UK Guideline for the use of HIV Post-Exposure Prophylaxis 2021

Post consultation version

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Abstract

We present the updated British Association for Sexual Health and HIV (BASHH) guidelines for post-exposure prophylaxis (PEP) to HIV following sexual exposures, occupational exposures and other non-occupational exposures in the community. This serves as an update to the 2015 BASHH guideline on PEP following sexual exposures and the 2008 Expert Advisory Group on AIDS guidelines on HIV PEP.

We aim to provide evidence-based guidance on best clinical practice in the provision, monitoring and support of PEP for the prevention of HIV acquisition following sexual, occupational and other non-occupational exposures in the community. The guideline covers when to prescribe PEP, what antiretroviral agents to use and how to manage PEP. This includes (i) evidence of PEP efficacy; (ii) evidence relating to individual-level efficacy of antiretroviral therapy to prevent the sexual transmission of HIV; (iii) data on detectable (transmissible) prevalence of HIV in specific populations; (iv) risk of HIV transmission following different types of sexual and occupational exposure; (v) baseline risk assessment; (vi) drug regimens and dosing schedules; (vii) monitoring PEP; (viii) baseline and follow up blood borne virus testing; (ix) the role of PEP within broader HIV prevention strategies e.g. HIV pre-exposure prophylaxis (PrEP). The guideline also covers special scenarios such as PEP in pregnancy, breastfeeding, chronic hepatitis B infection, and when PEP should be considered in people using HIV PrEP.

The guidelines are aimed at clinical professionals directly involved in PEP provision and other stakeholders in the field. A proforma to assist PEP consultations is included. A public consultation process was undertaken prior to finalising the recommendations.

New in the 2021 guideline

1. The indications for, and management of, PEP following occupational exposures, specifically sharps (percutaneous) injuries, splash (mucocutaneous) injuries and bites is covered in this guideline.

2. Inclusion of indications for PEP following injecting drug use, including sexualized drug use.

3. Where the source is of unknown HIV status, we no longer use the prevalence of HIV within the source population, instead we use the prevalence of detectable HIV viraemia in the source population when determining the HIV transmission risk. This is because the majority of HIV-positive people in the UK are aware of their status, on effective antiretroviral therapy with an undetectable viral load, which we now know prevents onwards transmission.

4. Further evidence on the negligible risk of HIV transmission following human bites is provided as well as the rare scenarios in which PEP could be considered.

5. Introduction of a new category of *'PEP generally not recommended'*, which is for exposures where the risk is negligible and PEP should not be given unless specific extenuating circumstances exist. This has been introduced due to feedback from the National AIDS Trust suggesting that PEP has been given for very low risk exposures as prescribers may feel anxious not to give PEP for some indications which were previously listed as *'consider'*.

6. Changes to PEP prescribing indications include:

    a. Receptive vaginal sex with a partner of unknown HIV status from high risk group – PEP is now *'generally not recommended'*.

    b. Insertive vaginal sex with a partner of unknown HIV status from high risk group – PEP is now *'not recommended'*.

    c. Sharing of injecting equipment with a partner of unknown HIV status from high risk group – PEP is now *'generally not recommended'*.

    d. Human bite – PEP is now *'generally not recommended'.*

7. The recommended first-line PEP regimen is tenofovir disoproxil 245mg/emtricitabine 200mg with raltegravir 1200mg once daily for a minimum of 28 days.

8. In light of the fact that starter packs can negatively impact completion of PEP, the full course of PEP should be provided at the first attendance where possible to facilitate completion of the course.

9. Final HIV testing is recommended at a minimum of 45 days after the PEP course is completed. If the 28 day course is completed, this is a minimum of 73 days (10.5 weeks) after exposure. For sexual exposures this can be performed at 12 weeks to align with syphilis testing.

10. Information on baseline and follow-up hepatitis B testing is more detailed and takes into consideration an individual's baseline hepatitis immunity through vaccination.
11. Hepatitis C PCR or hepatitis C antigen is suggested following high risk exposures as antigen-based tests have a shorter window period than hepatitis C antibody.
12. Indications and management of HIV PEP in the context of chronic hepatitis B infection is included.
13. HIV PEP regimens for breastfeeding mothers are described.
14. Indications for use of PEP in populations using HIV PrEP are discussed.
15. A revised PEP proforma is included which is aimed to facilitate assessment by non-HIV specialists.
16. For ease of reference key recommendations are available through the British HIV Association guidelines mobile phone application.

Executive summary

This summary for clinicians assessing need for and/or providing post-exposure prophylaxis (PEP) outlines five key areas from the BASHH 2021 UK Guideline for the use of HIV PEP:

1) When to offer PEP.
2) What PEP to prescribe.
3) When to start PEP.
4) Baseline tests.
5) Follow-up.
6) Additional considerations for all patients receiving PEP.

This summary does not cover special scenarios such as pregnancy, breastfeeding, chronic hepatitis B, and PEP in people using HIV pre-exposure prophylaxis (PrEP) – please to the full guideline.

1. When to offer PEP (section 6):

Where the index partner is HIV-positive, has been on antiretroviral therapy for at least 6 months with an undetectable plasma HIV viral load (at the time of last measurement and within the last 6 months) and with good reported adherence then PEP is not indicated following any type of exposure.

PEP should be routinely offered to reduce risk of HIV transmission in the following scenarios:

1) Following receptive anal intercourse with an index partner of unknown HIV status or known to be HIV positive with an unknown or detectable HIV viral load.
2) Following receptive vaginal sex with an index partner known to be HIV positive with an unknown or detectable HIV viral load.
3) Following an occupational exposure (sharps or mucosal splash) from an index case known to be HIV positive with an unknown or detectable HIV viral load.
4) For people who inject drugs after sharing needles/equipment if their index injecting partner is known to be HIV positive with an unknown or detectable HIV viral load.

PEP should be considered in the following circumstances:

1) Insertive vaginal intercourse with an index partner known to be HIV-positive with an unknown or detectable HIV viral load.
2) Insertive anal intercourse with an index partner of unknown HIV status.

PEP is generally not recommended for the following scenarios and should only be considered if there is a clear specific extenuating factor which increases the risk of transmission, see table 4:

1) Sharps and splash injuries, sharing of injecting equipment, receptive or insertive vaginal intercourse when the index case is from a high risk group but the HIV status is unknown.
2) Human bite if the index case is HIV-positive with an unknown or detectable HIV viral load.

IN ALL OTHER SCENARIOS PEP IS NOT RECOMMENDED. For further information see table 4.

2. What PEP to prescribe (section 7):

The first-line regimen is tenofovir disoproxil 245mg/emtricitabine 200mg fixed dose combination plus raltegravir 1200mg once daily for 28 days.

Antacids (containing aluminium, magnesium or calcium), multivitamins and iron supplements should be avoided whilst on raltegravir once daily. For further information on drug interactions see section 7.4, or www.hiv-druginteractions.org/checker. For alternative options where the attendee has a clinically relevant drug interaction, has renal impairment, is pregnant, or where the index case has a history of antiretroviral therapy failure refer to section 7 and table 5.

3. When to start PEP (section 8):

PEP should be initiated as soon as possible after exposure, preferably within 24 hours. PEP should not be initiated beyond 72 hours after exposure.

4. Baseline tests (section 9):

All exposures:

1. Creatinine (and eGFR)
2. Alanine transaminase
3. HIV-1 Ag/Ab
4. If not known to be vaccinated with documented HepBsAb >10 IU: Hepatitis B serology (HepBsAg, HepBsAb, HepBcAb)

Sexual exposure: as for 'all exposures', plus chlamydia, gonorrhoea and syphilis testing. Hep C screening in MSM and others at risk of hepatitis C.

Occupational exposure: as for 'all exposures' plus hepatitis C screening in all.

A pregnancy test should be done for all women of childbearing age considering PEP.

5. Follow-up (section 9):

1) Routine renal and liver function test monitoring after initiation of PEP is not necessary unless clinically indicated or if baseline blood tests are abnormal.
2) Follow-up testing for HIV can be performed 45 days after the completion of the PEP course. If a 28-day course is completed this is a minimum of 10.5 weeks post-exposure. For sexual exposures HIV testing can be undertaken at week 12 after the exposure to align with syphilis testing.
3) Follow up testing for hepatitis B should be guided by hepatitis B vaccination status and baseline immunity (Table 6, Figure 1).
4) Chlamydia, gonorrhoea and syphilis testing following the incubation period.
5) For occupational exposures, we recommend individuals are followed-up by their occupational health department as soon as possible, ideally within 72 hours of the event. Occupational health services are responsible for testing the index case, supporting the individual during PEP and follow-up testing.

6. Additional considerations for all individuals receiving PEP:

1) Provide emergency contraception where indicated.
2) Hepatitis B vaccination in the absence of baseline immunity (Figure 1).
3) Individuals with ongoing risk should be transitioned immediately from PEP to PrEP. Refer to an appropriate professional to discuss risk reduction (including PrEP) where appropriate.
4) Reinforce the importance of good adherence and completion of the 28-day PEP course.
5) Provide the British Association in Sexual Health and HIV leaflet on HIV PEP.

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1 Objectives:

We provide evidence-based recommendations for the most appropriate use of HIV post-exposure prophylaxis (PEP) following sexual, occupational and other non-occupational exposures in the community 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 PEP within the broader context of HIV prevention strategies and sexual health. We also provide guidance on PEP use in people who inject drugs, particularly sexualized drug use, which has become an increasingly reported phenomenon since the prior guideline.

This is the first time that PEP following occupational exposures has been discussed within the British Association for Sexual Health and HIV (BASHH) guidelines; the intention is to harmonise PEP use and delivery across the disciplines to ensure high quality, streamlined PEP clinical care pathways underpinned by evidence-based guidelines. The guideline is intended to be supersede the 2013 Department of Health and Expert Advisory Group on AIDS (EAGA) guidance on PEP in occupational settings (1).

This guideline is aimed primarily at clinicians and policy-makers in occupational health, sexual health, sexual assault referral centres (SARCs), and primary and emergency care providers within the UK. The guideline is intended to support the development of appropriate local care pathways for PEP. It is likely that it 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, or adolescents deemed Gillick competent by the prescribing clinician, and may not be appropriate for use in all situations. Decisions to follow these recommendations must be based on the professional judgment of the clinician and consideration of individual patient circumstances.

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 PEP and HIV transmission. All writing group members underwent GRADE training. The recommendations are the result of a series of four face-to-face and a number of virtual meetings of the writing committee and incorporate input from the public consultation process (comments available on request).

The population intervention comparator outcome (PICO) framework was utilised with the question formulated as follows:

- POPULATIONS: HIV-negative individuals at potential risk of acquiring HIV following sexual, occupational (percutaneous injury / mucosal or cutaneous exposure to infectious body fluid) or non-occupational needlestick exposure (injecting drug use) or bite
- 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, adherence, sexual behaviour, 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), Health Service Executive Ireland and Australian Society of HIV Medicine guidelines were reviewed (6). New literature arising since the time of last guideline development was sought through comprehensive literature review using Medline, Embase, Cochrane Library by a trained medical librarian (TR) on the following topics:

1. January 2014 to February 2019 for all articles relating to HIV post-exposure prophylaxis following sexual exposures (265 abstracts reviewed).
2. For occupational exposures the search dated back to 2008.
3. Injecting drug use
4. Hepatitis B
5. Pregnancy and breastfeeding
6. PrEP and PEP

Search terms for each search are included in supplementary materials. Conference abstracts from Conference on Retroviruses and Opportunistic Infection (CROI), International AIDS Conference, Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), HIV Drug Therapy from 2014 to 2019 were reviewed. Study selection: A two-stage sifting process was employed: (1) at title and abstract; and (2) at full text level. All studies reporting on PEP were considered with the following exclusion criteria applied: (1) any study not written in English (2) narrative reviews not adding new data or new analysis of data to existing knowledge. Sifting was performed in duplicate independently by two reviewers.

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), Expert Advisory Group on AIDS (EAGA), Society of Sexual Health Advisers (SSHA), HIV Pharmacy Association (HIVPA), the Terrence Higgins Trust (THT) and the National AIDS Trust (NAT) and Public Health England (PHE). Patients' perspectives will be considered by involvement of THT and NAT, reviewing the literature for information from patient surveys and the public consultation process.

3 Summary of recommendations

Section 6: When to prescribe PEP		
6.1 When to prescribe PEP following sexual exposure		
1	We recommend the use of PEP following sexual exposure where there is a significant risk of HIV transmission (Table 4).	1C
2	The risks and benefits of providing PEP for adolescents should be weighed carefully in the context of UK laws and judgements about autonomy in healthcare decision-making (e.g. Gillick competency), and balanced against protecting young people from harm.	GPP
6.1.1 Index partner is of unknown HIV status		
3	Proactive attempts should be made to establish the HIV status of the index partner; this should not however delay initiation of PEP where indicated (Table 4).	1C
6.1.2 Index partner known to be HIV-positive		
4	Attempts should be made at the earliest opportunity to determine the plasma HIV viral load, resistance profile and treatment history of the index partner.	GPP
5	PEP is not recommended if the index partner has been on ART for at least 6 months with an undetectable plasma HIV viral load (at the time of last measurement and within the last 6 months) and with good reported adherence	1A
6	Individuals should be encouraged to undergo a formal PEP assessment and verification of index partner's HIV details even when they believe the partner has an undetectable HIV viral load.	GPP
7	If there are any doubts about the ART history, the index partner's adherence to ART or the viral load, then PEP should be given following condomless receptive anal intercourse.	GPP
6.2 When to prescribe following occupational exposures and other non-occupational exposures in the community.		
6.2.1.1 Sharps and mucosal splash injuries with an index case known to be HIV-positive		
8	PEP is recommended following a high-risk injury (sharps or mucosal splash) if the index case is known to be HIV-positive and is not on ART for >6 months with a suppressed viral load within the last 6 months.	1C
9	PEP is generally not indicated following a sharps injury if the index case has been on ART for at least 6 months with an undetectable plasma HIV viral load (at the time of last measurement and within the last 6 months) and with good reported adherence, however due to lack of direct evidence, a case by case decision can be made depending on the nature of the injury.	2C
10	PEP is not recommended following a splash injury If the index case is known to have a sustained undetectable viral load.	1C
11	PEP is not recommended where there is no or negligible risk of HIV transmission e.g. through intact skin that comes into contact with HIV infected blood or other bodily fluids.	1C
6.2.1.2 Sharps and mucosal splash injuries with an index case of unknown HIV status		
12	PEP is not recommended following a sharps or mucosal splash injury if the index case is untested but from a low risk group. Table 4	1C
13	PEP is generally not recommended following a sharp or mucosal splash injury if the index case is untested and from a high-risk group (e.g. MSM or PWID), unless there were other factors that increased likelihood of transmission (e.g. a deep injury or blood bolus injected or a sharps injury from a PWID in the context of a local outbreak). Table 4	1C
14	All efforts should be made to seek prompt voluntary HIV testing of the index case.	1C
15	Testing the index case should not delay PEP initiation where indicated.	GPP

16	If the index case is unable to give informed consent for HIV testing (e.g. unconscious, altered mental status) then HIV testing can be performed if it is the best medical interest of the index case.	GPP
6.2.2 Needlestick injuries in the community		
17	PEP is not recommended following a community needlestick exposure.	2D
6.3 When to prescribe PEP following human bites		
18	In general PEP is not recommended following a bite as, although the precise risk of transmission is unknown, it is likely to be negligible	2D
19	However, PEP could be considered for patients who fulfil ALL of the three following criteria: a) the biter's saliva was visibly contaminated with blood; b) the biter is known or suspected to have a plasma HIV viral load >3.0 log copies/ml; and c) the bite has resulted in severe and/or deep tissue injuries.	2D
6.4 When to prescribe PEP to people who inject drugs (PWID)		
20	Individuals who report the use of any injectable drugs, should be asked specifically if they are currently injecting and if so, is equipment ever shared.	GPP
21	The HIV status and, if positive, viral load and ART history of their injecting partners should be ascertained.	GPP
22	PEP is recommended for PWID after sharing needles/equipment if their index injecting partner is HIV-positive and not ART for > 6 months with a suppressed viral load.	1C
23	PEP is generally not recommended in PWID after sharing needles/equipment with an injecting partner of unknown HIV status from a high prevalence country / risk-group but PEP can be considered on a case-by-case basis for PWID in the context of a localised outbreak.	GPP
24	Existing harm-reduction strategies such as needle exchange and opiate substitution programmes should be encouraged for people who inject drugs.	1D
25	MSM should be specifically asked about chemsex and injecting drug use.	GPP
Section 7: What to prescribe for PEP		
7.1 First-lines		
26	We recommend the use of tenofovir disoproxil 245mg/emtricitabine 200mg and raltegravir 1200mg once daily as the regimen of choice for PEP (table 5).	1B
27	If there is evidence that the index case has a current or past history of ART failure, expert advice should be sought as to whether the PEP regimen should be modified in relation to ART history and/or resistance testing.	1D
28	For women who are pregnant or at risk of pregnancy, raltegravir 400mg twice daily is preferred (with tenofovir disoproxil 245mg/emtricitabine 200mg). Where accessing raltegravir 400mg might cause delay, we recommend using raltegravir 600mg twice daily and switching at the earliest opportunity.	1D
7.3 Side effects		
29	Where an individual reports significant current or previous intolerance to one or more PEP agents an alternative agent(s) should be considered.	2D
7.4 Drug-drug interactions		
30	An accurate verified medication history should be obtained, including the use of over the counter medication, vitamins/minerals, herbal remedies and recreational drugs before PEP is prescribed to ensure no significant drug-drug interactions are present.	1D
Section 8: Timing and duration of PEP		
31	PEP should be initiated as soon as possible after exposure, preferably within 24 hours, but can be considered up to 72 hours.	1D

