Post-Exposure Prophylaxis (PEP) Guidelines for children and adolescents potentially exposed to blood-borne viruses

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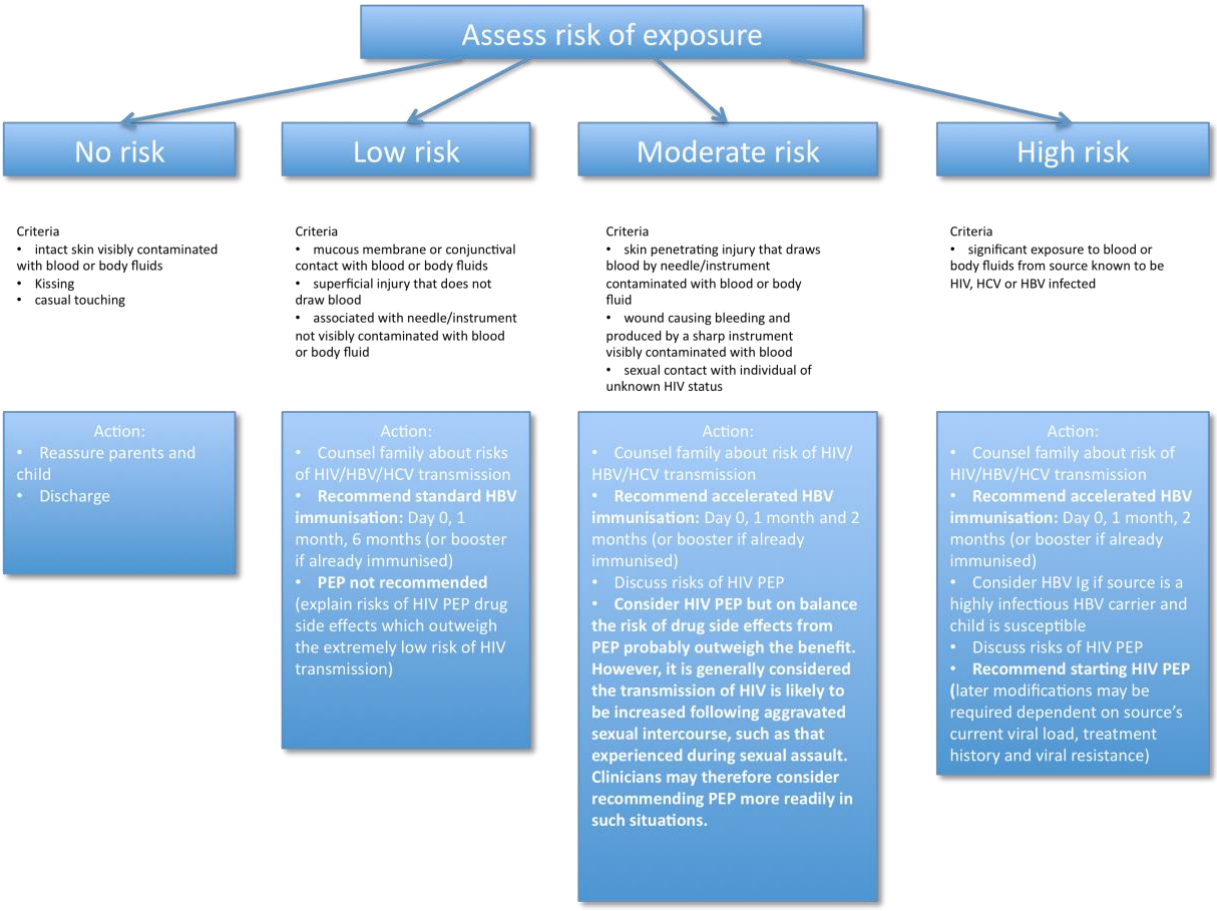
Scope of Guideline: Following exposure to blood-borne viruses, it should be remembered that the risk of transmission is highest for Hepatitis B, then Hepatitis C and then HIV. As this document has been prepared for the CHIVA website its focus is on HIV. However, it is important to consider risk of pregnancy and sexually transmitted infections following high-risk sexual exposure, and any safeguarding concerns.

New in Guideline 2015 update:

1. Switch from Kaletra®-based PEP to raltegravir-based regimens for older children who are able to swallow tablets and inclusion of chewable raltegravir as an option in younger children in centres where chewable raltegravir is available. The switch is in line with the change in adult guidelines prompted by MHRA warnings against the use of antiemetics in conjunction with ritonavir-containing regimens, due to the increased risk of cardiac events (prolonged QT interval) in adults. Raltegravir based ART was recommended by the Public Health England Expert Advisory Group on AIDS as it has been extensively tested in HIV infected adults with no significant safety issues and is better tolerated than Kaletra® so switching is likely to improve adherence and hence the efficacy of PEP.
2. Reduction in the window period for repeat HIV testing from 12 weeks to 8 weeks post completion of PEP using 4th generation antigen/antibody assays following the BASHH/EAGA statement on HIV window period in October 2014 (www.bashh.org).

