9.1.6 Timing of neonatal PEP

All infant PEP should be started within 4 hours of delivery.

There are no clear data on how late infant PEP can be initiated and still have an effect, but all effective studies of infant PEP have started treatment early and animal data show a clear relationship between time of initiation and effectiveness, with no benefit demonstrated if commenced after >72 hours [48-50]. Immediate administration of PEP is especially important where the woman has not received any ART.

9.1.7 Maternal genotypic resistance

For infants born to women on fully suppressive cART, zidovudine monotherapy PEP remains reasonable, even where the woman has a previous history of zidovudine exposure with resistance (thymidine-associated mutations). On cART, the risk of transmission from a woman with fully suppressed viral replication is extremely low (~0.1%) and, although history of zidovudine resistance in maternal virus and infant PEP regimen has not been dissected, the frequency of transmission of zidovudine-resistant virus is concomitantly very low.

Despite minimal supporting evidence, this has been standard practice in the UK for several years without a signal from cohort data that transmissions are occurring in this context. Theoretical support for this approach comes from evidence that wild-type virus may be preferentially transmitted in the context of a maternal mixed population including zidovudine-resistant virions [51]. Furthermore, Swiss cohort data demonstrated no transmission among six infants born to women with zidovudine-resistant virus [52]. A substudy of the ACTG 076 trial showed that low-level zidovudine resistance was not associated with an increased risk of transmission [53]. Retrospective data from the US found no significant association between maternal zidovudine resistance and risk of transmission [54].

Historical French cohort data demonstrated possible transmission of zidovudine-resistant virus following failed zidovudine prophylaxis in a very small number of woman–infant pairs, although in all these cases (where data were available) the woman had detectable viral load at the time of delivery [55]. In the WITS cohort, presence of zidovudine-resistance mutations was shown in multivariate analysis to be associated with increased risk of transmission, although a significant proportion of women in this study had detectable HIV at the time of delivery [56].

There is therefore very little data on the risk of transmission of zidovudine-resistant HIV in the context of fully suppressed maternal viral load at time of delivery and infant zidovudine monotherapy. However, observational data from the UK have not shown this to be a practice associated with increased transmission risk.

Some clinicians prefer to choose another antiretroviral, with no history of maternal resistance, for infant post-exposure monotherapy. The established alternatives, nevirapine and lamivudine, have potent antiretroviral effect but a low (single-point mutation) barrier to resistance. In the event of transmission, the likelihood of an infant developing new resistance on zidovudine monotherapy is probably less than with nevirapine or lamivudine. The dosing and safety issues with lopinavir/r and raltegravir are outlined above. With infant feeding patterns, it is difficult to separate drug dosing from feeds, so drugs without food restrictions are preferred; this is another advantage of zidovudine.

Neonatal zidovudine monotherapy therefore remains a reasonable approach for infants born to women with a plasma viral load <50 HIV RNA copies/mL, even if there is a previous history of zidovudine resistance.

There are no data available on the efficacy of modified combination PEP when maternal zidovudine and/or nevirapine resistance has been demonstrated. Expert advice should be sought and use of alternative drug combinations should be considered following careful risk assessment.

9.1.8 HIV-2

9.1.8	If a woman is known to have HIV-2 infection, follow the same advice as for HIV infant PEP but if HIGH RISK (combination PEP indicated), nevirapine will not be effective. Seek expert advice. If advice is not immediately available, commence zidovudine, lamivudine and raltegravir until	2C

	guidance is available (see Appendix 3).	

There are no data available to suggest that babies born to women living with HIV-2 who are at VERY LOW or LOW RISK of vertical transmission should be managed any differently from those born to women with HIV. If the maternal viral load is undetectable at or after 36 weeks' gestation, the same guidance should therefore be followed as described above for HIV-exposed infants.

HIV-2 is intrinsically resistant to NNRTIs. There are no data to guide practice in the event of a HIGH-RISK delivery in the context of HIV-2 infection. The same guidance for the use of three-drug PEP should be followed as in section 9.1.3, replacing nevirapine with raltegravir. If raltegravir is not available, lopinavir/r could be used but with caution, as discussed in the previous section. Infants receiving raltegravir or lopinavir/r PEP should be monitored for toxicity in the first few days of life as per Appendix 3. Blood samples for infant testing should be sent to a UK laboratory that routinely provides HIV-2 testing.