32	We do not recommend initiating PEP beyond 72 hours after exposure.	1D
33	The duration of PEP should be 28 days.	1D
Section 9: How to provide HIV PEP		
34	For PEP to be maximally effective a 24-hour service is recommended.	1C
35	It is recommended that local policies include 24-hour access to advice from an experienced HIV clinician, particularly for complex cases.	1D
9.2 Initiating PEP		
36	Routine safety blood test monitoring after initiation of integrase inhibitor-based PEP is not necessary unless clinically indicated or if baseline blood tests are abnormal.	2C
37	Take a contraceptive history and perform pregnancy testing in all women of childbearing age considering PEP and offer emergency contraception where indicated.	1D
38	Pregnancy and breastfeeding should not alter the decision to start PEP.	2D
39	Women must be counselled that antiretroviral agents used for PEP are unlicensed in pregnancy and their risks/benefits must be carefully discussed (see section 10.2).	1D
40	An ultra-rapid course of Hepatitis B vaccination should be offered if clinically indicated in the absence of baseline immunity (see Figure 1, section 9.4.2)	1B
41	Use of starter packs can negatively impact the completion of PEP, therefore a full course of PEP should be provided at the first attendance unless there are operational reasons why this is not possible.	1C
9.3 Baseline BBV testing of the index case		
42	Following occupational exposures informed consent for testing for blood borne viruses (fourth generation HIV test (HIV-1 Ag/Ab), hepatitis B surface antigen (HepBsAg), hepatitis C antibody (Hep C Ab)) should be sought from the index case by another member of staff who is not the recipient of the occupational exposure.	GPP
43	If the index case is a child then age appropriate HIV, HBV and HCV testing should be used - depending on age and developmental stage of child, consent from the parent or legal guardian of the child, and consent or assent from the child. Discuss with a clinician with relevant expertise (e.g. paediatrician, paediatric ID/microbiologist/virologist) if uncertain.	GPP
44	Where the index case is high risk for hepatitis C (e.g. PWID) then a hepatitis C PCR (HCV PCR) or hepatitis C antigen (HCV Ag) can be done instead of Hep C Ab.	GPP
45	Where it is not possible to seek consent from the index case (e.g. patient comatose or lacks mental capacity) then testing can be undertaken if it is in the best medical interests of the index case.	GPP
9.4 Baseline and follow-up blood testing of recipient		
46	Baseline and follow up tests are summarised in Table 6 **All exposures:** blood testing before PEP initiation should include creatinine (and eGFR), alanine transaminase, HIV-1 Ag/Ab, hepatitis B serology (if not known to be immune with HepBsAb ≥10 IU). PEP initiation should not be delayed by waiting for blood results. **Sexual exposure:** Tests shown in 'All exposures' plus Syphilis serology and Hep C Ab in MSM and others at risk of hepatitis C **Occupational exposure:** Tests shown in 'All exposures' plus Hepatitis C in all.	1B
47	Baseline pregnancy test in women of childbearing age considering PEP.	1D
48	Routine renal and liver function test monitoring after initiation of PEP is not necessary unless clinically indicated or if baseline blood tests are abnormal.	2C
49	Follow-up testing for HIV should be undertaken at a minimum of 45 days after completion of the PEP course. If the 28-day PEP course is completed this is 73 days (10.5 weeks) post exposure.	1B

50	Follow up testing for hepatitis B should be guided by hepatitis B vaccination status and baseline immunity as shown in Table 6, section 9.4.1 and Figure 1, section 9.4.2.	1b
51	For occupational exposures, after initiating PEP, we recommend individuals are followed-up by their occupational health department as soon as possible, ideally within 72 hours of the event.	1D
9.4.3 Sexual health considerations		
52	Perform chlamydia, gonorrhoea and syphilis testing (based on clinical situation) at baseline and repeat testing following the incubation period.	2C
53	Emergency contraception should be offered were indicated.	1B
54	Offer MSM hepatitis A and human papilloma virus vaccines (in addition to hepatitis B virus vaccine) if clinically indicated as per the 2016 British Association of Sexual Health and HIV men who have sex with men guidance.	1B
55	Individuals presenting for PEP who may be at higher risk of future acquisition of HIV and should be encouraged to attend for regular sexual health checks and considered for referral to risk-reduction services including HIV Pre-Exposure Prophylaxis.	2C
56	Provision of PEP should be fully integrated into counselling around safer sex strategies including opportunity to meet with an appropriate health care professional competent in sexual health advising.	1C
Section 10: Special scenarios		
10.1 Chronic hepatitis B infection		
57	Baseline hepatitis B virus (HBV) testing should be undertaken in those of unknown HBV status, and vaccination (and HBIG, depending on risk of exposure) initiated in those who are not known to be immune whilst awaiting results.	GPP
58	Consider the use of a standard PEP regimen for individuals known to have chronic HBV and on either a nucleos(t)ide analogues (except if on combined therapy with tenofovir [TDF]/lamivudine or TDF/emtricitabine [FTC]) or peg IFN-alpha based HBV treatment, where high-risk HIV exposure has occurred.	1B
59	Individuals found to have HBV infection at baseline should receive PEP as needed without delay.	1B
60	Individuals found to be HBV-infected at baseline should be assessed by a specialist in HBV infection with regard to continuing HBV therapy post-PEP. If the hepatitis assessment does not fall within the 28-day PEP course then tenofovir/emtricitabine should be continued pending the assessment.	1B
10.2 Pregnant and breastfeeding mothers		
61	Take a contraceptive history and request a baseline pregnancy test in women of childbearing age considering PEP.	1D
62	Pregnancy and breastfeeding should not alter the decision to start PEP.	2D
63	For women who are pregnant raltegravir 400mg twice daily is preferred (with tenofovir disoproxil 245mg/emtricitabine 200mg). Where accessing raltegravir 400mg might cause delay we recommend using raltegravir 600mg twice daily and switching at the earliest opportunity.	1C
64	For women at risk of pregnancy or known to be within the first 6 weeks of pregnancy who cannot use first-line for PEP for any reason, we recommend avoiding the use of dolutegravir as an alternative third agent (table 5, section 0).	1C

65	For women beyond 6 weeks pregnant, dolutegravir can be used as an alternative third agent.	1C
66	Women should be counselled that antiretrovirals used for PEP are unlicensed in pregnancy and that their risks/benefits must be carefully discussed (see section 10.2).	1D
67	Women who are breastfeeding must be counselled regarding the transfer of antiretrovirals to the infant via the breastmilk.	1D
10.3 Use of PEP in populations using PrEP		
68	The need for PEP (i.e. a significant potential risk within the last 72 hours) should be considered in all individuals requesting PrEP, prior to transitioning to PrEP.	1B
69	Decisions about the need for PEP in the setting of people on PrEP but with less than optimal PrEP adherence depends on length of time since the last dose of PrEP and the site of exposure.	1C
70	Anal sex: If the only exposure has been though anal sex and where fewer than three tablets have been taken within the last 7 days or where the last dose was more than 7 days ago, PEP is recommended.	1A
71	Vaginal: Where the potential HIV exposure is through vaginal sex and PrEP adherence has been suboptimal, PEP should be considered if more than 48 hours have elapsed since last dosing or if fewer than six tablets have been taken within the previous 7 days.	1B
72	Frontal or neovaginal sex: Where the potential exposure to HIV is through frontal sex in trans men or through neovaginal sex in trans women, then PEP should be considered if more than 48 hours have elapsed since last dosing or if fewer than six tablets have been taken within the previous 7 days.	1C
10.5 Seroconversion during PEP		
73	Individuals experiencing a skin rash or flu-like illness while or after taking PEP should be advised to attend for urgent review to exclude an HIV seroconversion.	2D
74	If the HIV test is positive after PEP has already been initiated, PEP should be continued pending review by an HIV specialist.	GPP
10.6 Further high-risk exposures while on PEP		
75	In the event of a further high-risk sexual exposure during the last two days of the PEP course, PEP should be continued until 48 hours after the last high-risk exposure for anal sex or until 7 days after the last high-risk exposure for vaginal/frontal sex.	2B
Section 11: Recommendations for PrEP in those with ongoing high-risk behaviour		
76	Repeat attenders should meet with a Sexual Health Adviser and/or psychologist and that provision of PEP is fully integrated into counselling around safer sex strategies.	1C
77	PEP should not be considered or encouraged as a first line method of HIV prevention.	1C
78	Individuals presenting for PEP who are likely to have ongoing high-risk behaviour should be transitioned immediately to PrEP. HIV testing with a combined antigen/antibody laboratory-based assay should be performed at the time of transition.	GPP

4 Background

Pathogenesis studies indicate that there may be a window of opportunity to prevent acquisition of HIV infection following exposure by inhibiting viral replication or preventing dissemination of infection, if ART is started as soon as possible. Once HIV crosses a mucosal barrier it may take up to 48 hours before it begins to replicate and up to five days before HIV can be detected in blood (7-9). Initiation of antiretroviral therapy (ART) has been shown to reduce dissemination and replication of virus in tissues if initiated early (<72 hours) after inoculation in a macaque animal model, though HIV infection is not universally prevented even if PEP is initiated within 4 hours (10).

4.1 Data supporting the use of PEP to prevent HIV transmission

4.1.1 Animal studies

Animal studies provide evidence for PEP efficacy and demonstrate the importance of time to initiation and duration of therapy. Differences in study design, size of inoculum and modes of administration may account for differing results, but the key points are that PEP is most effective when administered within 24 hours of exposure, with possible efficacy up to 72 hours post-exposure, and with a duration of 28 days (11-14).

4.1.2 Human studies

Prospective randomised 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. However, important data informing understanding of PEP efficacy in humans is available from an observational study of PEP following sexual exposures, data on occupational PEP use and studies on vertical transmission.

4.1.2.1 Occupational exposure to HIV

A retrospective case-controlled study among health-care workers (HCW) occupationally exposed to HIV between 1983 and 1994 demonstrated that a 28-day course of zidovudine was highly protective, resulting in an 80% reduction in HIV seroconversions compared to those who did not receive PEP (odds ratio (OR) 0.19 (95% confidence interval (CI) 0.06–0.52) (15). Since 1997 when the surveillance of serious occupational exposures began, there has been only one documented case in the UK of HIV seroconversion in a HCW after occupational exposure in 1999 despite the use of combination PEP, however the index case was highly treatment experienced (16). Data from UK HPA from 2004 to 2013 showed that there were 4830 healthcare associated occupational exposures to body fluid reported in the UK, 71% of which were percutaneous injuries. During this time, 598 HCW were started on HIV PEP, of whom 97% (580/598) were started within 72 hours following occupational exposure to HIV. There were no new cases of HIV infection during follow-up (17, 18). The rare cases where PEP has failed to prevent HIV infection following occupational exposure are largely historical (19-21). Factors that have contributed to PEP failure are discussed in **section 4.2**.

4.1.2.2 Sexual exposure to HIV

Clinical effectiveness evidence for PEPSE is weak due to both paucity and quality of data available. A systematic review published in 2009 (22) included only a single observational study of PEPSE use in high-risk MSM in Brazil. Participants were given a 4-day 'starter pack' of zidovudine and lamivudine and instructed to begin PEP immediately after exposure. For eligible exposures, an additional 24-day supply was subsequently provided. PEP was initiated 109 times by 68 participants over a 2-year period. HIV incidence in the cohort as a whole (2.9 per 100 person-years) was very similar to that expected in this population (3.1 per 100 person-years, p > 0.97). However, only 1 seroconversion (1.4%) occurred in the PEP group (n=68) compared to 10 (7.5%) in the group not receiving PEP (n=132). The single PEP failure in the PEP group was thought to be due to transmitted resistance to lamivudine (M184V mutation detected) (23).

In the EXPLORE study (2010), a behavioural intervention trial of 4,295 MSM which assessed the use of non-occupational PEP over 4 years in six cities across the United States, no association was found between risk of HIV seroconversion and PEP use. Three seroconversions occurred at 384 visits (1.56 per 100 person-years) with PEP use compared to 210 seroconversions in the 25,550 visits (1.64 per 100 person years) with no PEP use (hazard ratio: 0.91, [95%CI: 0.29, 2.86]) (24). However, a number of factors influence efficacy of PEP (**section 4.2**).

4.1.2.3 Injecting drug use and sharps injuries

There are very limited data on PEP efficacy in people who inject drugs (PWID). Much of the data on PEP use in PWID is limited to retrospective analyses of PEP use in the non-occupational exposure setting, of which PWID contribute to a minority of cases (25).

4.2 Factors influencing the efficacy of PEP

4.2.1 Seroconversion following PEP for sexual exposures

When initiated promptly, taken appropriately and repeat exposures are avoided, PEP is likely to be highly effective. From 2015-2018, a number of cohort studies have reported on the clinical outcomes in people receiving PEP for sexual exposures (26-31). In the cohorts described, seroconversions most commonly resulted from ongoing risk behaviour after completing PEPSE.

Reported reasons for HIV seroconversion include:

- Delayed initiation of PEP (11, 12, 15, 26, 32, 33)
- Poor/non-adherence to PEP regimen (32)
- Further high-risk sexual exposures after cessation of PEP (26, 28, 29)
- Early primary HIV infection already established at the time of PEP initiation (34)

In a recent case-series of 19 HIV diagnoses after PEPSE initiation found that only one was a chemoprophylactic failure related to suboptimal dosing of lopinavir/ritonavir (LPV/r) in the first week of treatment; the other 18 had primary HIV at baseline (34). PEP completion rates to 28-days have been historically poor in the UK (range 42-82%) although the use of the less tolerable drugs in these studies may have had an impact (35-44). A 2017 cohort study using a single tablet regimen elvitegravir/cobicistat/tenofovir-disoproxil (DF)/emtricitabine for PEP found that 71% of study participants completed the course, this was higher than historical completion rates with raltegravir-based PEP (57%) and protease-inhibitor based PEP (39%) both of which required twice-daily dosing; despite this, no seroconversions occurred with all regimens (30). Adherence counselling and support therefore remains a central component of PEP provision.

4.2.2 Seroconversions following PEP for occupational exposures

As mentioned above there have been no cases of occupational HIV transmission in the UK since 1999. PEP failure in this case report was thought to be due to transmission of resistant HIV. The source patient was treatment experienced and had a high viral load with evidence of genotypic resistance. PEP (zidovudine, lamivudine and indinavir) was initiated within 2 hours of the penetrating needlestick injury but seroconversion was confirmed at 3 months. (16, 18). In Australia, there has been a more recent occupational transmission, despite prompt PEP initiation, due to an inoculum of HIV-infected blood being accidentally injected into the finger pulp of a nurse during a sharps injury (21).

4.2.3 Potential for transmitted drug resistance and use of PEP

In 2016, the prevalence of transmitted drug resistance (TDR) in diagnosed PLWH in the UK increased slightly compared to previous years; 9.6% of persons tested had any detectable drug resistance mutation (45, 46). Prevalence of transmitted resistance mutations to protease inhibitors (PI) remained low and stable at 2.2%. There was a small rise from the previous year (2015) in the prevalence of nucleoside reverse transcriptase inhibitors (NRTI) resistance conferring mutations from 3.4% to 4.2%, and for non-nucleoside reverse transcriptase inhibitors (NNRTI) from 3.3% to 4.1%. TDR to the integrase inhibitor (INSTI) class is considered rare but data are limited by lack of routine baseline testing. Only 1 major INI mutation was detected in 96 baseline INI sequences in a study in the West of Scotland (47). Unpublished data from the UK Drug Resistance Database demonstrates only 1 major mutations in approximately 1,000 baseline sequences [Personal Communication Anna Tostevin, Oliver Stirrup & David Dunn, February 2020].

4.3 Possible risks of PEP

4.3.1 Safety

Currently recommended PEP regimens are very safe and well-tolerated. However, the potential benefit of PEP must be balanced with the possibility of side effects or toxicity, taking into account any comorbidities.

4.3.2 Behavioural implications

Historically there were concerns that PEP availability would undermine other prevention strategies such as condom use. However, the EXPLORE study (2010), a behavioural intervention trial in the US of 4,295 MSM which assessed perceptions and use of PEP over 4 years, demonstrated that previous PEP use was not found to be associated with higher odds of high-risk sex (24).

5 Risk of HIV transmission

5.1 Risk of HIV transmission through condomless sexual exposures

The risk of HIV transmission following a sexual exposure depends on:

i. The type of sexual exposure
ii. HIV viral load of the index partner
iii. Susceptibility of the recipient if the sexual partner is not virologically suppressed e.g. genital ulcer disease (48).

Where individuals have multiple exposures within 72 hours, it is important to consider the potential for increased risk.

Table 1 (section 5.3.1) shows the estimated prevalence of people with detectable HIV viraemia (including both diagnosed and undiagnosed infection) in adults aged over 15-74 years in the UK in 2018. Latest HIV prevalence in other countries can be found on the website https://aidsinfo.unaids.org

5.2 Individual-level efficacy of antiretroviral therapy to prevent the sexual transmission of HIV

There is now compelling data from a number of studies in a variety of geographical settings indicating that virological suppression prevents transmission of HIV to sexual partners. HPTN-052 was a randomised controlled trial amongst serodifferent heterosexual couples randomised to early or delayed (CD4 guided) ART with 8509 person-years follow-up in the HIV-negative partners. Early ART resulted in a 93% lower risk of within couple transmission (hazard ratio 0.07; 95% CI, 0.02 to 0.22). There were 8 phylogenetically linked transmissions in the early ART arm, but 4 occurred in initial period of ART prior to viral suppression and 4 much later (>3 years), when the index cases had treatment failure and detectable VL. Crucially, there were no documented transmissions while the index case was virologically suppressed (defined as HIV-1 VL <200

copies/ml) (49). However self-reported condom use was also high in this study with participants reporting not using condoms for a total of only 63.4 couple-years of follow-up (CYFU).

