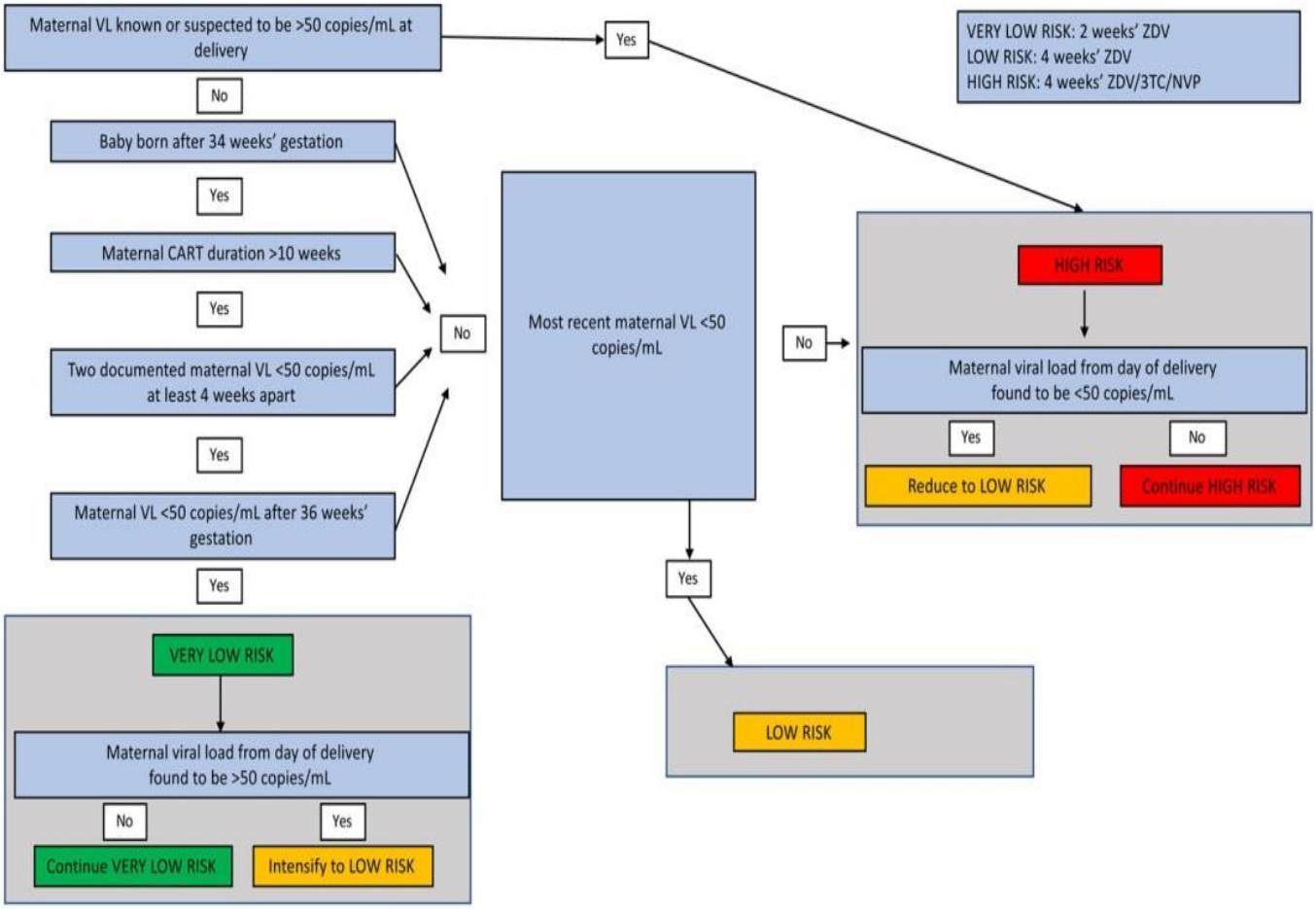

Figure 9.1. Algorithm for infant treatment

9.1.1 VERY LOW RISK

Zidovudine monotherapy for the infant has been part of the prevention of vertical transmission of HIV strategy since the publication of the results of the ACTG 076 trial in 1994 [1]. The relative contributions of the antenatal, peripartum and infant components have been difficult to quantify. In the ACTG 076 study, neonatal zidovudine 2 mg/kg every 6 hours was given for 6 weeks.

