Management of Babies born to HIV Positive Mothers - Full Paediatric Clinical Guideline – Joint Derby and Burton

Reference no.: NIC IN 16

Introduction:

Vertical transmission of HIV from mother to baby can occur before and during birth or postnatally through breast-feeding. There is a close linear correlation between maternal viral load and risk of transmission. The number of children diagnosed before their 16thbirthday with vertically acquired HIV infection in the UK increased from the early 1990's until reaching a peak of 164 in 2003. This number then declined in 2011 to 74 and to 22 in 2017 (United Kingdom neonatal HIV surveillance data tables No.1.2:2018, Public health England).
All pregnant women who are HIV positive are discussed in the HIV MDT meeting (Paediatrician, GUM consultant, Obstetric consultant and specialist nurses) once a month and management plan made for the infants when they are born.

1. Risk Stratification:

As the risk of transmission of HIV from the mother to baby depends on few factors like maternal viral load, duration of undetectable viral load, prematurity etc. Thus the risk stratification is done depending on the above factors and classified as Very low risk, low risk and high risk and the management varies accordingly.

1.1 VERY LOW RISK

In the context of extremely low transmission rates in the UK, 2-week course of zidovudine is recommended in VERY LOW RISK situations.
Two weeks of infant zidovudine is 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.

1.2 LOW RISK

Two weeks of zidovudine is only recommended if all criteria in 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.
If the criteria in section 1.1 are fulfilled and the infant commence 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.

1.3 HIGH RISK

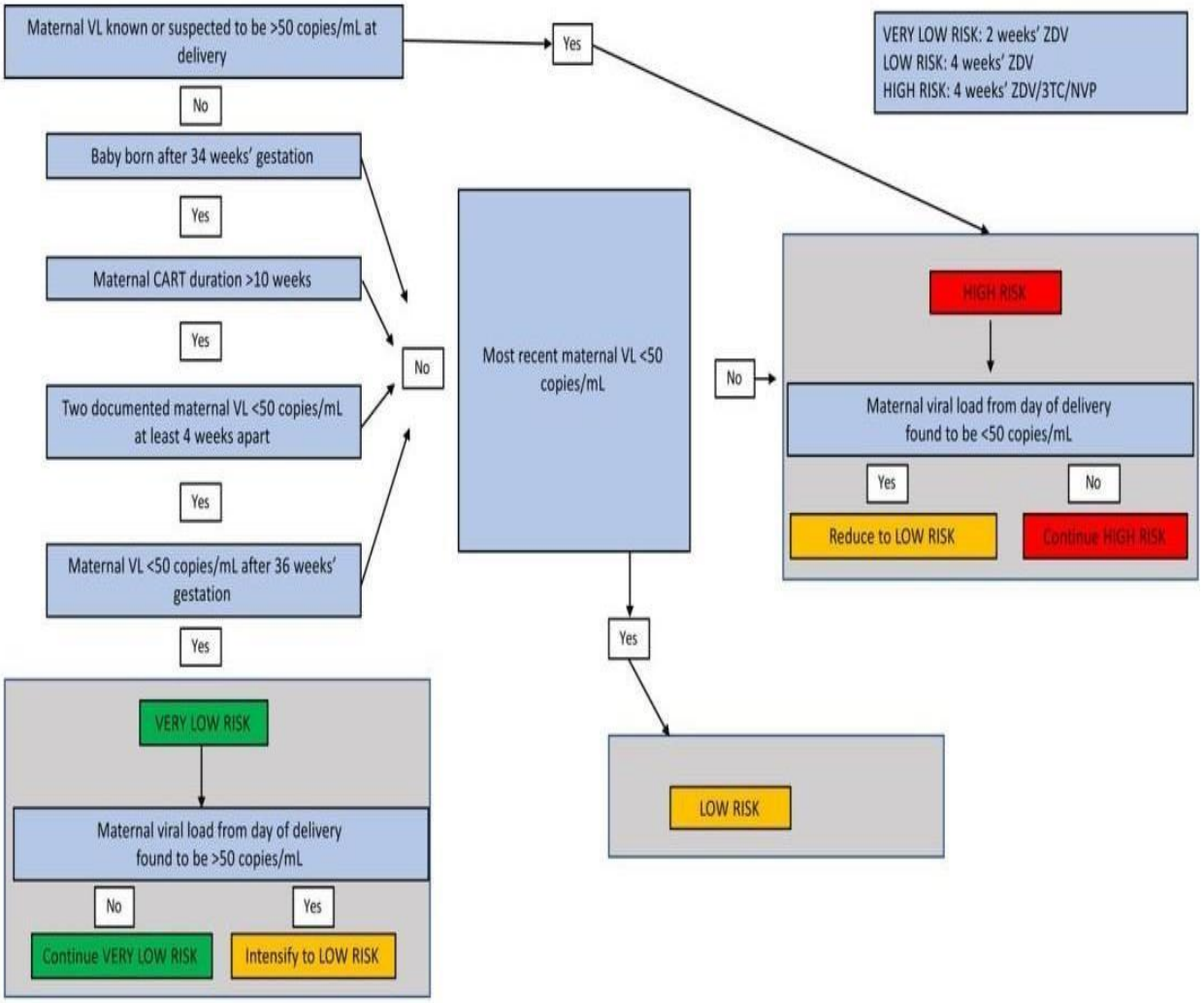
There is one large randomised controlled trial of combination therapy in neonates born to women who did not receive ART prior to delivery. Infants were randomly allocated at less than 48 hours of age to: 6 weeks of zidovudine monotherapy; 6 weeks of zidovudine with three doses of nevirapine in the first 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.