The Europe-wide PARTNER study was a prospective, observational study in two phases. PARTNER1 recruited both gay and heterosexual serodifferent couples from 2010-2014, and PARTNER2 recruited and followed MSM couples from 2014-2018. In PARTNER1 no phylogenetically linked transmissions were found in 888 serodifferent couples (548 heterosexual and 340 gay couples) during 1,238 eligible CYFU in PARTNER1 when the positive partner was on virally suppressive ART with a plasma HIV-1 RNA <200 copies/mL (50).

In PARTNER1, the upper 95% confidence limit for transmission rate for MSM was 0.84/100 CYFU, almost double that for heterosexual couples at 0.46/100 CYFU. PARTNER2 therefore continued recruitment and follow up only in gay men from 2014 to 2018 to improve precision of transmission risk estimates in gay serodifferent partnerships. After 782 MSM couples provided 1593 eligible CYFU including 76,088 reported episodes of condomless sex there were zero phylogenetically linked within-couple transmissions, reducing the upper 95% confidence limit to 0.23/100 CYFU.

The Opposites Attract observational study, also reported zero cases of HIV transmission in MSM couples during 232 CYFU when condom-less anal intercourse was reported, HIV-positive partners were virally suppressed and HIV-negative partners did not use PrEP (51).

In light of this definitive evidence it is clear that that risk of HIV transmission from an HIV-positive individual on suppressive ART through condomless sex is effectively zero regardless of sexual orientation. This concept has gained attention as 'Undetectable = Untransmissible' ('U=U'), after the launch of a global campaign. The U=U global consensus statement has to date been endorsed by over 900 organisations in 100 countries.

5.3 Prevalence of detectable (transmissible) levels of HIV amongst specific populations in UK

In England, the number of people living with undiagnosed HIV infection is at an all-time low (see table 5.3.1), the vast majority of persons living with HIV are diagnosed and on treatment and are virally suppressed (>85% of total PLWH in UK are on ART and supressed). The estimated prevalence of detectable HIV viraemia among PLHIV is therefore low. In 2018, in England, an estimated 12,000 MSM aged 15-74 years were living with HIV with a detectable virus. This represents a prevalence of detectable HIV viraemia of 23 per 1,000 MSM (aged 15-74 years) and the highest prevalence was among MSM living in London (32/1,000 for those aged 15-74 years, see Table 1). The estimated prevalence of detectable HIV viraemia was considerably lower in other populations (Table 1).

5.3.1 Table 1: Number and prevalence of people with detectable (transmissible) levels of HIV per 1000 population aged 15-74 years, England 2018

		Estimated number of people with detectable virus*	Estimated population size	Rate per 1000
Gay and bisexual men	England	12,000	518,050	23.0
	London	5,000	155880	32.1
	Elsewhere	7,000	361090	20.9
Heterosexual men	Black African	1,900	331950	5.8
	Non-black African	3,840	19,563,630	0.2
Heterosexual women	Black African	3,240	373330	8.7
	Non-Black African	2,530	20,308,360	0.1
PWID	All	700	104,470	6.7
	Men	400	77,340	5.3
	Women	300	26,710	11.5

Based on PHE 2018 data
Number of diagnosed persons are based on HARS (HIV & AIDS Reporting System).
Estimates of the undiagnosed from MPES (Multi-Parameter Evidence Synthesis) using the upper bound of the estimates to be conservative.

*Viral load undetectable is defined as <200 copies/ml and above this figure is considered detectable and 'transmissible'. Assumptions made that all persons living with undiagnosed HIV have detectable (transmissible) virus. Also added to this, is the number persons living with diagnosed HIV who did not have evidence of undetectability in 2018 (either because of treatment failure, not started ART, not retained in care, missing viral load measurement).

5.4 Transmission risk varies by type of exposure where the index case is known to be HIV-positive and not on suppressive antiretroviral therapy

The risk of HIV transmission per exposure from a known HIV-positive individual not on suppressive ART is summarized in table 2.

5.4.1 Table 2: Risk of HIV transmission per exposure from a known HIV-positive individual not on suppressive antiretroviral therapy

Type of exposure	Estimated risk of HIV transmission per exposure from an HIV-positive individual who is NOT on suppressive ART*	Refs
Receptive anal intercourse	1 in 90	(52-58)
Receptive anal intercourse with ejaculation	1 in 65	(52-59)
Receptive anal intercourse no ejaculation	1 in 170	(59)
Insertive anal intercourse	1 in 666	(52, 54, 55, 60)
Insertive anal intercourse not circumcised	1 in 161	(59)
Insertive anal intercourse and circumcised	1 in 909	(59)
Receptive vaginal intercourse	1 in 1000	(52, 57, 61-67)

Insertive vaginal intercourse	1 in 1,219	(56, 57, 61-67)
Semen splash to eye	<1 in 10,000	(68)
Receptive oral sex (giving fellatio)	< 1 in 10,000	(55, 62, 67, 68)
Insertive oral sex (receiving fellatio)	< 1 in 10,000	(54, 67)
Mucocutaneous	1 in 1000	(69)
Blood transfusion (one unit)	1 in 1	(70)
Needlestick injury	1 in 333	(15, 68, 71)
Sharing injecting equipment (includes chemsex)	1 in 149	(69)
Human bite	< 1 in 10,000	(72, 73) (74)
*These figures are estimates that have been deduced from cohort and modelling studies		

5.5 Calculating the risk of HIV transmission from a single exposure

The risk of an individual acquiring HIV following an exposure can be calculated by multiplying the risk that the index case is HIV-positive with a detectable viral load (Table 1) and the risk per exposure (Table 2):

Risk of HIV transmission = risk that source is HIV positive with a detectable HIV viral load X risk per exposure

For example, if a man presents for PEP following condomless receptive anal sex with ejaculation with male partner of unknown HIV status in London:

Risk of HIV transmission = 32/1000 x 1/65 = 32/65000 = 1/2031 (or 0.05%)

If the index case is not on suppressive ART, certain factors may further increase the risk of HIV transmission and must be considered and discussed in a PEP consultation, see box 1:

Box 1: Factors increasing the risk of HIV transmission if the index case is HIV-positive and NOT ON ART:

1. A high plasma HIV viral load (VL) in the index case – 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] (75). This may be particularly relevant during primary HIV infection (62).
2. Breaches in the mucosal barrier such as mouth or genital ulcer disease and anal or vaginal trauma following sexual assault or first intercourse (76, 77).
3. Menstruation or other bleeding – theoretical risk only
4. Pregnancy or postpartum – per-act probability of HIV acquisition higher in late pregnancy (adjusted relative risk [aRR] 2.82, p=0.01) and the postpartum period (aRR, 3.97, p=0.01) as compared to that during the non-pregnant period.(78)
5. Sexually transmitted infections in HIV positive individuals not on ART (79, 80) or HIV negative individuals with genital ulcer disease (81).

5.6 Risk of HIV transmission following occupational exposures

5.6.1 Definition of exposure and infectious fluid in occupational settings

In an occupational setting 'exposure' means contact with potentially infectious bodily fluids or tissue which poses risk of transmission of HIV through either:

A. A percutaneous injury (e.g. a needlestick or cut with a sharp instrument contaminated with the index case's blood or other bodily fluids).

B. A mucous membrane (e.g. splash injury to the eye) or non-intact skin (e.g. exposed skin that is abraded, or afflicted with dermatitis) exposure.

C. A bite if the skin is broken as a result of trauma.

Body fluids implicated in the transmission of HIV are: blood, semen, vaginal secretions and other body fluids contaminated with visible blood. Other body fluids that could be potentially infectious are cerebrospinal fluid, synovial, pleural, peritoneal, pericardial, and amniotic fluid. Fluids that are not considered infectious (unless they contain blood) include faeces, nasal secretions, saliva, gastric secretions, sputum, sweat, tears, urine and vomit (82).

5.6.2 Immediate actions following occupational exposure to reduce transmission risk

Following an exposure to blood or other body fluids, the exposed site should be immediately cleansed as follows:

1. For skin exposures, the site should be washed with soap and water. Small wounds and punctures may also be cleansed with an antiseptic, for example an alcohol-based hand hygiene solution. Alcohol is virucidal to HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV). Other antiseptics, such as iodophors, chloroxylenol, and chlorhexidine also inactivate HIV (83).
2. In cases of mucosal exposure, the exposed mucous membranes should be flushed with a copious amount of water. Eyes should be irrigated with saline or water.

Squeezing the wound to express blood is not recommended.

5.6.3 Needlestick and sharps injuries

The risk of HIV transmission from a percutaneous exposure ('sharps injury') from an HIV-positive index case NOT on suppressive ART is estimated to be 0.3% (1 in 333) (15, 84). A pooled analysis of prospective studies in healthcare workers published in 1997 identified factors associated with increased odds of HIV seroconversion (15, 84):

1. Deep injury (OR 15, 95% CI, 6.0 to 41)
2. A device visibly contaminated with the patient's blood (OR 6.2, 95% CI, 2.2 to 21)
3. Needle placement in a vein or artery (OR 4.3, 95% CI 1.7 to 12)
4. Terminal clinical AIDS in the index case (OR 5.6, 95% CI, 2.0 to 16) – this is likely to indicate a high viral load in the index case

UK HPA data from 1999 to 2018 have found no new cases of HIV after 8765 reported significant occupational exposures among healthcare workers (18). The key studies informing our understanding of occupational seroconversion are summarized in Table 3 (section 5.6.5).

5.6.4 Mucocutaneous exposures or splash injuries

The risk of HIV acquisition from a mucocutaneous 'splash' injury (e.g. eye) is estimated to being around 0.1% (1 in 1000 exposures) if the HIV-positive index case is not on ART, considerably lower than a percutaneous 'sharps' injury. Globally, in a systematic review and meta-analysis, 8 cases of HIV transmission attributable to splash injuries were identified, almost always from a blood splash exposure rather than other bodily fluids (84).

HIV cannot be transmitted through intact skin. The risk of HIV transmission through non-intact skin (e.g. abrasions, cuts, sores) is considered to be negligible; to our knowledge there have not been any reported case of HIV transmission through skin cuts or other forms of loss of skin integrity.

5.6.5 Table 3: Summary of evidence relating to HIV transmissions from occupational exposures

Author, year	Setting	Study type	Duration of follow-up	Number of occupational exposures	Number (%) of exposures where index case was HIV-positive	Type of exposure	Other BBV	Received PEP	Number of HIV seroconversions
Li Hui, 2013 (21)	Australia	Case report	N/A	1	100%	Sharps injury[1]	No	100%	100%
Sin, 2016 (85)	Hong Kong	Retrospective cohort.	12 months[2]	1525	50 (3.3%)	Sharps 89% Splash 11%	HBV 7.4% HCV 1.6%	3.1%	None
Nwaiwu, 2017 (86)	USA	Prospective cohort.	13 years	266	266 (100%)	Sharps 53% Splash 43% Unknown 4%	No	21%	None
Rajkumar, 2014 (87)	India	Prospective cohort.	6 months	356	8 (2.2%)	Sharps 85% Splashes 15%	HBV 3.1%	None	None
Himmelreich 2013 (88)	Germany	Prospective cohort.	18 months	519	51/449 (11.4%)	Sharps 100%	HCV 9.8% HBV 3.6%	No	None
Gupta, 2008 (89)	India.	Prospective cohort.	2 years	557	88 (16%)	Sharps 81.1% Splash 18.8%	No	48% of 'high-risk' exposures	None
Cardo, 1997 (15)	USA	Case-control study.	7 years	33	N/A	Sharps 100%	No	9%	33
Tomkins, 2002 (19)	Worldwide	Surveillance	1999 - 2002	Unknown	N/A	Unknown	No	100%	24 (6 definite cases and 18 possible)
Evans, 1999 (20)	Worldwide	Surveillance	1984-1999	Unknown	N/A	Sharps 89% Splash 8% Unknown 3%	No	Unknown	286 (95 definite[3] and 191 possible)
Woode, 2014 (18)	UK	Surveillance	2004-2013	4830	1270/4766 (30%)	Sharps 71% Splash 29%	Known / possible HCV 54% HBV 9%	77%	None

Public Health England, 2020 (17)	UK	Surveillance	1997 - 2018	8,765	8,292 HIV-positive / unknown HIV status	Unknown	Unknown	46%	None

BBV = blood borne virus NSI = needlestick injury HCV = hepatitis C virus HBV = hepatitis B virus

1= Large volume inoculum from HIV-positive index case with viraemia (>100,000 copies/ml). Single-genome sequencing of plasma viral RNA identified 15 drug susceptible transmitted/founder HIV genomes responsible for productive infection. Sequences emanating from these genomes exhibited extremely low diversity, suggesting virus sequestration as opposed to low-level replication as the cause of breakthrough infection.
2 = Only 6-months of follow-up if PEP not prescribed
3 = Most (85/95; 89%) of the definite occupationally acquired HIV infections followed percutaneous exposure. Among the 10 remaining cases, eight were from mucocutaneous exposure and for two the exposure was not specified.

5.6.6 Biting and spitting

In 2018, a systematic review was conducted to review the risk of HIV transmission through biting or spitting (74). No cases of HIV transmission relating to spitting were identified, supporting the conclusion that there is no risk of HIV transmission from spitting. Healthcare workers, emergency workers or members of the public can be fully reassured that there is no indication for PEP following spitting incidents. Nine cases of possible HIV transmission following biting episodes were identified in the systematic review. There was however, considerable heterogeneity in the quality of the published literature. Poor-quality case reports included those in which: 1) the recipient had no documented HIV test at baseline; 2) the recipient had other significant potential risk factors for HIV transmission; 3) HIV seroconversion was reported to have occurred at a time interval incompatible with transmission secondary to the bite. In only three cases was the linked transmission confirmed by RNA sequencing and in total only four cases of HIV transmission were thought to plausibly result from a bite. In each case, the perpetrator had advanced HIV infection and was not on ART and was therefore likely to have high-level HIV viraemia. In three of the four cases, the bite resulted in a deep wound and the perpetrator had blood in their mouth at the time of the incident. In the fourth case, multiple bites were sustained from an HIV-positive individual who was reported to have bleeding gums, but who had unknown HIV viral load and ART status; it was not reported whether the bites resulted in skin breakage. Considering these factors together, the review concluded that that the overall risk of acquiring HIV from a bite by an HIV-positive person is negligible, but the risk is increased by presence of blood in the saliva plus a high viral load of the perpetrator plus deep wounds being inflicted (90).

5.7 Risk of HIV transmission through injecting drug use

HIV and other blood-borne viruses, including hepatitis B and C, can be transmitted between PWID through the sharing of needles and other injecting equipment contaminated with infected blood (84, 91, 92). In 2018, the prevalence of HIV among PWID who participated in the unlinked anonymous seroprevalence monitoring survey in England was low at 1.2% (95% Cl, 0.08%-1.6%) (93). In 2018, there were 94 new HIV diagnoses which were likely to have been acquired through injecting drug use in the UK (94-96). Overall, the number of people acquiring HIV through injecting drug use in the UK has been low since the early epidemic, except in the context of localised outbreaks. Although first identified in early 2015, an outbreak of HIV among PWID in

Glasgow remains ongoing in 2019. Since its onset, over 150 individuals have been diagnosed with HIV as part of that outbreak, related to transmission among a population who inject psychoactive drugs within Glasgow city centre. This population were often homeless, with high levels of involvement in the criminal justice system. Between 2011 and 2018, HIV prevalence in PWID rose from 0·1% (95% CI 0·0–0·6) to 4·8% (3·4–6·2) overall, and from 1·1% (0·2–6·2) to 10·8% (7·4–15·5) in Glasgow city centre (97). This ongoing outbreak demonstrates that the availability of needle exchanges and opioid replacement therapy, may be insufficient to prevent outbreaks in this vulnerable group and PEP should be considered in a broader package of HIV prevention measures in PWID during an outbreak situation.

5.7.1 Sexualised drug use

Sexualised drug use refers to the use of drugs in a sexual context. This includes 'chemsex', which describes the use of certain recreational drugs, particularly crystal methamphetamine, GHB/GBL (gamma hydroxybutyrate / gamma butyrolactone) and mephedrone, before or during planned sexual activity to sustain or enhance the experience (98, 99). In a 2018 survey of 836 MSM attending sexual health clinics, 17% reported sexualised drug use in the last 6 months and 10% reported injecting ("slamming") chemsex drugs in the last 6 months (100), which leads to potential exposure to HIV and other blood borne viruses (BBVs). High levels of function in other aspects of life are often maintained and men may not self-identify as injecting drug users. Individuals who report drug use in a sexual context should therefore be asked about injecting and about sharing of equipment (101).

It is difficult to separate the risk of HIV transmission through sharing injecting equipment from the risk of HIV transmission from condomless anal sex. New PEP consultations are an ideal opportunity to identify those at risk and offer evidence-based interventions such as PrEP to reduce the risk of acquiring HIV.

6 When to prescribe PEP

The is no evidence to inform the exact risk threshold at which PEP is indicated from an individual, population level and cost-effectiveness perspective. The 2015 PEP guidelines suggested that if the risk of HIV transmission is >1/1000 then PEP is recommended, between 1/1000 and 1/10,000 PEP should be considered and <1/10,000 PEP is not recommended. These thresholds were not evidence-based so have been removed but we recognise they may assist services in making decisions on a case-by-case basis. In this latest iteration of the guidelines we have included four categories which were informed by similar thresholds:

- Recommended: the benefits of PEP are likely to outweigh the risks, PEP should be given unless there is a clear reason not to.