Fig 1. Immediate Action Algorithm



Background

The risk of community acquired HIV in children is extremely low. However, children and adolescents are potentially at risk of contracting HIV from a variety of exposures, including needlestick injury, sexual abuse and consensual sexual activity in adolescence.[1] There have been no reported school-related transmissions.

The HIV status of the source is often unknown and difficult to establish. Body fluids presenting a risk of HIV transmission include blood, breast milk, semen or any body fluid if visibly bloodstained.[2] The risks of HIV being transmitted from a variety of exposures are shown in Table 1. HIV-infected fluids cannot penetrate intact skin. Sexual abuse represents a particular risk because of possible multiple exposures, mucosal trauma and the cervical ectopy and vaginal epithelial thinness found in children.[3]

Up to 40% of 15 year olds in the UK are sexually active. Following the widespread use of HAART (Highly Active Antiretroviral Therapy) children with perinatally acquired HIV-1 infection are surviving into adolescence and entering sexual relationships with their HIV negative peers who may present for PEPSE (Post Exposure Prophylaxis following Sexual Exposure). Please refer to BASHH Guidelines http://www.bashh.org/documents/4076.pdf [4] however it should be noted that following consensual unprotected vaginal sex PEPSE is no longer recommended where the HIV positive partner is known to be on effective antiretroviral therapy with an undetectable plasma HIV viral load[4]. **Please note:** at time of writing of this

guideline the BASHH PEPSE guidance is under review, the forthcoming updated recommendation will include raltegravir as discussed above.

Table 1. Estimated risks of HIV transmission according to type of exposure from a known HIV positive individual with detectable HIV viral load [4,5]

Type of HIV exposure	**Risk of transmission**
Occupational needlestick injury that punctures skin	0.3% or 1 in 333
Unprotected receptive anal sex	1.11% or 1 in 90
Unprotected receptive vaginal intercourse	0.1% or 1 in 1000

If the HIV status of the source is not known, the risk can be calculated from the following formula:
**Risk of HIV transmission = Risk that source is HIV positive x Risk of exposure*

The risks of transmission of Hepatitis B (HBV) and Hepatitis C (HCV) from a community acquired needle stick injury are significantly higher than for HIV.

Table 2. UK seroprevalence data for blood-borne infections in people who use intravenous drugs (from 2014 report)[6]:

	London	**Outside London**
HIV Prevalence	3.9%	0.9%
HBV Prevalence	32%	17%
HCV Prevalence	59%	49%

IVDU HIV seropositivity rate in London in 2013 was 3.9% (several fold higher than rates in rest of UK).[6] Given a 0.3% risk of transmission if the source was HIV positive, the risk from a community acquired needle stick injury can therefore be assessed as about 1:10,000 in London to less than 1:50,000 elsewhere. Note that quoted risks are based on injuries from needles contaminated with fresh blood: old blood in a syringe and needle found in the park is likely to carry a lower risk of transmission. In studies where a small amount of blood is retained in a syringe, viable HIV cannot be detected after 24 hours[7].

The risk of HBV seroconversion following a needle-stick from **known** high risk HBV infected source (HBe Ag +ve) is 37-62%[8] and around 5% following needle-stick from a **known** low risk HBV infected source (HBe Ag –ve). The average HCV seroconversion rate following needle-

stick from **known** HCV positive source is 1.8%[8]. Data for risk of transmission of HBV or HCV from single sexual exposure are not robust. HCV is inefficiently transmitted. Risks from high risk HBV infected source may be as high as 50% for seroconversion (lower for clinically symptomatic HBV infection).