1. Infant PEP

1.1	**VERY LOW RISK**
	Two weeks of zidovudine monotherapy (4mg/kg 12 hourly orally) is recommended if all the following criteria are met: • The woman has been on cART for longer than 10 weeks; **AND** • Two documented maternal HIV viral loads <50 HIV RNA copies/mL during pregnancy at least 4 weeks apart; **AND** • Maternal HIV viral load <50 HIV RNA copies/mL at or after 36 weeks.
1.2	**LOW RISK**
	Extend to 4 weeks of zidovudine monotherapy (4mg/kg 12 hourly orally): • If the criteria in 1.1 are not all fulfilled but maternal HIV viral load is <50 HIV RNA copies/mL at or after 36 weeks; • If the infant is born prematurely (<34 weeks) but most recent maternal HIV viral load is <50 HIV RNA copies/mL.
1.3	**HIGH RISK**
	Use combination PEP, Triple therapy for 4 weeks • If maternal birth HIV viral load is known to be or likely to be >50 HIV RNA copies/mL on day of birth, • If uncertainty about recent maternal adherence or if viral load is not known. Triple Therapy: 1. Zidovudine 4mg/kg 12 hourly orally for 4 weeks (If baby is NBM, Zidovudine 1.5mg/kg IV 6 hourly infused over 30 minutes) 2. Lamivudine 2mg/kg BD orally for 4 weeks 3. Nevirapine 2mg/kg OD orally 1st week, then 4 mg/kg OD 2nd week and stop.
1.4	Neonatal PEP should be commenced as soon as possible after birth, and at least within 4 hours
1.5	In the context of known maternal resistance to zidovudine with VERY LOW or LOW RISK, zidovudine monotherapy is still recommended for infant PEP.

1.6	If HIGH RISK (combination PEP indicated) and there is a history of documented maternal zidovudine and/or nevirapine resistance, seek expert advice. If advice is not immediately available, commence standard three-drug PEP (zidovudine, lamivudine and nevirapine) until guidance is provided.

Figure 1. Algorithm for infant treatment



2. Care of the neonate

- Skin to skin should be encouraged as soon as possible. There is no need to bath the baby first.