9.1.9 PEP beyond 4 weeks

9.1.9	Infant PEP should not be given beyond 2 weeks for VERY LOW-RISK or 4 weeks for LOW-RISK infants even if the infant is breastfed	1C
	PEP should not be restarted unless significant subsequent exposure (e.g. maternal viral load detectable during breastfeeding). Seek expert advice regarding need for PEP following breast milk exposure during an episode of maternal viraemia.	1D

Indications for PEP outside the neonatal period (e.g. following breast milk exposure to HIV) involves a complex risk assessment in relation to timing of HIV exposure, which may be staggered. Expert advice should be sought. See section 9.4 for further information on monitoring during breastfeeding.

9.2 Pneumocystis pneumonia (PCP) prophylaxis

9.2.1	Co-trimoxazole prophylaxis is recommended from 1 month of age if HIV PCR screening is positive at any stage or if the infant is confirmed to be diagnosed with HIV. This should only be stopped if HIV infection is subsequently excluded.	1C

Pneumocystis pneumonia (PCP) in infants with HIV is associated with high mortality and morbidity. However, as the risk of neonatal HIV infection has fallen to <1% where interventions for the prevention of vertical transmission are in place, the necessity for PCP prophylaxis has declined and in most European countries it is no longer prescribed routinely for HIV-exposed infants, even when a baby is born to a woman with a viral load >50 HIV RNA copies/mL.

Co-trimoxazole should be prescribed from 4 weeks of age for infants with a positive PCR screening test for HIV before 4 weeks of age. This should be continued if infection is confirmed and stopped if infection is excluded. Infants with a first positive HIV molecular diagnostic test result at any age between 4 weeks and 1 year should be started on co-trimoxazole prophylaxis immediately until HIV infection is confirmed or excluded (see Appendix 3 for dose).

9.3 Immunisation

9.3.1	Immunisations should be given as per the national schedule outlined in the Green Book [57].	1C
9.3.2	Rotavirus vaccine is not contraindicated (unless HIV diagnosis has been confirmed and infant is severely immunosuppressed).	1C
9.3.3	If there is VERY LOW or LOW RISK of HIV transmission and BCG at birth is indicated, this should not be delayed.	1D

Rotavirus vaccine should be given to all HIV-exposed infants unless confirmed infected and shown to be severely immunosuppressed. If uncertain about administration of live vaccines, expert advice should be sought. Infants considered at VERY LOW or LOW RISK of HIV transmission (i.e. maternal viral load <50 HIV RNA copies/mL at or after 36 weeks' gestation) may be given BCG at birth if indicated according to UK guidelines for HIV-unexposed infants.

9.4. Infant feeding

There are no data on the risk of HIV transmission via breast milk in high-income countries. In low- to middle-income settings, the overall postnatal risk of HIV transmission via breast milk when women are treated with cART has been reported as 1.08% (95% CI 0.32–1.85) at 6 months and 2.93% (95% CI 0.68–5.18) at 12 months, however in these studies women only received cART for 6 months and often breastfed for longer [58]. In the more recent PROMISE trial, women received cART throughout the breastfeeding period, and the transmission rate was 0.3% (95% CI 0.1–0.6) at 6 months and 0.6% (95% CI 0.4–1.1) at 12 months [59].

Factors that increase the risk of HIV transmission via breast milk when women are not on cART include:

- Detectable HIV viral load;
- Advanced maternal HIV disease;
- Longer duration of breastfeeding;
- Breast and nipple infection/inflammation;
- Infant mouth or gut infection/inflammation;
- Mixed feeding, in particular solid food given to infants less than 2 months of age [60].

Where a woman is on cART and breastfeeding, it is presumed that the same factors are relevant, albeit less so, depending on adherence and viral load suppression.

Historically the risk of HIV transmission in women not on cART was affected by feeding other solid foods to young infants. The transmission risk for exclusive breastfeeding is 9.0/100 child-years; for predominantly feeding breast milk with other liquids is 9.5/100 child years; and for giving early solid foods rises to 41.2/100 child-years [60]. Whether this risk persists with feeding of solid foods when women breastfeed on cART with full viral suppression is not yet known.

An analysis of data from four African studies published before 2012, where women were on cART from before conception, estimated that the postnatal HIV transmission probability was around 0.16% per month of breastfeeding [61]. However, this estimated transmission risk is at least twice that seen in infants enrolled in the PROMISE trial at 12 months of age [59].