Mechanism of action of HIV PEP

The presumed mechanism for HIV PEP is that shortly after an exposure to HIV a window period exists during which antiretroviral therapy may help to diminish or end viral replication. In a small case controlled study, AZT reduced the transmission rate of HIV by 79%.[9] In addition, combination antiretroviral therapy has been shown to markedly reduce vertical transmission of HIV from mother-to-child**[10]** Previously Department of Health recommendations for PEP in adults were Truvada® (a combination of tenofovir + emtricitabine) and Kaletra® (lopinavir/ritonavir), a reflection of the rapid genital tract penetration of tenofovir and efficacy of Truvada®/Kaletra® against most current viral isolates in the UK.[11] There are no DOH recommendations for PEP in children. However, recently adult national PEP guidelines have moved to the combination of raltegravir with Truvada® prompted by MHRA warnings against the use of antiemetics in conjunction with ritonavir containing antiretroviral regimens due to the increased risk of cardiac events (prolonged QT interval) in adults. Raltegravir is an integrase inhibitor licensed for use as first line therapy for treatment naïve adults and in treatment experienced children. Raltegravir is dosed at full adult dose of 400mg (single pink film coated tablet) twice daily for children from 25kg. Alternative chewable formulations of raltegravir are available for children over 11kg (see table 4 for dosing). **It should be noted that the film coated tablet and the chewable preparations are not bioequivalent.**

Given the safety of HBV vaccination, the risk-benefit ratio favours vaccinating all exposed children following needle stick injuries or sexual assault, unless they have a documented prior history of successful HBV immunisation. Baseline testing and 3-month serological follow-up testing for HCV and HBV are recommended. It is recommended to request HCV IgG, and HBsAg, HBsAb and HBcAb.

Procedure for Children and Adolescents presenting with possible exposure to HIV

1. Risk assessment

Careful history and examination to assess the risk of exposure to HIV. Establish whether exposure occurred within the last 72 hours. Detailed plan in Immediate Action Algorithm (Fig 1).

2. Investigations

Source

In rare situations the source may be known and if the individual gives consent HIV, HBV and HCV serology may be tested. If the source is already known to be HIV positive, obtain details of present and past antiretroviral medications, known previous resistance mutations and consider further resistance testing (if viral load detectable), although the latter should not delay commencement of PEP. Most virologists now do NOT recommend testing of source materials such as needles found in public places, since the test results are of low sensitivity and should not be used to guide management.

Child/Adolescent

Obtain baseline HCV, HBV and HIV antibody status. If antiretroviral therapy is to be started also request FBC, U&E and LFTs. Ascertainment that the child / adolescent is not already HIV infected is important, as treatment with PEP in that circumstance would be inappropriate (although awaiting this result should not delay PEP as it can be started and subsequently stopped or switched if necessary). The baseline HIV test result on the child/adolescent should be available at the first follow up visit (within 24-72 hours of PEP initiation). Baseline Point of Care testing (POCT) is not recommended in this situation.

3. Management

HIV PEP

HIV PEP is most effective if started within 1 hour of exposure, but may be beneficial up to 72 hours after. The child's family should be counselled about likely side effects (Table 4) and given contact phone numbers in case of concerns during or after the treatment period. An appointment to see a paediatrician/HIV physician ideally within 24-72 hours of starting HIV PEP should be made. Initially 5 days of PEP should be prescribed. A full 4 weeks should **NOT** be prescribed at the first appointment. A further prescription for **a total of 4 weeks** should be given at consultant review if PEP is to be continued. PEP regimens may sometimes need modification if the index case is known to or likely to harbour drug resistant virus. Seek expert help but do not delay starting PEP.

Regimens

The regimens below are based on age bandings; however accurate weight and height measurements should be used to calculate individual drug doses as per Table 4 or the CHIVA antiretroviral dosing table (http://www.chiva.org.uk/). Preferred regimens reflect changes in adult PEP guidance, however **the start of PEP should not be delayed whilst obtaining paediatric formulations of newer agents and hence alternative regimens are provided.**

In centres where chewable raltegravir is not readily available, if a child is unable to tolerate Kaletra®, zidovudine and lamivudine, referral to a tertiary centre for consideration of an alternative regimen is recommended.

Table 3. Suggested PEP regimens (see dose table below)

Age (years)	PEP - preferred	PEP - alternative	Notes
10 +	Raltegravir + Truvada® (emtricitabine 200mg/tenofovir disoproxil fumarate 300mg) NB if under 35kg, in centres where TDF paediatric formulations are immediately available, we would recommend age and weight appropriate dosing of raltegravir + TDF + lamivudine	1. Raltegravir + lamivudine 150mg/zidovudine 300mg combined tablet 2. Kaletra® + lamivudine 150mg/zidovudine 300mg combined tablet	As per adult guideline with an alternative for tenofovir in those with renal insufficiency.
6-9	Raltegravir + lamivudine + zidovudine	1.Kaletra® + lamivudine + zidovudine 2.Raltegravir or Kaletra® + paediatric tenofovir + lamivudine	Adult dose raltegravir for children above 25kg. Note that the chewable formulation of raltegravir is not bioequivalent to the tablets (see table 4)
2- <6	Kaletra® + lamivudine + zidovudine	1. Raltegravir+ lamivudine + zidovudine 2. Raltegravir or Kaletra® + paediatric tenofovir + lamivudine	Alternative option for centres with access to chewable raltegravir
<2	Kaletra® + lamivudine + zidovudine		Liquid formulations