In the last version of the BHIVA pregnancy guidelines, 4 weeks of oral zidovudine was recommended for all infants except in specific HIGH-RISK circumstances relating to detectable or unknown maternal viral load at time of delivery [2]. This has been part of a hugely successful strategy to reduce the vertical transmission rate in the UK and Ireland with transmission now occurring only under exceptional circumstances [3].

In Germany, in an attempt to reduce neonatal exposure to zidovudine further, a strategy of using 2 weeks of neonatal zidovudine in the lowest-risk situations has been recommended for over 10 years with no signal that this has resulted in increased transmission [4].

French cohort data have provided further evidence that reducing neonatal PEP duration would be safe. No transmissions occurred among 2651 infants born to women receiving ART before conception, continuing ART throughout pregnancy and delivery with an HIV viral load <50 HIV RNA copies/mL (upper 95% CI 0.1%) [5]. Although this report does not specify the nature of neonatal PEP received, the absence of any transmission in this 'real world' setting gives support to the recommendation of reducing the duration of infant PEP as long as specific criteria are fulfilled.

In the pre-cART era, a randomised placebo-controlled trial of zidovudine monotherapy in Thailand compared four strategies for the prevention of vertical transmission of HIV:

- Maternal zidovudine monotherapy from 28 weeks' gestation through to delivery and neonatal zidovudine for 6 weeks (long-long);
- Maternal zidovudine from 35 weeks' gestation and neonatal zidovudine for 3 days (short-short);
- Maternal zidovudine from 28 weeks' gestation and neonatal zidovudine for 3 days (long-short);
- Maternal zidovudine from 35 weeks' gestation and neonatal zidovudine for 6 weeks (short-long).

Analysis demonstrated the efficacy of the 'long-short' regimen to be equivalent to that of the 'long-long' regimen. This led the authors to conclude that a regimen of 3 days of PEP would be sufficient when the woman had commenced zidovudine at 28 weeks' gestation [6].

Adult PEP guidelines for sexual exposure to HIV now recommend against PEP in the context of known viral load <50 HIV RNA copies/mL, based on strong evidence provided by large randomised trials investigating treatment as prevention of transmission [7]. In Switzerland, this evidence has now been extrapolated to the context of the prevention of vertical transmission of HIV, supporting the national guidelines recommending no PEP to infants born to women on cART with documented viral load <50 HIV RNA copies/mL on the two most recent measurements prior to delivery. For all other situations three-drug combination PEP is recommended [8].

It is the writing group's opinion that adult 'treatment as prevention' studies should be extrapolated to the prevention of vertical transmission with caution. The HIV transmission risk for peripartum exposure is much higher than for sexual or occupational exposure (10–20% *vs* 0.1–1.5%) [7,9]. The nature of exposure is also different. The fetus may be exposed at any time from conception to delivery; exposure at the time of delivery carries a particularly HIGH RISK.

Mother-to-infant trafficking of maternal cells (including CD4 cells) occurs and these cells can persist in the infant circulation after birth [10]. Although the relevance of this process in HIV transmission is not known, it has recently been suggested to have implications for vertical transmission of HBV [11]. Of note, this was the justification for 6 weeks of neonatal PEP in the original ACTG 076 study [1].

For these reasons, a 'no PEP' strategy is not included in this current BHIVA guideline. However, in the context of extremely low transmission rates in the UK, the writing group now recommends a shortened, 2-week course of zidovudine in VERY LOW RISK situations.

European cohort data indicate that risk of transmission remains LOW and stable if maternal cART is initiated more than 10 weeks prior to delivery [12]. Two weeks of infant zidovudine is therefore recommended if a woman has been on cART for more than 10 weeks, with a viral load <50 HIV RNA copies/mL on the most recent two occasions during pregnancy prior to delivery (at least 4 weeks apart) and a viral load <50 HIV RNA copies/mL at or after 36 weeks' gestation. There is no need to extend the duration of PEP to 4 weeks for breastfed infants if all the criteria for very low risk are met (see section 9.4.4 on breastfeeding).

9.1.2 LOW RISK

Two weeks of zidovudine is only recommended if all criteria in section 9.1.1 are met. If these criteria are not met but the maternal viral load is <50 HIV RNA copies/mL at time of delivery, zidovudine therapy should be extended to 4 weeks as in the 2014 BHIVA guidelines [2]. Cohort data indicate that prematurity is still possibly a risk factor for transmission [13]. Although it is difficult to determine the contribution of reduced duration of ART to this increased risk, the writing group recommends the use of 4 weeks of infant zidovudine if the woman commenced ART in pregnancy and delivers prematurely (<34 weeks) with a viral load <50 HIV RNA copies/mL.