9.4.1 Breastfeeding advice for women with HIV living in the UK

9.4.1	In the UK and other high-income settings, the safest way to feed infants born to women with HIV is with formula milk, as there is on-going risk of HIV exposure after birth. We therefore continue to recommend that women living with HIV feed their babies with formula milk (but see also section 9.4.4).	1D

Current WHO advice on breastfeeding for women with HIV is aimed at low- and middle-income countries where there is a high risk of infant morbidity and mortality from diarrhoea, pneumonia and other infections, and where formula feeding is not safe or affordable for many families. All women with HIV are advised to start cART as soon as possible after HIV diagnosis and continue lifelong treatment. They are advised to breastfeed their infants exclusively for the first 6 months, while adhering to cART, then to add complimentary foods as appropriate after this time. They are advised not to stop breastfeeding until other safe and adequate foods are available, and to continue up to 12–24 months of age [62].

Suppressive maternal cART significantly reduces, but does not eliminate, the risk of vertical transmission of HIV through breastfeeding. The undetectable=untransmittable (U=U) statement applies only to sexual transmission, and we currently lack data to apply this to breastfeeding. Other considerations are the lack of lactation studies for most antiretroviral agents, meaning that the pharmacokinetic properties of ART in breastmilk are poorly understood, and the potential effects of exposure to ART in the breastmilk on infants who do not acquire HIV [63].

The writing group therefore continues to recommend formula feeding by women living with HIV to eliminate the risk of postnatal transmission.

9.4.2 Supporting women living with HIV to formula feed

9.4.2	Abstaining from breastfeeding can have financial and psychological repercussions for women, requiring support from the HIV MDT.	1C
	Women advised not to breastfeed for their baby's health should be provided with free formula feed to minimise vertical transmission of HIV.	1D

It is important to be aware that not breastfeeding can come at an emotional, financial and social cost to women living with HIV [64,65], and we advise that women receive appropriate support from their HIV MDT (which may include peer support, psychological and practical support, and financial support for formula feeding) [64-66].

We advise discussing infant feeding intentions early in pregnancy so that appropriate information and support can be provided. When women living with HIV are advised not to breastfeed, this can have a significant financial impact. There is a risk that some women with insufficient finances will forgo their own nutritional needs in order to afford formula for their infant, thus compromising their own health and potentially compromising the effectiveness of their HIV treatment [65]. Women with irregular immigration status and no recourse to public funds and women with a low income are particularly vulnerable to these barriers [65]. The provision of free formula milk, and the appropriate equipment to use it, alleviates any financial burden attached to this key prevention tool [64]. This ensures that women can make decisions on how to feed their infant without being influenced by cost. Free provision of formula milk also has the potential to improve women's retention in HIV care postpartum [67,68].

We acknowledge that provision of free formula for women living with HIV remains inconsistent across the UK. We advise clinics and voluntary sector organisations to map local services. There are different ways in which formula milk may be provided (see Box 1). Other examples of formula milk schemes can be found in the National AIDS Trust Policy Briefing on access to formula milk for women living with HIV [65].

> Jonathan Mann Clinic runs a scheme that provides vouchers for pregnant women and new mothers living with HIV, enabling the purchase of sterilisers, bottles and formula milk. The scheme is available to women who deliver at Homerton Hospital or who are residents of Hackney and attending HIV care at other clinics. At 30 weeks, pregnant women receive an entitlement letter from their midwife that they take to their HIV department, helping with compliance with care and treatment. They are given an initial voucher for £120 in the form of a Tesco payment card, which is then followed up with a further £80 at their 6-week postnatal appointment, and another £80 after 3 months. The scheme has been well received by women who report that it has removed much of the fear they had about not being able to breastfeed. The scheme is funded by the local authority and supports approximately 50 women per year.

Box 1. Formula milk scheme at Jonathan Mann Clinic, Homerton Hospital, London, UK

9.4.3 Suppression of lactation

9.4.3	Women not breastfeeding their infant by choice, or because of viral load >50 HIV RNA copies/mL, should be offered cabergoline to suppress lactation.	1C

Cabergoline is an ergot derivative introduced in the mid-1990s to inhibit puerperal lactation. It can also be used in the treatment of Parkinson's disease, prolactinomas, acromegaly and amenorrhea and galactorrhea secondary to neuroleptic use [69,70]. Cabergoline is a dopamine agonist with a higher affinity and specificity for the dopamine D_2 receptor than bromocriptine [71]. The suppression of prolactin release is more prolonged with cabergoline than with bromocriptine [72], such that a single dose of 1 mg cabergoline may be used to inhibit lactation on day 1 postpartum giving the equivalent effect of 2 weeks of bromocriptine. Adverse effects are similar to those reported with other ergot derivatives, but cabergoline appears to be better tolerated [73].

