screen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
<td></td>
<td>Renal</td>
<td></td>
<td></td>
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<tr>
<td>Hep A IgG (MSM non-immune)</td>
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<td></td>
<td>Liver</td>
<td></td>
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</tr>
<tr>
<td>HBCAb (no history of vaccination)</td>
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<td></td>
<td>Urinalysis / uPCR</td>
<td></td>
<td></td>
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<tr>
<td>HBsAb (history of vaccination)</td>
<td></td>
<td></td>
<td>Pregnancy test (if indicated)</td>
<td></td>
<td></td>
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<tr>
<td>Hep C IgG</td>
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CHARACTERISTICS OF EXPOSURE

<table>
<thead>
<tr>
<th>Date of exposure</th>
<th>Time of exposure</th>
<th>Hours since exposure</th>
</tr>
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<tbody>
<tr>
<td>Sexual Assault</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Condom</td>
<td>used</td>
<td>not used</td>
</tr>
<tr>
<td></td>
<td>broke</td>
<td>fell off</td>
</tr>
<tr>
<td>Receptive anal sex</td>
<td>ejaculation</td>
<td>withdrawal</td>
</tr>
<tr>
<td>Insertive anal sex</td>
<td>circumcised</td>
<td>uncircumcised</td>
</tr>
<tr>
<td>Receptive vaginal sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insertive vaginal sex</td>
<td>circumcised</td>
<td>uncircumcised</td>
</tr>
<tr>
<td>Fellatio (giving)</td>
<td>ejaculation</td>
<td>withdrawal</td>
</tr>
<tr>
<td>semen splash in eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharing injecting equipment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human bite</td>
<td></td>
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</tbody>
</table>

CHARACTERISTICS OF SOURCE

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<thead>
<tr>
<th>Source details</th>
<th>Source risk factor</th>
<th>HIV status</th>
<th>HIV details</th>
<th>BBV details</th>
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</thead>
<tbody>
<tr>
<td>No. of partners ...</td>
<td>MSM</td>
<td>Positive</td>
<td>No / Unknown ART</td>
<td>Hep B +</td>
</tr>
<tr>
<td>Male</td>
<td>High prev. country</td>
<td>Suspected</td>
<td>On ART</td>
<td>Hep C +</td>
</tr>
<tr>
<td>Female</td>
<td>Specify...............</td>
<td>Unknown</td>
<td>HIV viral load</td>
<td>c/ml Date</td>
</tr>
<tr>
<td>Transgender</td>
<td>Injecting drug use</td>
<td></td>
<td>HIV viral load</td>
<td>c/ml Date</td>
</tr>
</tbody>
</table>

PEP ASSESSMENT

| Comorbidities              | PEP recommended? | yes | no |
| Medication history         | Hep B vaccine required? | yes | no |
| Drug allergies             | Contraception required? | yes | no |
| Adherence concerns         | 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

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Grading of evidence</th>
</tr>
</thead>
</table>
| **1 Strong recommendation** | **A. High quality evidence**  
For patients – most people in this situation would want the recommended course of action and only a small proportion would not  
For clinicians – Most people should receive the intervention  
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. |
| **2. Weak recommendation** | **B. Moderate quality evidence**  
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 and be prepared to discuss that evidence with patients, as well as their values and preferences  
Benefits clearly outweigh risk and burdens or vice versa  
Evidence from randomised 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. |
| **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
REFERENCES:


43


112. de Vrieze NHN, van Rooijen MS, van de Loeff MS, de Vries HJC. Additional gonorrhea and Chlamydia Infections found with rapid follow-up screening in men who have sex with men.