If the criteria in section 9.1.1 are fulfilled and the infant commences zidovudine monotherapy but the maternal delivery HIV viral load is subsequently discovered to be greater than 50 HIV RNA copies/mL the duration of infant PEP should be extended to 4 weeks.

9.1.3 HIGH RISK

There is one large randomised controlled trial of combination therapy in neonates born to women who did not

receive ART prior to delivery [14]. Infants were randomly allocated at less than 48 hours of age to: 6 weeks of zidovudine monotherapy; 6 weeks of zidovudine with three doses of nevirapine in the first week of life; or 6 weeks of zidovudine, with nelfinavir and lamivudine for 2 weeks. The HIV vertical transmission rate was 8.5%, and in multivariate analysis only ART arm and maternal HIV viral load were significantly associated with transmission. Perinatal transmission was two-fold higher in the zidovudine alone arm compared to the multiple ART arms (*P*=0.034). There was no significant difference in transmission rates between the two multiple ART arms. Neonatal neutropenia was significantly higher in the three-drug arm.

In a randomised African study, babies born to women presenting at delivery received single-dose nevirapine or single-dose nevirapine and 1 week of zidovudine. Of those HIV negative at birth, 34 (7.7%) who received nevirapine plus zidovudine and 51 (12.1%) who received nevirapine alone were infected (*P*=0.03); protective efficacy was 36% for the dual combination [15].

However, in two other randomised African studies where the women received short-course ART, for infants who did not acquire HIV at birth there was no significant difference in transmission rate at 6 weeks for dual versus monotherapy short-course regimens for the infant: zidovudine plus lamivudine versus nevirapine [16]; or zidovudine plus nevirapine versus nevirapine [17].

NSHPC data from the UK and Ireland (2001–2008) demonstrate how the use of combination PEP in neonates has increased over time [18]. In total, 99% of 8205 infants received any PEP; for the 86% with data on type of PEP, 3% received dual and 11% triple regimens. The use of triple PEP increased significantly over this period, from 43% to 71% for infants born to untreated women, and from 13% to 32% where women were viraemic despite cART. HIV infection status was known for 89% of infants with information on PEP; 14.7% of infants who received no PEP were infected (5 of 34, all born vaginally to untreated women compared to 1.0% of those who received any PEP [72 of 7286]). Among infants born vaginally to untreated women, those who received PEP were significantly less likely to be infected than those who did not (8.5% [4/47] *vs* 45.5% [5/11]; *P*=0.002). However, in this cohort study, because of the overall low rate of transmission and selective use of triple PEP for infants at higher risk of HIV, it was not possible to explore the association between type of PEP and infection status.

Data from the European Pregnancy and Paediatric Cohort Collaboration (EPPICC) has shown increasing use of combination PEP across Europe. In 5285 HIGH-RISK mother–infant pairs (27.7% no antenatal or intrapartum antiretroviral prophylaxis, 17.3% only intrapartum prophylaxis, 55.0% detectable viral load at delivery despite antenatal ART), 23.9% of infants received combination PEP. Study results did not indicate an advantage of combination PEP compared to single-drug neonatal prophylaxis; however, the authors concluded that this observation may result from confounding or combination PEP only being effective in a subgroup of HIGH-RISK infants [19].

There are no randomised trials of combination PEP for infants where women are receiving cART. In a French study, transmission rates with dual therapy (zidovudine and lamivudine) given to both the neonate and woman (1.6%) were lower than zidovudine monotherapy reported in historical controls (6.8%; OR 0.22; 95% CI 0.2–0.5) [20].

When an infant has been started on combination PEP because the maternal viral load was considered likely to be >50 HIV RNA copies/mL at delivery and subsequently the delivery maternal viral load is shown to be <50 HIV RNA copies/mL, it is reasonable to simplify the infant PEP to zidovudine monotherapy as in section 9.1.2.

9.1.4 Choice of triple combination PEP for neonates

Most neonates born in the UK to women known to have HIV will be exposed to ART *in utero*, during delivery and in the first month of life. The range of combinations of ART to which neonates are being exposed *in utero* continues to increase. Neonatal drug metabolism is generally slower than that of older infants or children and is even less efficient in premature neonates. Due to a lack of neonatal pharmacokinetic and efficacy studies and suitable formulations, ART dosing regimens remain restricted to a small proportion of antiretrovirals (Appendix 3).