- It is important the infant is kept warm.
- Baby is to be fed whilst receiving skin-to-skin as soon as possible (within 1 hour of birth) with the mother's choice of formula milk. If mum wishes to breast feed, see section 4; infant feeding.
- It is not necessary for a paediatrician to be present for delivery if no other obstetric risk factors have been identified.
- The baby will require oral ART as soon as possible after birth, preferably within 1 hour, but within 4 hours of birth.
- The midwife responsible for the care of mother and baby should arrange a hospital number for the infant via the receptionist.
- Contact the paediatrician promptly, who will review the infant and prescribe Zidovudine on the paediatric drug chart (the birth weight is required for dose calculation).
- Zidovudine syrup is usually available on labour ward. Once the first dose is administered, please ensure the bottle, with paediatric drug chart on which weight and hospital number is documented, is taken to pharmacy for labelling. If there are any issues with labelling such as pharmacy being closed at the time of birth, then please don't delay administration of the medication. The dose can be given with the drug chart and the label can be added before discharge home.
- Consider synchronizing the times of administering oral ART to the baby, with the timing of the mother's HAART for her convenience.
- Administration of Vitamin K, with parental consent, is not contra-indicated.
- BCG vaccination - Refer eligible babies in the usual way and write BBV positive on the referral form}
- Mother and baby can be transferred to the postnatal ward and follow postoperative and infection control guidelines for recovery.

3. Medication:

Please contact pharmacy to order medications for baby when mother is admitted to labour ward.

Monotherapy:

Zidovudine 4mg/kg 12 hourly orally for 2 - 4 weeks (depending upon risk stratification) and then stop.

- ***1st dose within 4 hours of birth, preferably with in 1 hour (start ASAP, can be started before blood tests)***
- *If unable to tolerate oral Rx: IV 1.5mg/kg infused over 30mins 6 hourly.*
- *If the mother is breast feeding, oral Zidovudine may be given for longer duration (eg: 6 weeks)*
- *Side effects: Lactic acidosis, Anaemia, Abnormal LFTs*

Triple Therapy:

1. *Zidovudine* 4mg/kg 12 hourly orally for 4 weeks
   (If baby is NBM, Zidovudine 1.5mg/kg IV 6 hourly infused over 30 minutes)
2. *Lamivudine* 2mg/kg BD orally for 4 weeks
3. *Nevirapine* 2mg/kg OD orally 1st week, then 4 mg/kg OD 2nd week and stop.

3.1 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.

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.

Nevirapine efficiently crosses the placenta and is well absorbed by the neonate. Neonatal metabolism of Nevirapine is induced where there has been antenatal in utero exposure; 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 . 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.

3.2 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. Reduced oral and intravenous dosing schedules for premature infants are available (Appendix 1).

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 1).

3.3 Timing of neonatal PEP

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

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 . Immediate administration of PEP is especially important where the woman has not received any ART.