Notes:

1. Young people from 10 years of age and over 35 kg who are able to swallow tablets should receive PEP as for adults:- raltegravir 400mg (1 tablet) bd + Truvada® 1 tablet od

2. Young people 10 years of age or older with renal insufficiency should not receive tenofovir and should therefore be given:- raltegravir 400mg (1 tablet) bd + a fixed dose combination of lamivudine 150mg/zidovudine 300mg 1 tablet bd

3. Tenofovir should be avoided in the context of renal impairment at any age if at all possible (seek expert advice)

4. Although raltegravir is currently licensed in children younger than 6 years, experience of use in children in this age group is very limited and chewable formulation is rarely immediately available even in specialist centres. For these reasons Kaletra® remains first line recommendation in children under 6 years of age with chewable raltegravir as an alternative.

Table 4 HIV PEP Drugs, Doses and Side effects

Dosing is correct as per date of guideline publication but for updated dosing please see CHIVA ART dosing table http://www.chiva.org.uk/

Drug	Formulation	Dose	Side Effects*
Raltegravir (RAL) NOTE: formulations are **not** bioequivalent; use chewable tabs for children 11-25kg and children >25kg who cannot swallow tablets	**Tablet:** 400mg **Chewable tablet:** 25mg, 100mg (can be chewed or swallowed)	**Tablet:** From 25kg: 400mg BD **Chewable tablet:** 11-14kg – 75 mg BD 14-20kg – 100mg BD 20-28kg – 150mg BD 28-40kg – 200mg BD >40kg – 300mg BD	Rash, nausea, hepatitis
Zidovudine (AZT, ZDV)	**Capsule**: 100mg, 250mg **Liquid**: 10mg/ml	**Capsule or liquid:** 180mg/m^2/dose BD to a maximum dose of 250mg BD (max. 300mg BD when used in combination products)	Granulocytopenia and/or anaemia, nausea, headache, myopathy, hepatitis, neuropathy.
Lamivudine (3TC)	**Tablet:** 100mg, 150mg **Liquid:** 10mg/ml	**Tablet or liquid:** 4mg/kg/dose BD to a maximum dose of 150mg BD	Peripheral neuropathy, nausea, diarrhoea, headache.
Truvada® (TDF+FTC) **Do not use if known renal impairment**	**Combined tablet:** TDF 300mg/FTC 200mg	**Combined tablet:** >35kg – 1 tablet OD	Headache, diarrhoea, nausea, vomiting, renal tubular dysfunction, bone demineralization

Tenofovir (TDF) Note: 300mg tenofovir disoproxil fumarate (TDF) = 245mg tenofovir disoproxil (TD) All doses expressed as TDF	**Tablet TDF (TD):** 300mg (245mg) **Paed tab TDF (TD):** 150mg (123mg) 200mg (163mg) 250mg (204mg) **Powder TDF (TD):** 40mg (33mg) per 1g scoop	**Tablet:** >35kg – 300mg OD **Paed tab:** 17-22kg – 150mg OD 23-28mg – 200mg OD 28-34kg – 250mg OD **Powder:** **2-12 yrs** 10-12kg – 2 scoops 12-14kg – 2.5 scoops 14-17kg – 3 scoops 17-19kg – 3.5 scoops 19-22kg – 4 scoops 22-24kg – 4.5 scoops 24-27kg – 5 scoops 27-29kg – 5.5 scoops 29-32kg – 6 scoops 32-34kg – 6.5 scoops 34-35kg – 7 scoops ≥35kg – 7.5 scoops	**Do not use if known renal impairment**
Lamivudine 150mg/zidovudine 300mg (Combivir® or generic equiv)	**Combined tablet:** 3TC 150mg/ZDV 300mg	**Combined tablet:** >30kg – 1 tablet BD	As for ZDV and 3TC
Kaletra® (LPV/RTV) 2 adult tabs = 4 paed tabs = 5ml of liquid ****All doses based on LPV****	**Liquid:** LPV 80mg/RTV 20mg per mL **Paed tablet:** LPV 100mg/RTV 25mg (yellow) **Adult tablet:** LPV 200mg/RTV 50mg (orange)	**Liquid:** 300mg/m^2/dose BD Dose in mls = $\frac{300 \times SA}{80}$ **Paed tablet**: 15-25kg – 2 tabs BD 25-35kg – 3 tabs BD >35kg – 4 tabs BD **Adult tablet:** >35kg – 2 tabs BD	Diarrhoea, abdominal pain, nausea, vomiting, headache.

$$\mathrm{BSA}(m^2) = \sqrt{\frac{\mathrm{height(cm)} \times \mathrm{weight(kg)}}{3600}}$$

*This list of side effects is not exhaustive – refer to product datasheet for detailed information on side effects, interactions with other medicines and other cautions for use.