For infants born to ART-naïve women, or where drug resistance is unlikely, zidovudine, lamivudine and nevirapine is a well-tolerated combination regimen with the most clinical experience [18,19,21-24] (see Appendix 3 for dosing).

Neonatal pharmacokinetic studies have been performed for zidovudine [25], lamivudine [26,27], tenofovir DF [28] and emtricitabine [29] and dosing regimens are available for most of the nucleoside analogues from age 1 month [30].

The pharmacokinetic profiles of nevirapine in neonates have been described in detail [31-35].

In contrast to the PIs, nevirapine efficiently crosses the placenta (see below) and is well absorbed by the neonate [36]. Neonatal metabolism of nevirapine is induced where there has been antenatal *in utero* exposure [31,32]; if this drug is given to the neonate when the women has taken it for 3 or more days, the full dose of 4 mg/kg/day should be started at birth, rather than the induction dose of 2 mg/kg/day (Appendix 3). In combination PEP, owing to its long half-life, nevirapine should be stopped 2 weeks before co-prescribed antiretroviral drugs to reduce the risk of nevirapine monotherapy exposure and the development of NNRTI resistance should transmission have occurred.

The recommended regimen for standard three-drug PEP is therefore a total of 2 weeks of nevirapine (at full or incremental dosing) with 4 weeks of zidovudine and lamivudine as shown in detail in Appendix 3.

Dosing for raltegravir for neonates has recently been described (IMPAACT P1110). This requires increasing doses after the first and fourth weeks of life [37] (see Appendix 3). As raltegravir may affect bilirubin metabolism, total and split bilirubin should be checked during the first week of life, although the risk of discontinuation due to hyperbilirubinaemia in the study was low [37]. Appropriate raltegravir dosing for premature neonates is not yet available, and they are more vulnerable to hyperbilirubinaemia.

The writing group therefore recommends that raltegravir should only be prescribed to preterm neonates in exceptional circumstances. Its use should only be considered after seeking expert advice and where there is multidrug resistance.

Pharmacokinetics-supported dosing is available for lopinavir/r based on infants who have acquired HIV initiating therapy in the first 6 weeks of life [38-40] and a study that included infants treated from birth [41]. However, evidence of adrenal suppression has been documented in some neonates treated with lopinavir/r, particularly preterm infants [42]. This is in addition to case reports of cardiac, renal and neurological toxicity, especially in, but not restricted to, premature infants, and including one death during PEP with lopinavir/r [43]. No effects have been observed with maternal lopinavir/r in the absence of neonatal dosing. It remains unclear whether these effects are related to lopinavir/r specifically or could be seen with other ritonavir-boosted PIs.

The writing group therefore recommends that lopinavir/r should be avoided in routine infant PEP and should only be prescribed to preterm neonates in exceptional circumstances. Its use should only be considered after seeking expert advice and where there is multidrug resistance. Close metabolic monitoring in hospital should be undertaken for the first 5 days of life.

9.1.5 Intravenous ART in the neonate

The only licensed ART available for intravenous use in sick and/or premature neonates who are unable to take oral medication is zidovudine [25,44]. Reduced oral and intravenous dosing schedules for premature infants are available (Appendix 3).

The very premature neonate is at risk of necrotising enterocolitis (NEC) if enteral feeding is commenced too soon or increased too rapidly. It is not known whether very early enteral administration of ART can exacerbate this risk. In a large French case-controlled study of NEC, being an infant of a woman with HIV was associated with an increased risk of NEC (OR 6.63; 95% CI 1.26–34.8; *P*=0.025), although the numbers were too small to ascertain the effect of maternal and/or infant ART [45]. Premature infants should be commenced on intravenous zidovudine until enteral feeding is established, when zidovudine may be given enterally. The premature dosing regimen should be used (Appendix 3).

The fusion inhibitor enfuvirtide is the only other antiretroviral that is administered parenterally, usually subcutaneously, in adults and children. Enfuvirtide does not cross the placenta. Although intravenous enfuvirtide has been given to a small number of infants born to women with multidrug-resistant HIV, no formal neonatal pharmacokinetic studies have been conducted to date. An unlicensed intravenous dosing regimen for infants at risk of multidrug-resistant HIV has been adapted from the paediatric subcutaneous treatment study [46] and an adult intravenous dosing study [47] (see Appendix 3 and seek expert advice).