- **Consider:** the risk of HIV transmission is low, the risk / benefit balance of PEP is less clear. The risk should be assessed on a case by case basis taking into consideration factors shown in footnotes c and d below.
- **Generally not recommended:** the risk of HIV transmission is very low, the potential toxicity and inconvenience of PEP is likely to outweigh the benefit unless there is a clear specific extenuating factor which increases the risk. We anticipate PEP should very rarely be given when the risk has been assessed and discussed. The risk here is generally <1/10,000 but specific factors may increase the risk to >1/10,000.

Not recommended: the risk of HIV transmission is negligible and PEP should not be given.

6.1 When to prescribe PEP following sexual exposure

1	We recommend the use of PEP following sexual exposure where there is a significant risk of HIV transmission.	1C
2	The risks and benefits of providing PEP for adolescents should be weighed carefully in the context of UK laws and judgements about autonomy in healthcare decision-making (e.g. Gillick competency), and balanced against protecting young people from harm.	GPP

A risk assessment and risk-benefit analysis should be undertaken for every individual presenting following an exposure and the decision to initiate PEP made on a case-by-case basis. This should consider both the risk of the index case being HIV-positive with a detectable viral load (**Table 1, section 5.3.1**), the risk of transmission according to exposure (**Table 2, section 5.4.1**) and the ART status and viral load in the index case, if known. Where the index case is known to be HIV-positive but not virologically suppressed, it is important to ascertain if they have experienced prior virological failure and/or have known drug resistance mutations. The recommendations for PEP with sexual exposure are summarised in **Table 4 (section 6.5)**. Awareness of the local HIV seroprevalence in the index partner should be factored into local protocols.

The risk calculation/assessments for an adolescent following sexual or occupational exposure should be the same as those for an adult. A decision on whether to offer PEP should be made in the same way. The decision about whether to complete the decision-making process and/or provide PEP with or without involvement of the parent or guardian should be made in the context of UK laws and judgements about autonomy in healthcare decision-making (e.g. Gillick competency), and balanced against protecting young people from harm.

6.1.1 Index partner is of unknown HIV status

3	Proactive attempts should be made to establish the HIV status of the index partner; this should not however delay initiation of PEP where indicated (Table 4).	1C

Proactive attempts should be made to establish the HIV status of the index partner whilst not delaying PEP initiation where indicated. If the index partner is from a risk-group or country of high HIV prevalence

(prevalence >1%) and is not known to be on suppressive ART then PEP is routinely recommended following receptive anal sex, see **Table 4 (section 6.5)**.

6.1.2 Index partner known to be HIV-positive

4	Attempts should be made at the earliest opportunity to determine the plasma HIV viral load, resistance profile and treatment history of the index partner	GPP
5	PEP is not recommended if the index partner has been on ART for at least 6 months with an undetectable plasma HIV viral load (at the time of last measurement and within the last 6 months) and with good reported adherence.	1A
6	Individuals should be encouraged to undergo a formal PEP assessment and verification of index partner's HIV details even when they believe the partner has an undetectable HIV viral load.	GPP
7	If there are any doubts about the ART history, the index partner's adherence to ART or the viral load, then PEP should be given following condomless receptive anal intercourse	GPP

In the setting where the individual is known to be HIV-positive and known not to be on suppressive ART, the risk per exposure can be calculated by multiplying the number 1 and the risk per exposure **(Table 2, section 5.4.1):**

Risk of HIV transmission = risk that source is HIV positive with a detectable HIV viral load X risk per exposure
= 1 x risk per exposure

For example, if a man presents for PEP following condomless receptive anal intercourse with ejaculation with an HIV-positive male partner who is not on ART:

Risk of HIV transmission = 1 x 1/65 = 1/65 = 0.015 (or 1.5%)

If the index partner 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 to determine if PEP is required and which regimen should be used in the context of detectable viraemia and potential for drug resistance. Both an RCT and observational studies have confirmed that individuals on suppressive ART cannot transmit HIV sexually regardless of sexual orientation (49, 51, 102-105). In light of this, PEP is not recommended for any kind of condomless sex with an HIV-positive person who has been on ART for at least 6 months with an undetectable HIV viral load (at the time of last measurement andwithin the previous 6 months) and reported good adherence, see Table 4 (1A). If there is any doubt about the index partner's viral load or adherence to ART, then PEP should be given as a precaution following condomless anal intercourse.

PEP is 'not-recommended' following fellatio with ejaculation as the risk is estimated to be very low at <1/10,000 (2C). A cohort study demonstrated that after an estimated total of over 19,000 condomless orogenital exposures with an HIV-positive partner, no HIV seroconversions occurred (67). A modelling study from 1999 estimated an upper limit of risk of 4/10,000 (54). There was only one single transmission pair (confirmed by sequencing), where both individuals independently reported only orogenital contact (106).

Other case reports of unproven linked orogenital transmission, featured dental procedures, pharyngitis, chemotherapy and periodontal diseases as additional risk factors (107). In extreme circumstances, such as primary HIV infection and oropharyngeal trauma / ulceration, PEP can be considered but in general PEP is not recommended. PEP is also not recommended following semen splash in the eye as the risk is negligible with no documented HIV transmissions via this route (GPP).

Following insertive vaginal intercourse with an HIV-positive partner not on ART, PEP should be 'considered' rather than routinely 'recommended' as the risk is <1/1219 (56, 57, 61) (2C). Again, presence of additional factors in **Box 1 (section 5.5)** should be reviewed and clinician discretion applied.

6.1.3 Sexual assault

There is concern (though no published evidence) 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 PEP more readily in such situations, particularly if the assailant is from a high prevalence group (108). If the assailant is from a low prevalence group in the UK, after the balance of risks and benefits are discussed with the patient, it is likely PEP provision will generally not be indicated.

6.1.4 Commercial sex workers

HIV prevalence among female sex workers varies by region but has remained low <1% in Western Europe and Central Europe (1% - 2%), but is higher in Eastern Europe ranging between 2.5% and 8% (109). HIV prevalence if highest in sex workers who inject drugs (109). HIV prevalence among male sex workers, reported from 27 countries, was 14% (110). The formula in section 5.5 can be used to determine the risk of HIV transmission.

6.2 When to prescribe following occupational exposures

6.2.1 Sharps and mucosal splash injuries

6.2.1.1 HIV-positive index case

8	PEP is recommended following a high-risk injury (sharps or mucosal splash) if the index case is known to be HIV-positive and is not on ART for >6 months with a suppressed viral load within the last 6 months.	1C
9	PEP is generally not indicated following a sharps injury if the index case has been on ART for at least 6 months with an undetectable HIV viral load (at the time of last measurement and within the previous 6 months) and reported good adherence, see Table 4 (1A). However due to lack of direct evidence, a case by case decision can be made depending on the nature of the injury.	2C
10	PEP is not recommended following a splash injury If the index case is known to have a sustained undetectable viral load	1C
11	PEP is not recommended where there is no or negligible risk of HIV transmission e.g. through intact skin that comes into contact with HIV infected blood or other bodily fluids.	1C

The extensive data informing elimination of transmission risk with suppressive ART only applies to sexual exposures. In the context of sharps and mucocutaneous splash injuries, the transmission risk when the index is on suppressive ART is likely to be negligible. PEP is not recommended following any splash injury where the index case has been on ART for at least 6 months with an undetectable plasma HIV viral load (at the time of last measurement and within the last 6 months) with good reported adherence, but can be considered if there is a blood splash to a mucosal surface and the index case is not known to be undetectable. Although it is highly likely that viral suppression eliminates the risk of HIV transmission through sharps injuries, the lack of evidence to support this should be discussed, and a case-by-case decision can be made in the context of high-risk sharps injuries. Where there are concerns about the viral load of the index case being detectable, or concerns around ART adherence or if the injury is particularly high risk (e.g. deep wound with hollow bore needle) then PEP could be considered.

6.2.1.2 Index case of unknown HIV status

12	PEP is not recommended following a sharps or mucosal splash injury if the index case is untested but from a low risk group. Table 4	1C
13	PEP is generally not recommended following a sharp or mucosal splash injury if the index case is untested and from a high-risk group (e.g. MSM or PWID), unless there were other factors that increased likelihood of transmission (e.g. a deep injury or blood bolus injected or a sharps injury from a PWID in the context of a local outbreak), see Table 4.	1C
14	All efforts should be made to seek prompt voluntary HIV testing of the index case	1C
15	Index case HIV testing should not delay PEP initiation where indicated	GPP
16	If the index case is unable to give informed consent for HIV testing (e.g. unconscious, altered mental status) then HIV testing can be performed if it is the best medical interest of the index case	GPP

When deciding whether PEP is indicated where HIV status of the index case is unknown and not obtainable or pending the HIV test result, the probability of the index case being HIV-positive must be estimated from **Table 1 (section 5.3.1)**, or if the index case is of non-UK origin, using this link https://aidsinfo.unaids.org. The equation described in **section 5.5** and shown below can be used to calculate the risk of HIV transmission from the incident.

Risk of HIV transmission = risk that source is HIV positive with a detectable HIV viral load X risk per exposure*

*1/333 for needle stick injury
*1/1000 for splash injury

For example, a female of British origin has a prevalence of detectable HIV viraemia of 0.1 in 1000 or 1/10,000 (**table 1, section 5.3.1**), which when multiplied by the risk of transmission from a needle stick injury (1/333) give a transmission risk from the incident of: 1/10,000 x 1/333 = 0.0000003 or 1/3,333,333. So, in the above example of a needlestick from a British female of unknown HIV status, PEP would not be recommended as the risk is negligible.

Conversely, in the example of a needlestick from an MSM in London the probability of the index case being HIV positive with a detectable viral load is 32/1000, which multiplied by the transmission risk of x 1/333, gives a risk of HIV transmission of: 32/1000 x 1/333 = 32/333000 = 1/10,405 (or 0.01%). This risk is also extremely small, so PEP would generally not be recommended unless there were other factors that increased likelihood of transmission, such as an inoculum of blood having been injected. In the case of an uncomplicated needlestick injury from an untested MSM, the extremely small risk of HIV transmission along with the potential toxicity and inconvenience of PEP should be directly discussed with the individual. We anticipate that in most cases following a risk assessment, and discussion about risks and benefits, PEP would generally not be given. However, the decision must be made on a case by case basis using clinician discretion and taking into account the preferences of the attendee.

6.2.2 Needlestick injuries in the community

17	PEP is not recommended following a community needlestick exposure	2D

In general, PEP is not recommended following a community needlestick exposure as the risk is extremely low risk (111) and usually not possible to determine: (i) whether the needle has been used and for what purpose; (ii) the HIV status of the index case and; (iii) the interval between the needle use and the exposure. Whilst there have been a handful of cases of hepatitis B and C transmission from community needlesticks there have been no reported cases of HIV transmission. The maximum potential risk of transmission from a needlestick injury from freshly discarded needle in the community can be calculated using regional HIV prevalence data **(table 1, section 5.3.1)**, and the following formula:

Risk of HIV transmission = risk that source is HIV positive with a detectable viral load X 0.3 (risk per exposure)

However, 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 (112). Therefore, this formula should only be used, and PEP considered following a community needlestick injury, if the recipient is confident that it was a freshly discarded needle.

6.3 Human bites

18	In general PEP is not recommended following a bite as, although the precise risk of transmission is unknown, it is likely to be negligible	2D
19	However, PEP could be considered for patients who fulfil ALL of the three following criteria: a) the biter's saliva was visibly contaminated with blood; b) the biter is known or suspected to have a plasma HIV viral load >3.0 log copies/ml; and c) the bite has resulted in severe and/or deep tissue injuries	2D

Further information on the evidence that supported this recommendation can be found in section 5.6.6 and guidance regarding the management of human bites is available at: http://cks.nice.org.uk/bites-human-and-animal#!scenario:1

6.4 People who inject drugs (PWID)

As described in section 5.7, overall the number of people acquiring HIV through injecting drug use in the UK has been low since the early epidemic, except in the context of localised outbreaks.

20	Individuals who report the use of any injectable drugs, should be asked specifically if they are currently injecting and if so, is equipment ever shared	GPP
21	The HIV status and, if positive, viral load and ART history of their injecting partners should be ascertained	GPP
22	PEP is recommended for PWID after sharing needles/equipment if their index injecting partner is HIV-positive and not ART for >6 months with a suppressed viral load.	1C
23	PEP is generally not recommended in PWID after sharing needles/equipment with an injecting partner of unknown HIV status from a high prevalence country / risk-group, but PEP can be considered on a case-by-case basis for PWID in the context of a localised outbreak.	GPP
24	Existing harm-reduction strategies such as needle exchange and opiate substitution programmes should be encouraged for people who inject drugs.	1D
25	MSM should be specifically asked about chemsex and injecting drug use.	2D

6.5 Table 4: Summary table of PEP prescribing recommendations

	Index HIV positive		Index of unknown HIV status	
	HIV VL unknown or detectable	HIV VL undetectable	From high prevalence country / risk-group (e.g. MSM) [a]	From low prevalence country / group
SEXUAL EXPOSURES				
Receptive anal sex	Recommend	Not recommended [b]	Recommend	Not recommended
Insertive anal sex	Recommend	Not recommended [b]	Consider [c,d]	Not recommended
Receptive vaginal sex	Recommend	Not recommended [b]	Generally not recommended [c,d]	Not recommended
Insertive vaginal sex	Consider [c]	Not recommended	Generally not recommended [c,d]	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
OCCUPATIONAL AND OTHER EXPOSURES				
Sharing of injecting equipment	Recommended	Not recommended [b]	Generally not recommended[e]	Not recommended
Sharps injury	Recommended	Not recommended [b]	Generally not recommended [c,e,f]	Not recommended
Mucosal splash injury	Recommended	Not recommended [b]	Generally not recommended[c]	Not recommended
Human bite	Generally not recommended [g]	Not recommended	Not recommended	Not recommended
Needlestick from a discarded needle in the community			Not recommended	Not recommended

Recommended: the benefits of PEP are likely to outweigh the risks, PEP should be given unless there is a clear reason not to.

Consider: the risk of HIV transmission is low, the risk / benefit balance of PEP is less clear. The risk should be assessed on a case by case basis taking into consideration factors shown in footnotes c and d below.

Generally not recommended: the risk of HIV transmission is very low, the potential toxicity and inconvenience of PEP is likely to outweigh the benefit unless there is a clear specific extenuating factor which increases the risk (see footnotes c, d, e, f below). We anticipate PEP should very rarely be given when the risk has been assessed and discussed (section 6.1.2 and 6.2.1.2)

Not recommended: the risk of HIV transmission is negligible and PEP should not be given

[a] High prevalence countries or risk-groups are those where there is a significant likelihood of the index case individual being HIV-positive. Within the UK at present, this is likely to be MSM (men who have sex with men), people who inject drugs from high-risk countries (see d 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 at https://aidsinfo.unaids.org

[b] The index case has been on ART for at least 6 months with an undetectable plasma HIV viral load at the time of last measurement and within the last 6 months) with good reported adherence. Where there is any uncertainty about HIV VL results or adherence to ART then PEP should be given. The viral load threshold considered 'undetectable' in the PARTNER 1 and 2 and HPTN052 studies was <200 copies/ml.

[c] Factors that influence decision-making in all exposures: More detailed knowledge of local HIV prevalence within index case sub-population [a]. The recommendations relate to high-risk groups living in the UK (based on the known prevalence of detectable HIV viraemia in the UK, guideline table 1). Where the index case is from a high risk group and normally resides outside the UK, the risk may be greater and where there is doubt PEP should be given.

[d] Factors that may influence decision-making include in sexual exposures:

1. Breaches in the mucosal barrier such as genital ulcer disease and anal or vaginal trauma following sexual assault or first intercourse
2. Multiple episodes of exposure within a short period of time e.g. group sex
3. Sexually transmitted infection in either partner
4. Individuals at higher risk of acquiring HIV e.g. transgender

[e] HIV prevalence amongst IDUs varies considerably depending on whether there is a local outbreak and 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.
[f] Factors that may influence decision-making include in occupational exposures: Deep trauma or bolus of blood injected
[g] PEP should only be considered after a bite if all three criteria are met: a) the biter's saliva was visibly contaminated with blood; b) the biter is known or suspected to have a plasma HIV viral load >3.0 log copies/ml; and c) the bite has resulted in severe and/or deep tissue injuries

7 What to prescribe for PEP

7.1 First-lines

26	We recommend the use of tenofovir disoproxil 245mg/emtricitabine 200mg and raltegravir 1200mg once daily as the regimen of choice for PEP (table 5).	1B
27	If there is evidence that the index case has a current or past history of ART failure, expert advice should be sought as to whether the PEP regimen should be modified in relation to ART history and/or resistance testing.	1D
28	For women who are pregnant, raltegravir 400mg twice daily is preferred (with tenofovir disoproxil 245mg/emtricitabine 200mg). Where accessing raltegravir 400mg might cause delay we recommend using raltegravir 600mg twice daily and switching at the earliest opportunity.	1D

In established HIV infection, combination therapy with at least three medications from two medication classes is recommended for initial therapy. It is thus recommended, to use a triple agent regimen for PEP (1D), though some international guidelines do recommend dual-class regimens in selected situations (113, 114). Simplification to two drugs could be considered in select rare situations if continuing a third agent is not possible.