A small prospective study in Canada included 22 women who received cabergoline postpartum [74]. Taken on days 2 and 15 postpartum, cabergoline successfully suppressed lactation with an absence of pain, swelling or nipple discharge in over 86% of women. However, side effects were common and seen in nine women on day 2

and in 10 women on day 15. Most frequently reported side effects were dizziness and hand or foot numbness, hand or foot pain and nausea, but overall women were satisfied with the treatment and would recommend its use to a friend.

The option of using cabergoline should be discussed in advance with each woman and included in her birth plan. It should be made clear that it will reduce the discomfort of lactation if not breastfeeding but will prevent her from breastfeeding once taken.

9.4.4 Choosing to breastfeed in the UK

9.4.4	Women who are virologically suppressed on cART with good adherence and who choose to breastfeed should be supported to do so, but should be informed about the low risk of transmission of HIV through breastfeeding in this situation and the requirement for extra maternal and infant clinical monitoring.	1D
	When a woman decides to breastfeed, she and her infant should be reviewed monthly in clinic for HIV RNA viral load testing during and for 2 months after stopping breastfeeding.	1D
	Maternal cART (rather than infant pre-exposure prophylaxis [PrEP]) is advised to minimise HIV transmission through breastfeeding and safeguard the woman's health.	1D

Women who choose to breastfeed should be advised of the small on-going risk of HIV transmission. They should be supported in their decision, if they fulfil the following criteria:

- A fully suppressed HIV viral load (for as long a period as possible, but certainly during the last trimester of pregnancy);
- A good adherence history;
- Strong engagement with the perinatal MDT;
- Prepared to attend for monthly clinic review and blood HIV viral load tests for themselves and their infant during and for 2 months after stopping breastfeeding (see section 9.5.1.2).

Information for women considering breastfeeding should also be provided in written form and can be adapted locally from patient information leaflets developed by the writing group (see the BHIVA website: www.bhiva.org/pregnancy-guidelines). Women who do not fulfil the above criteria should be advised against breastfeeding. Women whose infants fall into the LOW-RISK category because of a short duration of cART and viral suppression or because of prematurity should be counselled that their risk of transmission may be higher because of a higher risk of transient viral expression in plasma and breast milk, and because of the immature neonatal gut. Women who breastfeed with a known detectable HIV viral load should be referred to social care as this places their infant at significant risk of HIV infection. A supportive and harm reduction approach of working openly together should be taken, to maintain trust and reduce the risk of women being pressurised to breastfeed in secret [64,75].

The risk of transmission in women on cART does still increase according to the duration of breastfeeding [76]. Women who wish to breastfeed (and meet the criteria specified above) should be advised to breastfeed for as short a time as possible, to exclusively breastfeed for the first 6 months, and to cease breastfeeding if they have breast infection/mastitis or if they or their infant has gastrointestinal symptoms. They should be given clear information, including how to manage common complications of breastfeeding, and have ready access to clinical advice and peer support. When weaning to solids, women should follow standard UK guidance, introducing complementary foods after 6 months of age, if still breastfeeding. Abrupt weaning from breast to formula and/or solids can be avoided, as long as the maternal HIV viral load remains fully suppressed.

In resource-poor settings, neonatal PrEP is equally effective as maternal cART in preventing HIV transmission via breast milk. In the PROMISE-PEP trial (ANRS 12174), infant regimens of daily lamivudine or lopinavir/r were equally effective up to 50 weeks (transmission rate on lopinavir/r: 1.4%, 95% CI 0.4–2.5; on lamivudine: 1.5%, 95% CI 0.7–2.5), with similar rates of grade 3–4 side effects of approximately 50% in both arms [76]. In the PROMISE trial, daily nevirapine as infant PrEP was comparable to maternal cART up to 12 months of breastfeeding, with a reported transmission rate of 0.3% (95% CI 0.1–0.6) at 6 months and 0.6% (95% CI 0.4–1.1) at 12 months [59].