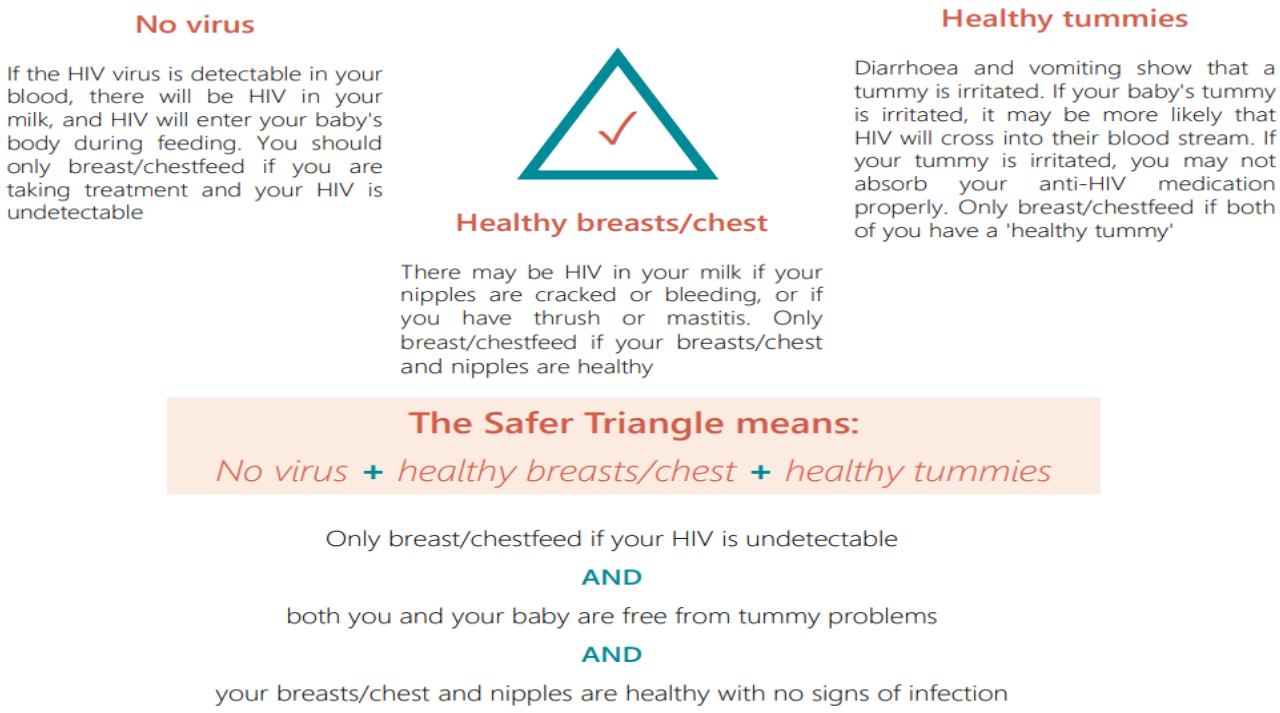
Indications for PEP outside the neonatal period (e.g. following breast milk exposure to HIV, where you may consider 6 weeks of oral Zidovudine while mum is breast feeding) involves a complex risk assessment in relation to timing of HIV exposure, which may be staggered. It should be a MDT decision.

4. Infant feeding

- Discussion about infant feeding should take place from early in antenatal period.
- Artificial/formula feeding is always recommended.
- Discuss option to have cabergoline.
- Other reasons for artificial feeding are discussed to assist the mother in talking to relatives/ friends.
- Explore the options of community/CHIVA support funds for formula feeds. Please discuss with specialist midwife for HIV' if required.

If the woman plans to breast feed:

- 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. There is no need to extend infant PEP beyond 2 weeks simply because of breastfeeding if all of the criteria for VERY LOW RISK are met.
- A meeting to discuss above options with Paediatric consultant and GUM consultant should be arranged as soon as where possible.
- The plan of care should include the decision re infant feeding and advice for staff to support women who choose to breast feed to do so safely.
- The leaflets 'General Information on Infant feeding for Women Living with HIV' and 'HIV and Breast Feeding your Baby' from BHIVA should be given to mothers considering breast feeding. See references for information leaflets.



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. 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.

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.

Suppressive maternal cART significantly reduces, but does not eliminate, the risk of vertical transmission of HIV through breastfeeding. The undetectable=untransmissable (U=U) statement applies only to sexual transmission, and we currently lack data to apply this to breastfeeding.

5. Immunisation

- Immunisations should be given as per the national schedule outlined in the Green Book.
- Rotavirus vaccine is not contraindicated (unless HIV diagnosis has been confirmed and infant is severely immunosuppressed).
- **BCG** - The birth plan should include a recommendation about BCG.
    - ‘low risk’ or ‘very low risk’: Where BCG is indicated it can be given as per the standard BCG guideline. (BCG Vaccination (TB) in the Newborn, Reference no.: NIC IN14 NICU)
    - ‘high risk’ :For mothers who are high risk the BCG should be arranged once the baby has had

three negative HIV RNA results.

6. Infant testing and follow up

The gold standard test for HIV infection in infancy was HIV DNA PCR on peripheral blood lymphocytes. In a number of studies, including the large French perinatal Cohort, equal or increased early sensitivity with amplification of viral RNA with no false positives has been reported.

All infants born to mothers infected with HIV should have a blood test for

- **HIV 1 proviral DNA screen and HIV RNA screen.**
- These are taken in **2 purple EDTA tubes of blood.**
- There is an order set 'bundle' on Lorenzo called '**Postnatal HIV bloods - Baby'** which should be sent as a paired set with the maternal samples ordered on '**Postnatal HIV bloods - Mother'**. Must be ordered on paper forms at QHB.