7.1.1 Nucleoside reverse transcriptase inhibitors (NRTI)

Emtricitabine (FTC) and tenofovir disoproxil (TD) are recommended as the NRTI backbone based on efficacy, tolerability, safety and convenience. Although most PEP and PrEP studies have used tenofovir-disoproxil fumarate (TDF), generic tenofovir-disoproxil is often formulated as a non-fumarate salt; since all approved salt formulations have demonstrated bioequivalence to tenofovir-disoproxil fumarate they are interchangeable. 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) (13) and good male and female genital tract penetration, including the rectal compartment, in human studies (115); these characteristics may be advantageous for PrEP and PEP (13). Phase 3 PrEP studies have demonstrated high efficacy rates for tenofovir disoproxil fumarate alone and tenofovir disoproxil fumarate/FTC in high-risk heterosexuals and MSM (116-119). A 2015 systematic review of antiretroviral drugs for PEP concluded that tenofovir disoproxil-based regimens have better completion rates than zidovudine-based regimens (78% versus 59%) and the rate of PEP discontinuation due to an adverse event was lower among people taking

tenofovir disoproxil-based PEP (0.3%; 95% CI, 0%–1.1%) vs a zidovudine (ZDV)-based regimen (3.2%; 95% CI, 1.5%–4.9%) (120).

Tenofovir-alafenamide (TAF), is a tenofovir prodrug and is considered a safer alternative than tenofovir-disoproxil in patients with chronic kidney disease and could be used where baseline eGFR is <50ml/min. Currently, there are no in-human data on the use of tenofovir-alafenamide for PEP, however in combination with FTC, tenofovir-alafenamide was at least as effective as tenofovir-disoproxil in a large PrEP trial in MSM (121), while data in women are not available.

Tenofovir disoproxil/FTC is generally well tolerated in practice; however very common side effects (≥1/10) include headache, dizziness, diarrhoea and nausea, and common side effects (≥ 1/100 to < 1/10) include insomnia and abdominal pain (122). These side effects are usually mild, transient and rarely treatment-limiting. Tenofovir-disoproxil is associated with renal toxicity and, although this is usually not clinically important in the context of short-course prescribing for PEP, individuals should undergo baseline assessment of renal function and an alternative NRTI backbone prescribed when the calculated creatinine clearance is below 50mls/min, see table 5 (section 0).

7.1.2 Integrase inhibitors (INSTI)

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) (123-125) in the context of triple therapy for HIV treatment. Raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) have been widely used in the UK. Bictegravir (BIC) was licensed in the UK in June 2018. Elvitegravir requires co-administration with cobicistat, a pharmacokinetic booster with a similar drug-drug interaction profile as ritonavir. A 600mg tablet of raltegravir was licensed in the UK in 2017, facilitating a 1200mg once daily dosing regimen. Unfortunately, the 600mg tablets are more hygroscopic and currently the summary of product characteristics (SPC) specifies that they must be stored in their original packaging – a sealed water-tight container with moisture absorbent – as stability data for non-original packaging is awaited. Therefore at this point in time, 5 day starter packs containing RAL 600 mg tablets cannot be produced and the minimum duration that can be dispensed is 30 days. Once daily raltegravir 1200mg remains the preferred third agent where the full 28-day PEP course is given at the initial attendance. We recommend a cessation of starter pack use where possible due to the reasons outlined in section 9.2. In services where PEP must be initiated with a 5 day starter pack, and if stability data for the RAL 600 mg in non-original packaging remains unavailable, then RAL 400 mg twice daily is the preferred third agent.

The most common clinical adverse events reported with INSTI are diarrhoea, nausea and headache. Suicidal ideation or behaviour is an uncommonly reported side effect of dolutegravir particularly in patients with a

pre-existing history of depression or psychiatric illness (126). INSTI are better tolerated than PI and rates of INSTI resistance in the UK are low (section 4.2.3).

This decision to use raltegravir 1200mg of as the preferred third agent was made due to a number of considerations: 1) concern about neural tube defects in women at risk of pregnancy which would complicate the counselling process for PEP providers 2) cost 3) good tolerability data from a UK observational study (127). The optimal regimen will be reviewed at the time of the next guideline update.

Raltegravir: Observational studies assessing raltegravir-emtricitabine-tenofovir as PEP in MSM conclude that it is well tolerated and results in high levels of adherence (128-130). A PEP RCT, showed that tenofovir/emtricitabine plus raltegravir 400mg bd was better tolerated than tenofovir/emtricitabine plus lopinavir/ritonavir (131). Recent data on raltegravir 1200mg once daily (with tenofovir 245mg/emtricitabine 200mg) as PEP from 143 adults in Belfast, found the regimen to be well tolerated with 123/143 (87%) reporting no side effects. Amongst the 19/143 (13%) who reported side effects headache, diarrhoea and nausea were the most common. One person reported poor sleep and suicidal ideation There were no serious laboratory adverse events. No HIV seroconversions were reported amongst those (109/143, 76%) who attended for follow up HIV blood testing (*in press, HIV Medicine*).

Elvitegravir: Three PEP studies of elvitegravir/cobicistat in combination with tenofovir (disoproxil or alafenamide)/emtricitabine including over 400 individuals demonstrated a high completion rates and good tolerability. One seroconversion was observed in an individual with multiple exposures before and after PEP (28). Elvitegravir/cobicistat in combination with a tenofovir/emtricitabine backbone is a single tablet regime option for PEP but is limited by the risk of drug-drug interactions due to the boosting agent cobicistat.

Dolutegravir: One open-label, single-arm study at three sexual health clinics and two emergency departments in Australia followed up 100 HIV-negative MSM requiring PEP who received dolutegravir and tenofovir/emtricitabine for 28 days (132). No participants acquired HIV through week 12. The most common clinical adverse events were fatigue (26%), nausea (25%), diarrhoea (21%), and headache (10%). Dolutegravir with tenofovir/emtricitabine is a safe and reasonably well-tolerated option for once-daily PEP. There is a BHIVA statement on a potential safety signal relating to neural tube defects (NTD) in infants born to women conceiving on dolutegravir in Botswana and this is discussed further in section 10.2. (https://www.bhiva.org/BHIVA-statement-on-safety-signal-in-infants-born-to-mothers-conceiving-on-dolutegravir, accessed 13/02/2020).

Bictegravir: There is no data available to support the use of bictegravir-based PEP.

7.1.3 Table 5. Recommended combinations for PEP

	NRTI backbone (2 medications)	Third agent
Recommended combination	Tenofovir disoproxil 245mg, emtricitabine 200mg [a] one tablet once daily	Raltegravir 1200mg once daily [b,c]
Alternative 1	eGFR [e] 30-50 ml/min: Descovy [f]: 25mg one tablet once daily eGFR [d] <30 ml/min: Seek expert advice from ID/GUM/Sexual Health team	<u>Integrase inhibitors</u> Raltegravir 400mg twice daily [b] OR Dolutegravir 50mg, one tablet once daily [b,d] <u>Protease inhibitors</u> Darunavir 800mg + ritonavir 100mg [g] once daily OR Atazanavir 300mg + ritonavir 100mg [g] once daily
Alternative 2	Elvitegravir 150mg/cobicistat 150mg/tenofovir-DF 245mg/emtricitabine 200mg FDC: one tablet once daily [g] If eGFR 30-70 ml/min elvitegravir 150mg/cobicistat 150mg/tenofovir-AF 10mg/emtricitabine 200mg FDC	

[a] Tenofovir disoproxil 245mg/emtricitabine 200mg FDC is the preferred agent in chronic hepatitis B virus infection

[b] Antacids and multivitamins (products containing metal cations e.g. magnesium / aluminium, which can chelate and reduce the absorption of INSTIs) should be avoided where possible during PEP with once daily raltegravir, see appendix A. An alternative non-interacting medication may be considered. Metal cation containing medicines must be separated by at least 4 hours from twice daily raltegravir and dolutegravir. See appendix A for other drug drug interactions including rifampicin.

[c] For women who are pregnant raltegravir 400mg twice daily is preferred as the third agent. Where accessing raltegravir 400mg might cause delay we recommend using raltegravir 600mg twice daily and switching at the earliest opportunity.

[d] For women who are at risk of pregnancy or under 6 weeks pregnant, we recommend avoiding the use of dolutegravir. For women who are more than 6 weeks pregnant, dolutegravir-based PEP can be used.

[e] eGFR should ideally be calculated using the Cockcroft Gault method

[f] tenofovir-alafenamide/emtricitabine (Descovy) may be preferred to tenofovir disoproxil fumarate 245mg/emtricitabine 200mg in patients with abnormal renal function at baseline. The dose of Descovy depends on the third agent chosen:
Descovy 200mg/25mg should be prescribed with dolutegravir or raltegravir. Descovy 200mg/10mg should be prescribed with the protease inhibitors darunavir/ritonavir and atazanavir/ritonavir. Note Descovy is more susceptible to drug interactions when combined with enzyme inducers; conduct thorough drug interaction check or seek specialist advice.

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

Swallowing difficulty - tenofovir/ emtricitabine can be dissolved in 100 ml of water or orange juice and taken immediately. Lopinavir/ritonavir can be used as an alternative to dolutegravir and is commercially available as an oral solution; the recommended dosage is 5ml twice daily with food. Where liquid formulations are unavailable, dolutegravir tablets may be split or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

7.2 Alternative regimens

7.2.1 Non-nucleoside reverse transcriptase inhibitors (NNRTI)

The prevalence of NNRTI resistance in the UK are significant (4.2% in 2016) and thus NNRTIs are not routinely recommended for use in PEP.

7.2.2 Protease Inhibitors (PI)

PIs are potent inhibitors of the cytochrome P450 system (CYP3A4), markedly increasing levels of some drugs metabolised through the same pathway, including some corticosteroids, recreational drugs (https://www.hiv-druginteractions.org/checker), antibiotics and antipsychotics amongst others. One study reports high levels of recreational drug use among MSM genitourinary medicine attendees, an additional interaction concern (133).

Darunavir/ritonavir (DRV/r) has been compared to lopinavir/ritonavir (LPV/r); the percentage with early discontinuation and adverse drug reactions was 6.5% and 68% in the DRV/r arm versus 10.0% and 75% in the LPV/r arm respectively, non-significantly different. Fewer of the DRV/r-receiving participants (16.1%) had at least one grade 2 or 3 adverse drug reaction compared with those receiving LPV/r (29.3%) (P = 0.006). No HIV seroconversions were reported during follow-up (134).

Atazanavir/ritonavir when compared to LPV/r with zidovudine/lamivudine as PEP had a similar rate of discontinuation with almost half of participants experiencing suffering side effects in both arms (135, 136).

7.2.3 CCR5-receptor antagonists

Maraviroc (MVC) is well-tolerated and reaches very high levels in genital tract tissues so its utility for PEP is being investigated. Two RCTs have concluded that a PEP regimen of Truvada plus MVC is better tolerated than Truvada plus LPV/r (131) (137) but as MVC-based ART is not recommended as first-line HIV treatment (138) and the possibility that non-CCR5-tropic virus can transmitted), MVC-based PEP is not recommended (139).

7.3 Side effects

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

Raltegravir with tenofovir disoproxil/emtricitabine as a PEP regime is generally well tolerated and routine provision of anti-emetics and anti-diarrhoeals is not recommended. Where anti-emetics are provided, domperidone should not be used with protease inhibitors due to a significant drug-drug interaction with ritonavir (140).

Where any individual has experienced treatment-limiting tolerability or toxicity issues on prior PEP, an alternative regimen should be prescribed depending on availability of other medication and on the nature and severity of the adverse event(s). Where prior adverse events were not serious and alternative PEP agents are not readily available (e.g. out of hours in an emergency department setting) then PEP should not be delayed and switch considered when practicable.

Although proximal renal tubular dysfunction and Fanconi's syndrome are reported in HIV-positive individuals on tenofovir-based ART, these have not been reported in the setting of PEP or PrEP to date (117). The most

common laboratory adverse event reported in the context of PEP was mildly raised alanine aminotransferase (22%), but there were no cases of clinical hepatitis (126).

Myopathy or rhabdomyolysis have been reported with INSTIs, (141, 142) therefore caution should be taken in individuals with a history of myopathy or who are using other medicinal products associated with these conditions, for example statins (143).

7.4 Drug-drug interactions

30	An accurate verified medication history should be obtained, including the use of over the counter medication, vitamins/minerals, herbal remedies and recreational drugs before PEP is prescribed to ensure no significant drug-drug interactions are present.	1D

We recommend that potential drug-drug interactions are checked using the Summary of Product Characteristics and/or the Liverpool University drug interaction website (https://www.hiv-druginteractions.org/checker) but summarise some key drug-drug interactions here and in Appendix A . Boosted drugs (protease inhibitors and elvitegravir) are associated with numerous drug-drug interactions e.g. several steroids (including intranasal and inhaled steroids) and statins (risk of rhabdomyolysis with particularly simvastatin).

Cations: Although raltegravir and dolutegravir pose a low risk for drug-drug interactions, **raltegravir binds to divalent cations such as iron, aluminium, magnesium, calcium and forms a complex at the level of the gastro-intestinal tract which results in less raltegravir being absorbed. Drug-drug interaction studies with antacids containing divalent cations have shown a more pronounced reduction in raltegravir minimum concentration (C_{min}) when raltegravir was administered once daily compared to a twice daily regimen** (144). A similar effect for iron supplements cannot be excluded. **Therefore, concomitant use of metal cation containing antacids, iron supplements and multivitamins should ideally be avoided with once daily raltegravir or should be separated by at least 4 hours from twice daily raltegravir 400mg** (144). Switch to a non-cation containing acid-reducing agent is recommended during INSTI-based PEP if clinically indicated and non-essential mineral supplements should be stopped.

Rifampicin: Rifampicin is contra-indicated with boosted drugs (protease inhibitors and elvitegravir). Raltegravir and dolutegravir require dose adjustment to 800mg twice daily and 50mg twice daily respectively.

Tenofovir alafenamide / emtricitabine: The interaction profile of tenofovir alafenamide (**Descovy®**) is significantly different to tenofovir disoproxil/emtricitabine, see **Appendix A** for further details.

8 Timing and duration of PEP

31	PEP should be initiated as soon as possible after exposure, preferably within 24 hours, but can be considered up to 72 hours.	1D
32	We do not recommend initiating PEP beyond 72 hours after exposure.	1D
33	The duration of PEP should be 28 days.	1D

Animal studies show that earlier initiation of PEP is more effective than later initiation; in one study, the efficacy of PEP was greater when initiated 12 hours and 36 hours after exposure compared to 72 hours after exposure (12). In a second study, efficacy was greater when PEP was initiated 24 hours after exposure rather than 48 hours or 72 hours after exposure (11). A maximum 72 hour window is further supported by an intrarectal SIV (simian immunodeficiency virus) inoculum study in rhesus monkeys where ART was initiated on day 3 post exposure; this blocked the 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 (145).

We therefore recommend that it is essential to initiate PEP as soon as possible after exposure, preferably within a matter of hours, but can be considered up to 72 hours. The attendee should be informed that the earlier the initiation of PEP, the more efficacious and that delay in initiation diminishes efficacy. In addition, complete adherence to PEP regimens should be emphasized, especially considering that this healthy population may not be accustomed to taking medication regularly.

In a retrospective review where 649 people were prescribed PEP for sexual exposures, the mean time from exposure to first PEP medication dose was 38.5 hours (33). A total of 69% completed the 4–6 week follow up visit, 44% completed the 3-month visit, and 24% completed a 6-month visit. There were a total of seven seroconversions among PEP users within the study period. The mean time from exposure to first PEP medication dose was 51.5 hours for people who seroconverted. However, it is unclear whether there were further exposures following PEP as the follow-up period included HIV testing 6 months after the initial exposure.

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. All of macaques treated for 28 days with PEP (PMPA following intravenous inoculation of SIV within the prior 24 hours) were protected from infection, compared to half of the macaques treated for 10 days with PEP, and none of those treated with 3 days of PEP (11); in the absence of better quality data showing that PEP is effective with a shorter duration we recommend a duration of a minimum of 28 days. Owing to the fact that the RAL 600mg tablets are more hygroscopic the current SPC mandates that they must be stored in their original packaging – a sealed water-tight container with moisture absorbent containing 30 days of medication. Since many antiretroviral agents

are produced in 30 day packs the provision of a 30 day pack minimises the amount of manipulation required by pharmacists which is potentially more cost-effective.

9 How to provide HIV PEP

34	For PEP to be maximally effective a 24-hour service is recommended.	1C
35	It is recommended that local policies include 24-hour access to advice from an experienced HIV clinician, particularly for complex cases.	1D

For PEP to be maximally effective, all year-round 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 out of hours PEP provision. Necessary support and training should be provided by local departments with expertise, such as occupational health, genitourinary (GU) medicine, HIV medicine, sexual and reproductive health clinicians, infectious diseases or virology/ microbiology departments. The training issues are essentially those outlined comprehensively in the DH/EAGA guidance on HIV PEP (1, 146).

Individuals receiving PEP from an emergency or urgent care service should be seen as early as possible by either their occupational health department or local sexual health clinic. PEP should not be withheld until such expertise is available. For occupational exposures, the occupational health service has the responsibility for testing of the index case in conjunction with the attending practitioner and according to local policy which define roles and responsibilities, advice to the PEP user during the course and the follow-up blood testing.

9.1 Baseline risk assessment

It is essential that an appropriate risk assessment for both sexual and occupational exposures be performed to enable provision of PEP according to the recommendations, as outlined in sections 5-7 and summarised in **Table 4 (section 6.5)**. 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**.