Drug interactions that may reduce the effectiveness of raltegravir:

- Rifampicin within the preceeding 2 weeks
- Aluminium/ magnesium containing antacids

Avoid co-administration of ritonavir with steroids including nasal/inhaled preparations of fluticasone and budesonide due to the interaction with ritonavir producing extremely high steroid levels impacting on bone metabolism. Further information on drug interactions with antiretrovirals can be obtained at http://www.hiv-druginteractions.org/ or discuss with a pharmacist.

Antiemetics: Gastrointestinal side effects are more likely to occur with regimens that contain Kaletra® when compared to raltegravir. For those with nausea and vomiting on Kaletra® based PEP a switch to paediatric raltegravir should be considered. Alternatively the addition of an anti-emetic to a Kaletra® based regimen requires a risk benefit discussion with the family (including discussion regarding the unknown risk of prolonged QT in the paediatric population inferred from adult data) and specialist advice from a tertiary centre and/or HIV pharmacist is recommended.

HBV

For a significant exposure to an unknown source an accelerated course of HBV immunisation (Day 0, 1 month and 2 months) should be offered. The HPA recommends the use of intramuscular hepatitis B immunoglobulin only if the source is known to be HBV infected, although would agree to its use with an unknown source if compelling circumstances existed.

HCV

There is no recognised PEP for HCV. Families may be counselled that, in the event of HCV seroconversion, therapy is increasingly successful.

Tetanus

The need for tetanus injection/booster should be assessed per usual practice.

4. Emergency contraception and screening for sexually transmitted infections

In cases of sexual assault refer to BASHH guidelines on management of adult and adolescent complainants of sexual assault www.bashh.org/documents/4450.pdf. Following sexual exposure it is important to consider emergency contraception in girls of reproductive age who may require a double dose of levonorgestrol if receiving Kaletra® based PEP and the need for screening/prophylaxis for other sexually transmitted infections. See BASHH Guidelines.[4]

NB: Children under 18 presenting with non-consensual sexual activity should be referred to the Child Protection Co-ordinator. For those cases where sexual trauma has occurred in a child with a risk of HIV transmission, those carrying out testing and PEP care need to be sensitive to reducing possibility of creating extra trauma or exacerbating distress. e.g. blood tests/investigations should be in a paediatric setting if younger child.

5. Follow-up

Prior to discharge from A&E families embarking on HIV PEP should have the following:

- An outpatient appointment, preferably within the next 72 hours to see a named clinician with experience in prescribing antiretroviral drugs
- Contact telephone numbers in case of concerns about any aspect of the HIV PEP including out-of-hours number.
- 5 days of antiretroviral therapy
- A letter for their GP, with patients/parents consent.

Clear guidance should be provided for family/child as well as involved services about what details will be communicated between services (those dealing with original abuse/rape or other incident and those managing the PEP).

Outpatients Visits

Within 72hrs: Review in clinic, assess adherence and toxicity, decide whether PEP should continue for the full four-week course. Document and give baseline HIV, HBV, HCV Ab results. Arrange psychological support as necessary.

Newly diagnosed Hepatitis B infection: If the exposed patient is HBsAg positive there is a risk of flare of hepatitis after Truvada® is stopped and specialist advice should be sought prior to the cessation of PEP

Day 14: Review in clinic, assess adherence and toxicity, check FBC, U&E, LFTs.

Day 28: Review in clinic, assess adherence and toxicity, check FBC, U&E, LFTs (if abnormalities on previous blood tests or clinically indicated).

A minimum of 4 weeks AFTER PEP completion (8 weeks from high risk exposure):
Follow-up HIV testing should be undertaken with a fourth generation combined HIV antibody/ antigen assay. Antibody screening for Hepatitis B and C is also recommended. Optimally this should be performed 4-8 weeks after completing the 3 doses of HBV vaccine, so that infection can be excluded (HBsAg and HBcAb) and to ascertain that the vaccine response was satisfactory (HBsAb >10mIU/ml). If ongoing risk of exposure to HBV then a 4th dose of HBV vaccine should be given at 12 months. If further HBV vaccination required arrange appropriate follow up (either clinic or GP based).

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