Once baby is weighed, the midwife should call the paediatrician who will prescribe the medication and will take bloods with parental consent. The midwife should ask the paediatrician for the two EDTA bottles, then

- **Take a maternal blood sample and take both samples paired to the lab**.

The paediatrician (ST1/ANNP) is responsible for referring the baby to

- **Please inform/email** Dr Bala Subramaniam, Paediatric consultant on bala.subramaniam1@nhs.net and the specialist midwifes on uhdb.perinatalHIVteamRDH@nhs.net and uhdb.perinatalHIVteamQHB@nhs.net with the details of the baby and the mother.

- **Arrange Dr Bala Subramaniam's Paediatric outpatient clinic** (VPBBC or VPBTB) for a 4-6 week follow up

This is held in the main outpatients' department at RDH on Thursdays. Contact ext. 85845 to arrange an appointment prior to discharge.

7. Investigations and follow ups

Day 1 (At birth):

- HIV 1 proviral DNA screen and HIV RNA screen (EDTA x 2)**.** Liaise with Microbiology & label 'Diagnostic Retroviral PCR'. Also send paired sample for mum.
- Book patient to Dr Bala Subramaniam's clinic VPBBC or VPBTB in 4-6 weeks (OPD appt: 86899/88756)

6 weeks:

- HIV 1 proviral DNA screen and HIV RNA screen (EDTA x 2).
- Ensure Zidovudine is stopped
- Look for Failure to thrive, hepatosplenomegaly & lymphadenopathy
- Check blood results from birth & Arrange follow up in clinic at 3 months

3 months:

- HIV 1 proviral DNA screen and HIV RNA screen (EDTA x 2).
- Look for Failure to thrive, hepatosplenomegaly & lymphadenopathy
- Check blood results from 6 weeks

2 years:

- HIV antibodies (Red top x1 – serum)
- If negative - discharge

If breast feeding:

- HIV 1 pro viral DNA and HIV RNA PCR (EDTA x 2)– 4 weekly until breast feeding
- 2 months after stopping breastfeeding

7. References (including any links to NICE Guidance etc.)

1. https://www.bhiva.org/pregnancy-guidelines
2. https://www.bhiva.org/file/5bfd30be95deb/BHIVA-guidelines-for-the-management-of-HIV-in-pregnancy.pdf
3. https://www.chiva.org.uk/professionals/guidelines/mother-child-transmission/
4. https://www.bhiva.org/file/FCUcXrfVgWsYl/BHIVA-pregnancy-guidelines-update-2014.pdf
5. https://www.bhiva.org/file/5bfd3080d2027/BF-Leaflet-1.pdf
6. https://www.bhiva.org/file/5bfd308d5e189/BF-Leaflet-2.pdf

Documentation Controls

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<tr><td>Reference Number
NIC IN 16</td><td colspan="2">Version:
2.0.0</td><td>Status
Final</td><td>Author: Dr Bala Subramaniam
Job Title: Consultant</td></tr>
<tr><td rowspan="3">Version / Amendment History</td><td>Version</td><td>Date</td><td>Author</td><td>Reason</td></tr>
<tr><td>2.0.0</td><td>Jun 2020</td><td></td><td>Review and merged into UHDB guideline in consultation with Derby and Burton NICU consultants.</td></tr>
<tr><td></td><td>Dec 2023</td><td>Dr Bala Subramaniam</td><td>Review</td></tr>
<tr><td colspan="5">Intended Recipients:
All Medical and nursing staff at UHDB</td></tr>
<tr><td colspan="5">Training and Dissemination: Cascade the information via BU newsletter and address training</td></tr>
<tr><td colspan="5">Development of Guideline: Dr B Subramaniam</td></tr>
<tr><td colspan="5">Linked Documents: State the name(s) of any other relevant documents</td></tr>
<tr><td colspan="5">Keywords:</td></tr>
<tr><td colspan="2">Business Unit Sign Off</td><td colspan="3">Group: Paediatric Business Unit Guidelines Group
Date: 20th December 2023</td></tr>
<tr><td colspan="2">Divisional Sign Off</td><td colspan="3">Group: Women and Children’s Clinical Governance Group
Date: 21st December 2023</td></tr>
<tr><td colspan="2">Date of Upload</td><td colspan="3">24/01/2024</td></tr>
<tr><td colspan="2">Review Date</td><td colspan="3">Jan 2027</td></tr>
<tr><td colspan="2">Contact for Review</td><td colspan="3">Dr Bala Subramaniam</td></tr>
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8. Appendix 1: Drug dosing for infants