9.2 Initiating PEP

36	Routine blood test monitoring after initiation of integrase inhibitor-based PEP is not necessary unless clinically indicated or if baseline blood tests are abnormal.	2C
37	Take a contraceptive history and perform pregnancy testing in all women of childbearing age considering PEP and offer emergency contraception where indicated.	1D
38	Pregnancy and breastfeeding should not alter the decision to start PEP.	2D

39	Women must be counselled that antiretroviral agents used for PEP are unlicensed in pregnancy and their risks/benefits must be carefully discussed (see section 10.2).	1D
40	An ultra-rapid course of Hepatitis B vaccination should be offered if clinically indicated in the absence of baseline immunity (see Figure 1, section 9.4.2).	1B
41	Use of starter packs can negatively impact the completion of PEP, therefore a full course of PEP should be provided at the first attendance unless there are operational reasons why this is not possible.	1C

Starter packs are pre-prepared with 5 day supplies of antiretrovirals which enables timely provision of PEP, especially out of hours or from emergency care facilities. This 'starter' PEP regimen can be continued or modified at initial review within 5 days, depending on further information about the index case's HIV status, the index case's viral load (and if viral load detectable, their resistance history) and the patient's tolerance of the medication. If the index case tests negative on a 4th generation laboratory assay, then PEP can be discontinued.

In a systematic review of the evidence on outcomes associated with starter packs for PEP compared to full prescriptions, PEP completion rates, stratified by prescribing practice, were pooled using random-effects meta-analysis. This included:

- Fifty-four studies providing data on 11,714 PEP initiations.
- Thirty-seven studies, including 3 randomised controlled trials (RCTs) providing information on starter packs (although none of the RCTs specifically assessed starter packs)
- Seventeen studies, including 2 RCTs, providing information on full prescriptions.

Overall, outcomes were non-significantly better when participants were offered a full 28-day PEP course at initial presentation to healthcare services, with fewer refusals (11.4% [95% CI 5.3% to 17.5%] vs 22% [95%CI 16.7% to 28.1%]), and higher self-reported completion rates (70% [95%CI 56.7% to 77.3%] vs 53.2% [95%CI 44.4% to 62.2%])(137, 148). More than a quarter (28% [95% CI 21.4% to 34.5%]) of individuals provided with a PEP starter pack failed to return for their subsequent appointment, therefore unable to receive the full course of PEP. The findings of this review suggested that starter packs do not improve acceptance and may negatively impact on PEP completion rates. The quality of the evidence overall however was rated as very low(and there may have been important differences in patient characteristics between studies that provided starter packs and those that provided full prescriptions), therefore more research is needed (148).

In Britain, robust national level data on PEP is lacking outside of Sexual Health services. However, recent audit data from two large centres in England has shown that around 80% of PEP initiated in Emergency Departments is prescribed for a high-risk indication, and therefore a full PEP course is required. . Furthermore, around 10% of these patients with a high-risk exposure did not return to their planned follow-

up appointment, and therefore discontinued PEP prematurely (unpublished data). It may therefore be preferable for the majority of patients who require PEP to be given the full course at the first visit, removing the need for a second face-to-face attendance within 5 days to continue PEP. The use of less-toxic drugs for PEP, and a simplified approach to risk stratification by non-specialists will facilitate this strategy of same-day full course PEP provision. This approach may be also advantageous to services where access to follow-up appointments within 5 days is challenging (e.g. due to pandemic related lockdowns). Based on the findings of the systematic review and audit data we therefore recommend that a complete 28 day supply should be prescribed at the first attendance (147). However, this change must be incorporated in PEP care pathways that ensure linkage to follow up of baseline bloods tests, STI testing, BBV follow-up, risk reduction interventions and transition to HIV PrEP where indicated.

If there are operational reasons why services need to use a starter pack, and stability data for RAL 600 mg in non-original packaging remain unavailable (section 7.1.2), then RAL 400 mg twice daily is preferred as the third agent alongside TDF/FTC.

We encourage the conduct of local audits, in collaboration with BASHH/BHIVA, to better understand the national landscape of PEP use in A+Es, SARCs, through private providers etc.

At presentation for PEP, and prior to administration of PEP, the following points (Box 2) must be discussed with the individual.

Box 2: Items to discuss with individual commencing PEP:

1. The rationale for PEP
2. The lack of conclusive data for the efficacy of PEP
3. Start PEP as soon as possible and importance of adherence to optimise efficacy
4. The potential side-effects of PEP
5. Drug interactions including over the counter drugs such as multivitamins/antacids/iron (iron should not be used with once daily raltegravir or if an essential medication, iron should be spaced at least 4 hours apart from twice daily raltegravir dosing)
6. Emergency contraception (if appropriate)
7. Seek urgent medical attention if they develop symptoms of possible seroconversion
8. The arrangement for early follow-up with either an occupational health or HIV/GU medicine clinic
9. Verbal consent and HIV test (4^{th} generation laboratory test)
10. The need to continue PEP for a minimum of 28 days if the baseline result is negative
11. The need to have a follow-up HIV test a minimum of 45 days after completion of the PEP course – this is a minimum of 10.5 weeks post-exposure if the 28 days course is completed
12. The need to use condoms until the follow-up HIV testing is negative
13. Coping strategies, assessment of vulnerabilities and social support

9.2.1 Management of anxiety

Risk assessment and counselling are important to determine whether PEP is indicated and to manage individual concerns. The decision to administer PEP should be based on the risk of HIV acquisition and not to manage a state of acute anxiety following a potential HIV exposure. Calculating the likely HIV transmission risk relating to the incident (see **section 5.5**) can be very reassuring to the attendee, who may frequently have overestimated the perceived risk. Referral for psychological support for individuals reporting anxiety related to the risk of HIV transmission may be beneficial.

9.3 Baseline BBV testing of the index case

42	Following occupational exposures informed consent for testing for blood borne viruses (fourth generation HIV test (HIV-1 Ag/Ab), hepatitis B surface antigen (HepBsAg), hepatitis C antibody (Hep C Ab)) should be sought from the index case by another member of staff who is not the recipient of the occupational exposure.	GPP
43	If the index case is a child then age appropriate HIV, HBV and HCV testing should be used - depending on age and developmental stage of child, consent from the parent or legal guardian of the child, and consent or assent from the child. Discuss with a clinician with relevant expertise (e.g. paediatric ID consultant, paediatric ID/microbiologist/virologist) if uncertain.	GPP
44	Where the index case is high risk for hepatitis C (e.g. PWID) then a hepatitis C PCR (HCV PCR) or hepatitis C antigen can be done instead of Hep C Ab.	GPP
45	Where it is not possible to seek consent from the index case (e.g. patient comatose or lacks mental capacity) then testing can be undertaken if it is in the best medical interests of the index case.	GPP

Partner notification is recommended to test the index case for HIV as soon as possible; however, this must not delay PEP initiation. One European study found that following sexual intercourse with a source of unknown HIV status it was possible to contact and test the source in 43% of cases and subsequently avoid/discontinue PEPSE in 41%; benefits in terms of both cost saving and testing in a high-risk group (149, 150).

In order to undertake HIV testing for the purpose of determining need to continue PEP, consent is required from the potential source. General Medical Council guidance should be followed for patients who lack capacity to consent [https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent/part-3-capacity-issues#paragraph-75 Accessed 24th April 2020]. If a patient suspected of having a serious communicable disease lacks capacity to decide about testing, and are not likely to regain capacity soon, they can still be tested if the team providing care determine it would be in their best interests to do so. In reaching that determination the team should have regard to best practice guidance and clinical advice such as that published by NICE, as well as what they know about the patient, their history condition and wishes.

As long as the primary purpose of the test is in the patient's best interests, it would seem sensible to use the result to guide decisions for the secondary purpose of whether to provide PEP to a colleague who has incurred a needlestick injury. As the information was acquired for a legitimate purpose, it would not seem reasonable to expect the care team to ignore the result for the purpose of the risk assessment. In a recent case the Supreme Court advised that, where there is evidence that a patient who currently lacks capacity would, had they had capacity, have been willing to agree to medical procedure for the benefit of others, the doctor may be entitled to authorise the procedure in the patient's best interests (Aintree University Hospitals NHS Foundations Trust vs David James [2013] UKSC 67)".

Since hepatitis C antibody positivity does not distinguish between past and current infection, where hepatitis C antibody is positive reflex testing for hepatitis C PCR should be done. Where the index case has a risk factor for hepatitis C (e.g. PWID) then hepatitis C PCR could be done initially.

9.4 Baseline and follow-up testing of recipient

46	Baseline and follow up tests are summarised in Table 6 **All exposures:** blood testing before PEP initiation should include creatinine (and eGFR), alanine transaminase, HIV-1 Ag/Ab, hepatitis B serology (if not known to be immune with HepBsAb ≥10 IU). PEP initiation should not be delayed by waiting for blood results. **Sexual exposure:** Tests shown in 'All exposures' plus Syphilis serology and Hep C Ab in MSM and others at risk of hepatitis C **Occupational exposure:** Tests shown in 'All exposures' plus Hepatitis C in all.	1B
47	Baseline pregnancy test in women of childbearing age considering PEP.	1D
48	Routine renal and liver function test monitoring after initiation of PEP is not necessary unless clinically indicated or if baseline blood tests are abnormal.	2C
49	Follow-up testing for HIV should be undertaken at a minimum of 45 days after completion of the PEP course. If the 28-day PEP course is completed this is 73 days (10.5 weeks) post exposure.	1B
50	Follow up testing for hepatitis B should be guided by hepatitis B vaccination status and baseline immunity as shown in **Table 6 (section** Error! Reference source not found.**) and Figure 1 (section 9.4.2).**	1B
51	For occupational exposures, after initiating PEP, we recommend individuals are followed-up by their occupational health department as soon as possible, ideally within 72 hours of the event.	1D

PrEP studies support the safety of tenofovir/emtricitabine in HIV-negative individuals, and despite small declines in renal function with daily tenofovir, these reverse on stopping tenofovir and the incidence of serious renal events was very low (117). The randomised controlled trial of raltegravir versus lopinavir/ritonavir PEP (combined with a Truvada backbone) did not report any liver, renal or haematological abnormalities in the raltegravir arm (131). Integrase inhibitors (INSTI) are less commonly associated with transaminitis and hepatic adverse events than protease inhibitors (151). The most at-risk group of liver

dysfunction are those co-infected with Hepatitis C (152). Closer monitoring is however recommended if new symptoms develop on PEPSE (e.g. rash, jaundice, muscle pain), if the recipient is pregnant, there is a risk of drug-drug interaction, 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 INSTI-based PEP.

9.4.1 Table 6. Baseline and follow up testing

	Baseline	2 weeks	12 weeks	6 months
SEXUAL EXPOSURES ONLY				
STI testing (per local policy)	✔	✔	✔ Syphilis only (and other STIs If further unprotected sexual intercourse)	
ALL EXPOSURES				
Creatinine and eGFR	✔	Only if abnormalities at baseline		
Alanine transaminase (ALT)	✔	Only if abnormalities at baseline or symptomatic		
Pregnancy test	✔	If appropriate	If appropriate	
HIV	**HIV1&2 Ag/Ab**		**HIV1&2 Ag/Ab***	**Not required unless further exposures**
Hepatitis B	**HBsAb, HBsAg, HBcAb** *For immunocompetent adults who have completed Hep B vaccination and responded (HBsAb ≥10 IU at any time) no baseline or follow up HepB testing is required*		*If unvaccinated or HBsAb <10 IU at the time of exposure:* **HBsAb, HBsAg**	*Only advised if HBsAb remains <10 IU at 12-weeks:* **HBsAg**
Hepatitis C	**HCV Ab**		**HCV Ab** *If high risk exposure e.g. HCV+ index, then HCV PCR or Hep C Ag is preferable as the window period is shorter for antigen-based tests and can be requested as early as 2 weeks post exposure*	*If high risk exposure e.g. HCV+ index case and testing at week 12 negative:* **HCV Ab**
* HIV testing can be done a minimum 45 days after completion of the PEP course (see BHIVA HIV testing guidelines for further information). If the 28-day PEP course is completed this is 73 days (~10.5 weeks) post-exposure. For sexual exposure, to align with syphilis follow-up testing at week 12, the HIV test can be done at the same visit.				

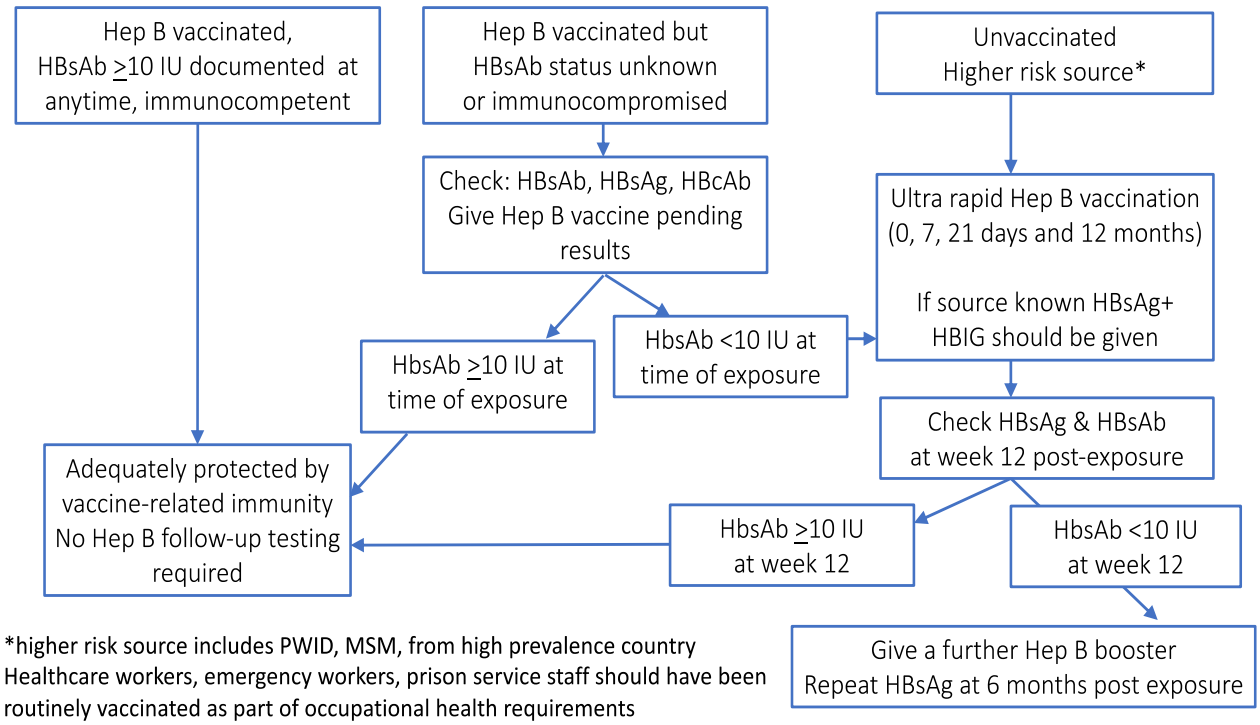
Several national audits report that the attendance for follow-up HIV testing at 12 weeks is poor (30-67%) (38-44) so we suggest services use local mechanisms, including text/email reminders, to encourage attendance for post-exposure HIV testing. The HIV test must be on a 4th generation laboratory assay.

Hepatitis B vaccination is routinely recommended for healthcare workers, laboratory staff, staff of residential accommodation, emergency service workers, PWID, MSM, sex workers, close contacts of individuals with chronic hepatitis B infection, as well as other scenarios outlined in the Green book (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/628602/Greenbook_chapter_18.pdf). Some employees presenting for PEP will be unaware of their HBsAb titre, so it is therefore advisable to present to OH departments during working hours as OH department should be privy to this information. Regardless of the type of exposure, if there is documentation of HBsAb titre of ≥10 IU year, this person is deemed a responder to vaccination with adequate immunity against hepatitis B and no further follow-up testing is required (153). A significant proportion of individuals present to Emergency Departments or Sexual

Health services following occupation or sexual exposures; for those in whom vaccination status is unclear or do not have documented immunity to hepatitis we suggest offering a booster/first dose of hepatitis B vaccine while results of HBsAb are awaited. If the individual is unvaccinated or HBsAb <10 IU at the time of exposure and the exposure is deemed higher risk, an ultra-rapid course of hepatitis B vaccination should be continued (or hepatitis B immunoglobulin (HBIG) if the index case is known to be HBsAg positive) as per BASHH guidelines and Greenbook chapter 18 (154).

Occupational health services have the responsibility for vaccinations and follow-up blood testing for occupational exposures.

9.4.2 Figure 1. Flowchart illustrating hepatitis B baseline testing and follow up



Hepatitis C is only extremely rarely transmissible through penile-vaginal intercourse or oral sex so baseline and follow-up hepatitis C testing is only indicated in MSM who have had condomless anal sex (further details in BASHH guidelines), PWID and occupational exposures. Where there has been a significant risk (e.g. needlestick from hepatitis C positive index case) a hepatitis C core antigen or hepatitis C RNA should be considered as these tests have a shorter window period, and can be considered as early as 2 weeks post exposure (155). Final testing for hepatitis C can be done at 12 weeks with hepatitis C core antigen or hepatitis C RNA, or at 6 months with a hepatitis C antibody test. Refer onto hepatology services where a hepatitis C infection is identified.

9.4.3 Sexual Health considerations

52	Perform chlamydia, gonorrhoea and syphilis testing (based on clinical situation) at baseline and repeat testing following the incubation period.	2C
53	Emergency contraception should be offered were indicated.	1B
54	Offer MSM hepatitis A and human papilloma virus vaccines (in addition to hepatitis B virus vaccine) if clinically indicated as per the 2016 British Association of Sexual Health and HIV men who have sex with men guidance.	1B
55	Individuals presenting for PEP who may be at higher risk of future acquisition of HIV and should be encouraged to attend for regular sexual health checks and considered for referral to risk-reduction services including HIV Pre-Exposure Prophylaxis.	2C
56	Provision of PEP should be fully integrated into counselling around safer sex strategies including opportunity to meet with an appropriate health care professional competent in sexual health advising.	1C

Observational studies have found 15 - 17% of PEP-recipients had an STI at baseline and an additional 4 - 5% had an STI diagnosed at 2 weeks post-exposure (156) (157). As loss to follow-up is common in PEPSE recipients, we recommend opportunistic STI testing at baseline, unless the patient presents for PEPSE following sexual assault, where, if still within the time frame where forensic samples may be obtained (usually within 7 days of assault), STI screening should be deferred until after forensic samples have been taken. We suggest offering MSM presenting for PEP, hepatitis A and human papilloma virus vaccines opportunistically as per the 2016 BASHH MSM guideline (101).

9.4.3.1 Risk reduction interventions

Provision of PEPSE should be fully integrated with advice and counselling around safer sex strategies. 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 (158, 159). Individuals presenting for PEPSE are at higher risk of future acquisition of HIV (160) and so should be encouraged to attend for future regular sexual health check-ups and considered for referral to risk-reduction services including HIV PrEP. We recommended that all MSM and other high-risk groups have documented discussions around PrEP use as per the BASHH PrEP guideline, see section 11 (161).

9.4.4 Occupational Health Considerations

Whilst it may be necessary for individuals to present to Emergency care departments out of hours, we recommend that they are seen by their occupational health department within 3 days of the event. Occupational health services have the responsibility for urgent testing of the index case (in conjunction with the index case's attending medical team), hepatitis B vaccinations if required, advice to the PEP user during the course and the follow-up blood testing. The Health and Safety Executive website provides information on actions following occupational exposures and how to report

(http://www.hse.gov.uk/healthservices/needlesticks/actions.htm). Occupational exposures where the index case has a blood borne virus should also be reported to Public Health England via the SigOcc system (https://www.gov.uk/government/collections/bloodborne-viruses-bbvs-in-healthcare-workers). Public Health England have produced guidance on management of exposure to BBV for emergency care workers and can provide guidance for HCWs undertaking exposure prone procedures following occupational exposure, or for health clearance in the case of subsequent (https://www.gov.uk/government/groups/uk-advisory-panel-for-healthcare-workers-infected-with-bloodborne-viruses) (82). Institutional policies on managing blood and body fluid exposures should be available to staff. The policy which covers the relevant legislation (e.g. Control of Substance Hazardous to Health) should be also readily available to the employees.

The stress experienced by some individuals is extreme. In most cases, counselling on the actual risk of the exposure is an effective tool in managing the employee's anxiety. In addition, the benefits and disadvantages of PEP should be discussed with the employee.

10 Special scenarios

10.1 Chronic Hepatitis B Infection

57	Baseline hepatitis B virus (HBV) testing should be undertaken in those of unknown HBV status, and vaccination (and HBIG, depending on risk of exposure) initiated in those who are not known to be immune whilst awaiting results.	GPP
58	Consider the use of a standard PEP regimen for individuals known to have chronic HBV and on either a nucleos(t)ide analogues (except if on combined therapy with tenofovir [TDF]/lamivudine or TDF/emtricitabine [FTC]) or peg IFN-alpha based HBV treatment, where high-risk HIV exposure has occurred.	1B
59	Individuals found to have HBV infection at baseline should receive PEP as needed without delay.	1B
60	Individuals found to be HBV-infected at baseline should be assessed by a specialist in HBV infection with regard to continuing HBV therapy post-PEP. If the assessment does not fall within the 28-day PEP course then tenofovir/emtricitabine should be continued pending the assessment.	1B

Chronic HBV remains the most prevalent of the blood-borne viruses globally. Current HBV management guidelines recommend treatment of chronic HBV based on age, HBV DNA levels, stage of fibrosis and for individuals at-risk of hepatocellular carcinoma. Therapy is either for finite duration with Pegylated interferon-alpha (milder disease), or finite or indefinite duration with HBV-active nucleoside analogues (NAs). Nucleos(t)ide analogues (NAs) with a high-barrier to resistance, tenofovir (TDF or TAF) and entecavir as single-therapy are recommended when NAs are chosen as the treatment option. Lamivudine is no longer recommended as single-agent therapy for chronic HBV due to its low genetic barrier to resistance. Both tenofovir (TDF and TAF) and lamivudine (and emtricitabine) have dual activity against HBV and HIV.

Current data and guidelines recommend tenofovir-DF and emtricitabine/lamivudine as effective pre-exposure prophylaxis (PrEP) against HIV, and tenofovir-DF as monotherapy, when emtricitabine contraindicated for PrEP in heterosexual men and women for prevention of sexual transmission of HIV (25, 116, 161, 162).

On-treatment hepatic flares have been noted in patients on NA-based therapy. Concerns have also been raised about NA-withdrawal hepatic flares, and their clinical consequences. However, the iPrEx study demonstrated that it was possible to use TDF-FTC in patients with chronic HBV and, importantly, demonstrated the ability to stop TDF-FTC safely in patients without cirrhosis and without the occurrence of significant hepatic flares, although this needs specialist input (163).

Whilst the use of dually-acting nucleoside-analogues have high-efficacy in preventing HIV-infection, either as PrEP (tenofovir-DF alone, or in combination with emtricitabine, lamivudine) or PEP (tenofovir-DF with emtricitabine or lamivudine or lamivudine-containing combination therapy), questions remain around:

a) the need for HIV post-exposure prophylaxis in patients with chronic HBV infection, established on continuous therapy with tenofovir for the treatment of their chronic HBV infection.
b) the safety of short-duration tenofovir and emtricitabine/lamivudine-based post-exposure prophylaxis for patients with chronic HBV not on HBV treatment

Our recommendation around HBV screening, vaccination and where necessary HBV immunoglobulin is an accordance with the BASHH hepatitis guideline (https://www.bashhguidelines.org/media/1161/viral-hepatitides-2017-update-18-12-17.pdf). Pegylated interferon-alpha, lamivudine, telbivudine and entecavir do not provide prophylaxis against HIV. TDF monotherapy has pre-exposure prophylactic efficacy against HIV in heterosexual men and women following sexual exposure. TDF monotherapy has not yet been reported in MSM though is likely to be effective in PrEP as TDF concentrates in rectal tissue. However, breakthrough infections have been described, probably associated with inadequate drug levels, and therefore, standard multi-drug PEP could be considered (164, 165). On-treatment hepatic flares are relatively rare in patients with chronic HBV on NA-based therapy, and when they do occur do not lead to hepatic de-compensation events in non-cirrhotic patients and may well be associated with HBsAg clearance (163). The risk of treatment-withdrawal flares also relatively rare, and self-limiting in patients with minimal/mild fibrosis not in need of HBV therapy (163, 166-168). The risk of tenofovir or lamivudine (or emtricitabine) HBV resistance with four weeks of therapy is also extremely unlikely.

10.2 Pregnant and breastfeeding mothers

61	Take a contraceptive history and request a baseline pregnancy test in women of childbearing age considering PEP.	1D
62	Pregnancy and breastfeeding should not alter the decision to start PEP.	2D

63	For women who are pregnant, raltegravir 400mg twice daily is preferred as the third agent. Where accessing raltegravir 400mg might cause delay we recommend using raltegravir 600mg twice daily and switching at the earliest opportunity.	1C
64	For women at risk of pregnancy or known to be within the first 6 weeks of pregnancy who cannot use first-line for PEP for any reason, we recommend avoiding the use of dolutegravir as an alternative third agent (table 5, section 0).	1C
65	For women beyond 6 weeks pregnant, dolutegravir can be used as an alternative third agent.	1C
66	Women should be counselled that antiretrovirals used for PEP are unlicensed in pregnancy and that their risks/benefits must be carefully discussed (see section 10.2).	1D
67	Women who are breastfeeding must be counselled regarding the transfer of antiretrovirals to the infant via the breastmilk.	1D

Pregnancy is not a contraindication for PEP. Pregnant women are at increased risk of HIV transmission and the high viraemia associated with primary infection would lead to a high likelihood of intrauterine infection.(78) We suggest that a thorough risk assessment should be undertaken in all women of childbearing age considering PEP, including a contraceptive history and pregnancy testing. It is important to explain that a negative urine pregnancy test at baseline is too early to exclude pregnancy as most urine pregnancy tests take 3 weeks from conception to become positive.

The Antiretroviral Pregnancy Registry (APR) (http://www.apregistry.com) is a surveillance study of pregnancy outcomes in women exposed to antiretrovirals during pregnancy in North America and Europe. At the time of writing the APR includes data from 01/01/1989 to 31/07/2019. Combined with animal toxicology studies and studies undertaken in pregnant women (e.g. pharmacokinetics), the APR can assist clinicians and patients in making treatment decisions. The SPC in relation to pregnancy for the antiretroviral agents used in PEP are summarised in Appendix D.

For darunavir, raltegravir and elvitegravir, there is sufficient data to be able to detect at least a two-fold increase in risk of overall birth defects and no such increases have been detected to date (APR accessed 09/01/2020). For tenofovir and emtricitabine, there is sufficient data to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems; no such increases have been detected to date (141).

For dolutegravir, although an initial meta-analysis suggested it appeared safe to use in pregnancy, in 2018, a preliminary unscheduled analysis of an ongoing birth surveillance study in Botswana reported an increased risk of neural tube defects (NTDs) (169). In 2019, further data from 1683 women in the Tsepamo study, a prospective surveillance study in Botswana reported five NTDs (prevalence 0.3%) in women conceiving on a dolutegravir (170). At the 2020 the IAS conference, the latest analysis found that the apparently elevated risk of NTD with dolutegravir has diminished further; prevalence of NTDs among women conceiving on dolutegravir has decreased to 0.19% (7 NTDs in 3591 deliveries), compared to 0.11% for other antiretrovirals, and the difference is no longer statistically significant (171).

In the latest data from the APR, there was only one NTD reported among 248 women exposed to dolutegravir during conception, leading to a prevalence of 0.4%, only slightly higher than with other antivirals (172). However, this estimate is based on a single NTD among a relatively small number of exposures. Having reviewed the available data, the guideline-working group suggests that for women at risk of pregnancy or known to be within the first 6 weeks of pregnancy, we suggest avoiding the use of dolutegravir where other suitable options exist pending further safety data.

The prescribing advice in pregnancy for antiretrovirals included in this policy, at the time of writing, is summarised in Appendix D but prescribers should ensure they check the most recent version of the Summaries of Product Characteristics and the BHIVA pregnancy guideline when prescribing PEP to pregnant women. It is important to note that antiretrovirals used for PEP are unlicensed in pregnancy, and therefore the writing group recommend that women should be counselled appropriately, including discussion of the risks and benefits. Women of childbearing age who are not pregnant at the start of PEP should be given accurate information regarding the full range of contraceptive choices available. Expert opinion from the guideline-working group is that, with the exception of dolutegravir in the first 6 weeks of pregnancy and elvitegravir in the second and third trimesters, any of the antiretrovirals below can be used as PEP in pregnancy since the benefits outweigh the risks.

10.2.1 Breastfeeding

Breastfeeding is also not a contraindication for PEP as the benefits outweigh the risks to both the woman and the infant. Although nearly all data relating to antiretroviral drug exposure in breastfed infants are from low- and middle-income countries, the guideline-writing group recommend that women who are breastfeeding should be counselled appropriately.

ART taken by the mother can enter breastmilk through active transport mechanisms and by passive diffusion and therefore be ingested by the breastfeeding infant (173). However, it is difficult to precisely quantify how much drug the breastfed infant is exposed to because the overall drug accumulation in breastmilk and the subsequent exposure to the breastfed infant is dependent on a number of maternal (e.g. maternal antiretroviral dosing, drug pharmacokinetics, stage of lactation) and infant (e.g. suckling pattern i.e. volume of milk consumed, frequency and timing relating to maternal concentrations) factors. It is thought that lower maternal dosing, drugs with a shorter half-life or higher protein binding are less likely to accumulate in breastmilk. The stage of lactation determines the protein and fat content in breastmilk which changes with the transition from colostrum to mature milk shortly after birth (174).

Although data are not available for all antiretroviral drugs, a meta-analysis conducted in 2015 of pharmacokinetic studies found that infants that are exclusively breastfed receive up to 10% of the weight-adjusted infant dose of NRTIs and NNRTIs (175). Data from a case report and a randomised controlled trial

have reported that transfer of dolutegravir to the infant occurs via breastmilk(176, 177). In the DolPHIN-1 study, where HIV-positive, treatment-naïve pregnant women in Uganda and South Africa were randomised to initiate either dolutegravir or efavirenz-containing ART in the third trimester and until 2 weeks post-partum, , breastfeeding led to significant plasma exposures in the infant, despite low plasma dolutegravir concentrations (176). It is also thought that there is delayed clearance of dolutegravir by the infant due to an immature UGT1A1 gene polymorphism, which can lead to prolonged exposure to dolutegravir in breastfed infants (178). There are no breastmilk pharmacokinetic data for other antiretrovirals recommended for PEP, including tenofovir alafenamide.

10.3 Use of PEP in populations using PrEP

68	The need for PEP (i.e. a significant potential risk within the last 72 hours) should be considered in all individuals requesting PrEP, prior to transitioning to PrEP.	1B
69	Decisions about the need for PEP in the setting of people on PrEP but with less than optimal PrEP adherence depends on length of time since the last dose of PrEP and the site of exposure.	1C
70	Anal sex: If the only exposure has been though anal sex and for people on daily PrEP, where fewer than 4 pills have been taken in the last 7 days. Or for people on event-based PrEP, PEP is indicated where PrEP has not been taken as recommended.	1A
71	Vaginal: Where the potential HIV exposure is through vaginal sex and PrEP adherence has been suboptimal, PEP should be considered if more than 48 hours have elapsed since last dosing or if fewer than six tablets have been taken within the previous 7 days.	1B
72	Frontal or neovaginal sex: Where the potential exposure to HIV is through frontal sex in trans men or through neovaginal sex in trans women, then PEP should be considered if more than 48 hours have elapsed since last dosing or if fewer than six tablets have been taken within the previous 7 days.	1C

People using PrEP are at high risk of HIV acquisition therefore, in the context of recent potential exposure to HIV, may be eligible for PEP due to imperfect PrEP adherence which places them at risk of incident HIV infection (179). Data from pharmacokinetic studies and PrEP clinical trials provide good evidence for the minimal adherence required for PrEP efficacy for anal sex (180, 181) and for vaginal sex (182, 183), there is less data for frontal sex in trans men on androgen therapy or for neovaginal sex in trans women but principles for levels of adherence to maintain protective tissue concentrations in peripheral blood mononuclear cells (PMBCs) can be extrapolated (183). In general, time to protection of tenofovir-disoproxil is shortest in lower gastrointestinal tract tissues, followed by blood PBMCs and then the female genital tract tissues. Therefore, adherence levels required for protection against HIV acquisition from anal sex is lower than that required for vaginal, trans vaginal or frontal sex, due to persistence of tenofovir/emtricitabine in rectal tissues. Therefore,

recommendations for PEP differ by site of exposure in terms of time since last dose and pattern of adherence prior to exposure

10.4 When to discontinue PEP due to missed doses

Individuals missing doses of PEP 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.

Pharmacokinetic studies have shown that the half-life of raltegravir 1200mg od is approximately 8-12 hours (184). Tenofovir/emtricitabine plasma half-life is 12-18 hours according to the Summary of Product Characteristics (185) but were longer in a recent study: 31 and 37 hours for tenofovir and emtricitabine, respectively (186). Tenofovir and emtricitabine are activated intracellularly and the median intracellular half-lives are approximately 150-160 hours (186, 187); and 39 hours (186), 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:

What if I miss my dose?

- *If you forget to take a dose, take it as soon as you remember it.*
- *However, if it is time for your next dose, skip the missed dose and go back to your regular schedule.*
- *Do not take a double dose to make up for a forgotten dose.*
- *If more than 48 hours has elapsed since the last dose then discontinue PEP.*

If interruption 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, section 6.5). For dolutegravir-based PEP if >72 hours has elapsed since the last dose then PEP should be discontinued.

10.5 Seroconversion during PEP

73	Individuals experiencing a skin rash or flu-like illness while or after taking PEP should be advised to attend for urgent review to exclude an HIV seroconversion.	2D
74	If the HIV test is positive after PEP has already been initiated, PEP should be continued pending review by an HIV specialist.	GPP

HIV testing is mandatory prior to, or shortly after, commencing PEP (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, greater likelihood of missing very early HIV infection. If a POCT is

reactive, a 4th generation serological test should be sent urgently, and expert advice sought prior to initiating PEP.

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 (188). Furthermore, stopping ART in the context of acute infection may result in significant viral rebound which could increase the risk of onward transmission (189).

10.6 Further high-risk exposures while on PEP

75	In the event of a further high-risk sexual exposure during the last two days of the PEP course, PEP should be continued until 48 hours after the last high-risk exposure for anal sex or until 7 days after the last high-risk exposure for vaginal/frontal sex.	2B

Tenofovir-disoproxil/emtricitabine has been shown to prevent acquisition of HIV infection when used as PrEP by MSM (118, 119). Individuals reporting further high-risk sexual exposures while receiving PEP do not need to extend the course of PEP beyond the initial 28 days. However, should this exposure be during the last two days of the course then extending the treatment for 48 hours after the last exposure should be advised for MSM, as this appears to have been highly effective in the IPERGAY study of intermittent PrEP (2B) (119). In the vagina/neovagina however, tenofovir levels decline rapidly after discontinuation, so in the event of a repeated high-risk exposure then PEP should be continued for 7 days after the last high-risk exposure (161).