<table>
<tr><th>DRUG</th><th>DOSE</th><th>COMMENTS/SIDE EFFECTS</th></tr>
<tr><td colspan="3">NRTIs: nucleoside reverse transcriptase inhibitors</td></tr>
<tr><td>Zidovudine
(ZDV) (Retrovir®)
Also known as azidothymidine (AZT)

Liquid – 10 mg/mL</td><td><u>Oral:</u>

<30/40 gestationatbirth
30–34/40 gestationatbirth

<u>Duration oral dosing:</u>
• Very low risk monotherapy – 2 weeks
• Low risk monotherapy – 4 weeks
• Combination therapy
– 4 weeks <u>Intravenous:</u>
• ≥34/40 gestation – 1.5 mg/kg four times a day
• <34/40 gestation – 1.5 mg/kg twice a day, change to four times a day at 34/40</td><td>Anaemia, neutropenia
<table><tr><th>Weight range (kg)</th><th>Oral dose (equivalent to 4 mg/kg) <u>TWICE A DAY</u></th><th>Volume to be given orally <u>TWICE A DAY</u></th></tr><tr><td>2.01–2.12</td><td>8.5 mg</td><td>0.85 mL</td></tr><tr><td>2.13–2.25</td><td>9 mg</td><td>0.9 mL</td></tr><tr><td>2.26–2.37</td><td>9.5 mg</td><td>0.95 mL</td></tr><tr><td>2.38–2.50</td><td>10 mg</td><td>1 mL</td></tr><tr><td>2.51–2.75</td><td>11 mg</td><td>1.1 mL</td></tr><tr><td>2.76–3.00</td><td>12 mg</td><td>1.2 mL</td></tr><tr><td>3.01–3.25</td><td>13 mg</td><td>1.3 mL</td></tr><tr><td>3.26–3.50</td><td>14 mg</td><td>1.4 mL</td></tr><tr><td>3.51–3.75</td><td>15 mg</td><td>1.5 mL</td></tr><tr><td>3.76–4.00</td><td>16 mg</td><td>1.6 mL</td></tr><tr><td>4.01–4.25</td><td>17 mg</td><td>1.7 mL</td></tr><tr><td>4.26–4.50</td><td>18 mg</td><td>1.8 mL</td></tr><tr><td>4.51–4.75</td><td>19 mg</td><td>1.9 mL</td></tr><tr><td>4.76–5.00</td><td>20 mg</td><td>2 mL</td></tr></table></td></tr>
<tr><td>Lamivudine (3TC)
(Epivir®)
Liquid 10 mg/mL</td><td><u>Oral:</u> usually as part of combination therapy
2 mg/kg twice a day – round dose <u>up</u> to nearest 0.5 mg to assist administration</td><td>Anaemia, neutropenia
(much less common than with ZDV)</td></tr>
<tr><td>Nevirapine (NVP)
(Viramune®)

Liquid 10 mg/mL</td><td><u>Oral:</u> usually as part of combination therapy
2 mg/kg once a day for 1 week, then 4 mg/kg once a day for 1 week
– round doses <u>up</u> to the nearest 0.5 mg to assist administration

If mother has already received >3 days of nevirapine:

4 mg/kg once a day – (round doses <u>up</u> to the nearest 0.5 mg)</td><td>Rash and liver dysfunction – rare in neonates
Stop NVP after 2/52, in view of long half-life, continue other PEP agents for full 4/52</td></tr>
</table>