11 Recommendations for PrEP in those with ongoing high-risk behaviour

76	Repeat attenders should meet with a Sexual Health Adviser and/or psychologist and that provision of PEP is fully integrated into counselling around safer sex strategies.	1C
77	PEP should not be considered or encouraged as a first line method of HIV prevention.	1C
78	Individuals presenting for PEP who are likely to have ongoing high-risk behaviour should be transitioned immediately to PrEP. HIV testing with a combined antigen/antibody laboratory-based test should be performed at the time of transition.	GPP

In a study on the outcomes in MSM given PEP following sexual exposures at sexual health clinics across England, between 2011–2014, PEP was prescribed at 24,004 total episodes, of which 16422 (68%) were to MSM. Compared with MSM attendees not prescribed PEP, MSM prescribed PEP were significantly more likely to subsequently acquire HIV (adjusted HR (aHR) single PEP course: 2.54; 95% CI 2.19 to 2.96); two or more

PEP courses: aHR 4.80; 95% CI 3.69 to 6.25). In the PROUD study some particularly high-risk subpopulations had high repeat PEP usage and, despite this, a high incidence of HIV acquisition (likely due to ongoing risk behaviour which may or may not be covered by PEP).

Repeated attenders be considered for repeat courses of PEP on each occasion according to their risk of HIV acquisition. Provision of PEP 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.

The writing committee believes it is crucial to consider PEP 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 PEP should not be considered as a first line method of HIV prevention (1C). Condoms are highly protective, although use is inconsistent (54, 190). Data in support of treatment of HIV-positive partners as a prevention strategy is strong (55, 56).

PrEP is an evidence-based and highly effective method of HIV prevention (https://www.bhiva.org/PrEP-guidelines) (191). Attending for PEP is an ideal opportunity to offer individuals PrEP (192). Individuals who are likely to have ongoing high-risk behaviour should be transitioned immediately from PEP to PrEP. HIV testing with a combined antigen/antibody laboratory-based test should be performed at the time of transition.

12 Awareness of PEP

It is important that individuals at risk of acquiring HIV are aware of PEP. 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 (193). 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). Sexual Assault Referral Centres should ensure that clients and police officers are aware of PEP, and the need for a risk assessment of HIV transmission in each case.

PEP should be proactively discussed with individuals diagnosed with HIV, particularly if in a serodifferent relationship, reporting frequent partner change or condomless sexual intercourse (GPP).

13 Cost-effectiveness

The medication cost of a full 28-day course of PEP (with generic tenofovir/emtricitabine and raltegravir) is approximately £549 (BNF list price Jan 2021), the lifetime costs of treatment for an HIV-positive individual are estimated to be approximately £360,000 (194). A 2009 systematic review of PEPSE included four economic evaluations. Methodological quality of the studies was variable but results suggest that PEP following non-occupational exposure to HIV was cost saving for men who have condomless receptive anal sex with men, whether the index partner is known to be HIV positive or not; heterosexuals after condomless receptive anal intercourse; and intravenous drug users sharing needles with a known HIV-positive person. PEP following non-occupational exposure to HIV was cost-effective for all male-male intercourse (condomless receptive and insertive anal sex, condomless receptive oral sex, and 'other') and was possibly cost-effective for intravenous drug users and high-risk women (22). This is in general accordance with a review by the Health Technology Assessment (22). The more recent recognition that an undetectable HIV viral load is effective in preventing onwards transmission may impact on future cost effectiveness analyses. A 28-day course of PEP could be substantially less expensive with the use of generic medications available now or in the future.

14 Surveillance on the use of PEP

14.1 Sexual exposures

Since January 2011 all episodes of PEP dispensed from GUM clinics 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 amongst MSM had risen annually, but appears to have declined in 2018 since PrEP has been more available.

14.1.1 Table 7. Reported use of PEPSE via GUMCAD 2014-2018

	2014	2015	2016	2017	2018
Male Heterosexual	1120	1382	1468	1537	1637
MSM	5904	8031	9083	9849	8413
Women heterosexual	1156	1285	1337	1631	1678
Women who have sex with women	26	47	57	38	50
Total	8415	10995	12146	13427	12372

14.2 Occupational exposures

There is no routine national data collected on the total number of occupational exposures or courses of PEP given following occupational exposures. Since 1997, PHE has collected data on significant occupational exposures (SOEs) where the index case is either known or thought to be living with HIV, hepatitis B and/or hepatitis C, the findings of which are summarised the Eye of the Needle Report (17). Many occupational exposures are seen in A+E and followed up in Sexual Health clinics so may contribute to the above GUMCAD figures.

15 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.

16 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.

These guidelines and the relevant literature will be reviewed at 5 years after publication as per the BASHH framework for guideline production. If any significant data is published in the interim there will be an interim guideline statement issued.

17 Auditable outcome measures:

We recognise that audit may be challenging where different services are providing the initial PEP prescription and follow-up. Services should therefore decide which outcome measures are more applicable to their setting. We suggest that occupational health services undertake annual notes review of occupational PEP to ensure practice consistent with non-occupational standards.

1. Proportion of PEP attendees having a baseline HIV test performed: aim 100% within 1 working day of presenting for PEP
2. Proportion of PEP attendees having a HIV test result available within 5 days: aim 97%
3. Proportion of PEP prescriptions that fit within recommended indications (consider or recommended): aim 90%
4. Proportion of PEP prescriptions administered within 24 hours of risk exposure: aim 70%
5. Proportion of individuals completing 4-week course of PEP: aim 75%
6. Proportion of individuals prescribed PEP undergoing testing for STIs: aim 90%
7. Proportion of individuals for whom completion of 4-week course of PEP is indicated who undergo HIV antibody/antigen test at least 45 days after the completion of PEP: aim 75%

8. Proportion of patients presenting for non-occupational PEP who have a documented discussion about PrEP if eligible: aim 90%.

18 Acknowledgements

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19 Conflicts of Interest:

NG received speaker fees from Gilead in November 2019. AR, FVC, JE, AS no conflicts.

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. A medicines reconciliation including the use of over-the-counter, supermarket and recreational drugs must be undertaken.

DRUG-DRUG INTERACTIONS WITH TENOFOVIR/EMTRICITABINE

Tenofovir disoproxil/emtricitabine has no significant drug-drug interactions although caution should be applied when tenofovir disoproxil/emtricitabine is co-administered with other potentially nephrotoxic agents. Enhanced renal monitoring may be warranted in this situation.

Descovy® (tenofovir alafenamide /emtricitabine) is transported by P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Medicinal products that strongly affect P-gp and BCRP activity (e.g. rifampicin, carbamazepine, phenobarbital) may lead to decreases in drug absorption and co-administration should be avoided. However, a drug interaction study showed that when tenofovir alafenamide is co-administered with rifampicin, therapeutic intracellular concentrations of the active moiety of tenofovir (tenofovir-diphosphate) are measurable, suggesting that the interaction is not clinically significant (195).

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.

Raltegravir binds to divalent cations such as iron, aluminium, magnesium, calcium and forms a complex at the level of the gastro-intestinal tract which results in less raltegravir being absorbed. Drug-drug interaction studies with antacids containing divalent cations have shown a more pronounced reduction in raltegravir minimum concentration (Cmin) when raltegravir was administered once daily compared to a twice daily regimen. A similar effect for iron supplements cannot be excluded. Therefore, concomitant use of metal cation containing antacids, iron supplements and multivitamins should ideally be avoided with once daily raltegravir or should be separated by at least 4 hours from twice daily raltegravir 400mg (144). Switch to a non-cation containing acid-

reducing agent is recommended during INSTI-based PEP if clinically indicated and non-essential mineral supplements should be stopped.

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.

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

DRUG-DRUG INTERACTIONS WITH DOLUTEGRAVIR

Since dolutegravir is an alternative agent detailed discussion of pharmacokinetics and drug-drug interactions is not included here. Like raltegravir, dolutegravir, interacts with magnesium/aluminium-containing antacids - these should be taken well separated in time from the administration of dolutegravir. Other significant interactions include rifampicin and enzyme-inducing anti-epileptics; we advise use of The Liverpool Drug Interactions website to check interactions with all concomitant medication.

DRUG-DRUG INTERACTIONS WITH BOOSTED REGIMENS (PROTEASE INHIBITORS, STRIBILD/GENVOYA)

As these are alternatives for PEP detailed discussion of pharmacokinetics and drug-drug interactions is not included here. Ritonavir and Cobicistat are associated with numerous drug-drug interactions e.g simvastatin and St John’s Wort are contra-indicated with all boosted regimens. Co-administration of Stribild and some medicinal products that are primarily metabolised by CYP3A may result in increased plasma concentrations of these products, which are associated with the potential for serious and/or life-threatening reactions Co-administration of ritonavir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects.

APPENDIX B

Post Exposure Prophylaxis Risk Assessment Proforma for use in Emergency Departments

This checklist is an aid to clinical practice only and does not replace local expert advice where indicated. For further information, please refer to the British Association of Sexual Health and HIV PEP 2021 guideline

Section 1:

Date:…….Time:…… …….. Seen by (Name / Designation):	Patient Name: DOB: Address:

Date of Potential/Actual Exposure ..../……/…… Time of exposure …….

Number of hours between exposure and consultation …….

Note: must be less than 72 hours since exposure to be eligible for PEP

Past Medical History:
……
……
……
……

Medication History: (including over the counter / herbal remedies / multivitamins / recreational drugs)
……
……
……

Allergies: ……

Contraception:……

Is the patient pregnant or at risk of pregnancy?.....

First day of Last Menstrual Period / cycle length (consider emergency contraception)

……..

Type of exposure (tick one)

☐ Occupational injury / Other Exposure, including injecting drug use **(proceed to section 2 on page 2)**

☐ Sexual Exposure **(proceed to section 3 on page 3)**

Section 2: Occupational injury / Other Exposure

Brief description of exposure**:**

……
……
……
……
……
……

☐ **Sharp instrument/needlestick**: ☐ hollow needle ☐ solid needle ☐ BM stick lancet ☐ Other:……

Were gloves worn? ☐ Yes ☐ No Did needle pass through glove ☐ Yes ☐ No ☐ Not known

☐ **Splash injury**: ☐ to eye/mouth ☐ Splash to broken skin ☐ Splash to intact skin

☐ **Bite/Scratch** ☐ Other (specify)…… Depth of injury: ……

Material exposed to: ☐ Blood / Plasma ☐ CSF ☐ Saliva ☐ Other (specify)……

Was wound made to bleed immediately? ☐ Yes ☐ No ☐ Not known

Was injury washed? ☐ Yes ☐ No ☐ Not known

If unknown HIV status, has index partner / patient been consented and tested for BBV (HIV, Hep B/C)?

☐ Yes ☐ No ☐ Not known

Details:……
……

Section 3: Sexual Exposure

Sexual Assault? ☐ Yes ☐ No Has patient attended SARC: ☐ Yes ☐ No
If not, please discuss (forensic examination and support)

Index partner details (the patients sexual contact): Male ☐ Female ☐ Trans ☐

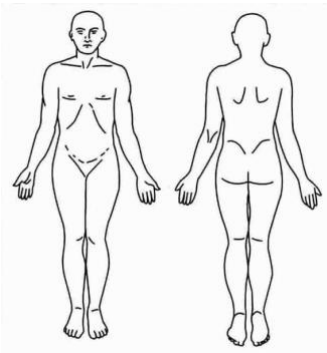
Ethnicity if known: .....

Duration of relationship: Regular ☐ Ex-Regular ☐ Casual ☐

Type of sexual contact:

		Condoms		Ejaculation	
		Yes	No	Yes	No
Anal receptive	☐	☐	☐	☐	☐
Anal insertive	☐	☐	☐	☐	☐
Vaginal receptive	☐	☐	☐	☐	☐
Vaginal insertive	☐	☐	☐	☐	☐
Oral	☐	☐	☐	☐	☐

Any other relevant comments i.e injury/bleeding: (use diagram)



Details of Index partner (the patient's sexual contact)

Name/ Description:……..……

DOB/Age:…….

Address/Area:…….

Tel number: …….

Known Hepatitis B positive: ☐ Yes ☐ No ☐ Not known

Known Hepatitis C positive: ☐ Yes ☐ No ☐ Not known

HIV status
☐ Definitely known HIV + (Status known to patient or HIV clinic)
☐ Probable HIV + (Patient told by contact or by someone else)
☐ Unknown HIV status

Is index partner / patient on antiretroviral treatment? ☐ Yes ☐ No ☐ Not known / unsure
Does the index partner / patient have an undetectable viral load? ☐ Yes ☐ No ☐ Not known / unsure
Index partner / patient HIV clinic location if known:……...

Section 4: Summary table on PEP eligibility

	Source HIV status			
	HIV positive		Unknown HIV status	
	HIV VL unknown / detectable	HIV VL undetectable	From high prevalence country / risk-group (e.g. MSM) [a]	From low prevalence country / group
SEXUAL EXPOSURES				
Receptive anal sex	Recommend	Not recommended [b]	Recommended	Not recommended
Insertive anal sex	Recommend	Not recommended [b]	Consider [c,d]	Not recommended
Receptive vaginal sex	Recommend	Not recommended [b]	Generally not recommended [c,d]	Not recommended
Insertive vaginal sex	Consider [c]	Not recommended	Generally not recommended [c,d]	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
OCCUPATIONAL AND OTHER EXPOSURES				
Sharing of injecting equipment	Recommended	Not recommended	Generally not recommended [e]	Not recommended
Sharps injury	Recommended	Not recommended	Generally not recommended [c,f]	Not recommended
Mucosal splash injury	Recommended	Not recommended	Generally not recommended [c]	Not recommended
Human bite	Generally not recommended [g]	Not recommended	Not recommended	Not recommended
Needlestick from a discarded needle in the community			Not recommended	Not recommended
Details of footnotes can be found in the full BASHH 2021 PEP guideline document online. https://www.bashh.org/guidelines				

Section 5: Patient eligible for PEP? (decision to be based on table in appendix below)

☐ Yes, recommended ☐ Not Recommended ☐ Consider

We recommend provision of the full 28 day PEP course of where possible

PEP starter pack prescribed ☐)

(See full guideline or seek URGENT specialist advice if any uncertainty or alternative regime required)

Emergency contraception given ☐ Yes ☐ No Details……..

Discussion points with the patient (Please tick)

The need for baseline bloods (including HIV test)	☐
Antiretrovirals are unlicensed for PEP	☐
Lack of conclusive data for PEP efficacy	☐
Importance of adherence to optimise efficacy	☐
Start PEP as soon as possible to maximise efficacy	☐
Advised too late if commenced after 72 hours	☐
Length of PEP is 28 days	☐
Drug side effects discussed	☐
Drug interactions including multivitamins, iron, antacids (advised to avoid whilst on PEP PEP)	☐
Seek urgent attention if symptoms of seroconversion (flu-like symptoms / rash)	☐
Advise condoms until final HIV test (in 10.5 weeks)	☐
Emergency contraception given (if applicable)	☐
Hepatitis B vaccine advised (if unsure if immune or in cases of sexual assault)	☐
Given PEP leaflet (patient leaflet from BASHH website)	☐
If given a starter pack (rather than the full 28 day course),advised of the need for urgent follow-up before the starter pack runs out to receive the rest of the course	☐
For occupational exposures: advised urgent follow up with occupational health ASAP and no later than within 72 hours	☐

Baseline tests to be obtained by Accident and Emergency clinician

Tests	Taken		Taken		Taken		Taken
HIV		Hep B core antibody*		Hepatitis C antibody		LFT (ALT)	
Hepatitis B surface Antigen*		Hepatitis B surface antibody*		Creatinine and eGFR		Pregnancy test (if applicable)	
*If the attendee has completed the hepatitis B vaccination course and has documentation of HepBsAb ≥10 IU at any time they are deemed a vaccine responder. If they are immunocompetent (e.g. HIV-negative) they do not require any further hepatitis B testing or follow up							

APPENDIX C

LEVELS AND GRADING OF EVIDENCE

<table>
<tr><th>Strength of recommendation</th><th>Grading of evidence</th></tr>
<tr><td rowspan="2">1 Strong recommendation

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</td><td>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.</td></tr>
<tr><td>B. Moderate quality evidence
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.</td></tr>
<tr><td rowspan="3">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 and be prepared to discuss that evidence with patients, as well as their values and preferences</td><td>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.</td></tr>
<tr><td>D. Very low-quality evidence
Benefits appear to outweigh the risk and burdens or vice versa
Evidence limited to case studies</td></tr>
<tr><td>GPP. Good practice point
Recommended best practice based on the experience of the guideline working group</td></tr>
</table>

APPENDIX D
Summary of Product Characteristics (SPC) advice relating to pregnancy

Antiretroviral	Summary of Product Characteristics (SPC) advice relating to pregnancy
Tenofovir disoproxil/emtricitabine TDF/FTC	The use of tenofovir disoproxil/emtricitabine may be considered during pregnancy, if necessary.
Tenofovir alafenamide/ emtricitabine TAF/FTC	Should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Zidovudine/lamivudine ZDV/3TC	A large amount of data on pregnant women taking lamivudine or zidovudine indicate no malformative toxicity.
Dolutegravir DTG	Due to the potential risk (~0.3%) of neural tube defects, dolutegravir should not be used during the first trimester unless there is no alternative (see text for a more detailed explanation).
Raltegravir RAL	Raltegravir 400 mg twice daily should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. There are no data for the use of raltegravir 1,200 mg once daily in pregnant women so it is not recommended during pregnancy.
Darunavir/ritonavir DRV/r	Darunavir should be used during pregnancy only if the potential benefit justifies the potential risk.
Elvitegravir / cobicistat / tenofovir DF / emtricitabine EVG/COBI/TDF/FTC	Due to lower concentrations of EVG & COBI in the second and third trimesters of pregnancy, neither should be initiated in pregnancy. It is the view of the writing group that EVG/COBI/TDF/FTC can be used for PEP during the first trimester of pregnancy if it is deemed the most clinically appropriate choice.

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