Sydney Children's Hospital, Randwick

Human Immunodeficiency Virus in Pregnancy: Prevention of Mother-to-child-transmission (MTCT)

A Guide to Management of HIV infection in Pregnancy and Prevention of mother-child-transmission

Policy Statement

Women with Human Immunodeficiency Virus (HIV) infection will receive a multi-disciplinary, patient-centred and individualised approach to treatment and care that supports the best possible outcome for both the mother and baby.

CONTENT

For regularly updated, information, access the USA HIV Treatment Information Service, perinatal guidelines at http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf or the British HIV Association website at www.bhiva.org

Royal Hospital for Women: Link to the RHW MTCT policy

http://www.seslhd.health.nsw.gov.au/rhw/manuals/documents/Antenatal_Pregnancy%20Care/HIV%20in%20pregnancybirthandpostpartumperiod.pdf

This policy was edited and modified by the NSW Statewide Paediatric HIV Service based at Sydney Children's Hospital in conjunction with services providing care to HIV positive women across the SESIAHS in 2014. It has been developed in conjunction with the Royal Hospital for Women (RHW), Randwick, Prince of Wales Hospital (POWH) and the Albion Street Clinic (ASC), Surry Hills.

NSW PAEDIATRIC HIV SERVICE

I. BACKGROUND INFORMATION

The Statewide Paediatric HIV Service based at Sydney Children's Hospital, Randwick provides care, counselling and support to HIV infected, pregnant women and their families to assist with the prevention of mother-to-child - transmission (MTCT) of HIV. The Service also provides a consultative service for clinicians caring for pregnant women who are HIV positive across NSW, and to physicians involved in the care of HIV infected children and their families. Please see the list below for contacts for the Paediatric HIV Service.

II. SERVICE DETAILS

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Dr Jeff Post	Infectious Diseases Physician, Prince of Wales Hospital Randwick. Tel: (02) 9382 3405 or Switchboard (02) 9382 2222
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III. CONTACTS

Business hours:

The best contacts during the week are:

Clinical Nurse Consultant (CNC) Geraldine Dunne	Phone: (02) 9382 1654 or (02) 9382 1111 – pager 44445 Mobile: 0413 085 469
Social worker on	(02) 9382 1851 or (02) 3982 1111 (switch board)

After hours or on weekends:

Infectious Diseases Service on call	Either the ID Consultant or the ID Fellow on Call. Tel: 9382 1111 and ask to be put through to the ID staff on call

CARING FOR POSITIVE WOMEN DURING PREGNANCY

Women who are HIV positive and pregnant require an integrated multidisciplinary approach to care. This includes HIV physicians, obstetricians, midwives and paediatric HIV specialists.

The Paediatric HIV Team at Sydney Children's Hospital is a multi-disciplinary team of medical staff, a Clinical Nurse Consultant, Medical Social Workers and a dietician. It is recommended that the Paediatric HIV team be consulted as early as possible in pregnancy in order to be involved in perinatal counselling for the woman. The objectives of early involvement by the paediatric HIV team are:

- To establish an early rapport with the parents
- To offer advice on the current strategies to minimise the risk of mother-to-child transmission (MTCT) To prepare the family for when the baby is born and what to expect in terms of medications and testing
- To prepare the family for the testing process involved in establishing a diagnosis in the baby
- To provide education and support to staff involved in the care of the woman

The team can also assist the health care professionals involved in the management of mother and baby in preparing a "Care Plan", after consultation with the woman. The Care Plan provides a guide to the MTCT strategies discussed antenatally including maternal pMTCT (prevention MTCT) measures, and newborn use of prophylactic anti-retroviral(s) after birth, follow up testing and clinical review of the infant (See Appendix 1). The "Care Plan" is sent to the referring physician, the obstetrician, delivery suite and a copy sent to the pregnant woman (and others e.g. GP, with consultation with the woman in recognition of maternal and family privacy).

It is also essential that the needs of the mother be met with vigilance. Optimal obstetric care will be provided at all times. The privacy of the woman and family must be respected and care and attention to her needs should also be observed.

CONFIDENTIALITY & PRIVACY

Health care providers **must not** assume that partners, parents, relatives, friends or even other health care workers are aware of the woman's HIV status. Neither can they assume that the woman is prepared for any or all of these contacts to know. Health care professionals need to be guided by the woman's wishes in this regard and should clarify such issues beforehand with the woman.

Confidentiality of all information regarding the mother and the infant should be maintained at all times. No correspondence regarding the diagnosis should be forwarded without the mother's consent.

I. HIV TESTING IN PREGNANCY

HIV may be transmitted from mother to baby during pregnancy, labour, or via breastfeeding. This type of transmission is called perinatal HIV transmission, vertical transmission (VT) or mother-to-child transmission (MTCT) of HIV. The most important information to enable the implementation of MTCT prevention strategies is to know the woman's HIV diagnosis prior to, or early in the pregnancy. Effective prevention MTCT (pMTCT) strategies significantly minimises the risk of MTCT of HIV. In developed countries such as Australia, the risk of MTCT is now as low as 1-2% when effective MTCT strategies are in place.[1-2]

- The National HIV testing Policy (2011) states that antenatal HIV testing should be recommended to all women at their first antenatal visit.[3] However, it should not be assumed that any pregnant woman has been tested for HIV unless you have specific information to that effect.
- HIV testing can only be performed with the informed consent of the woman. Routine HIV testing without consent is not appropriate or acceptable practice.[3]
- All women contemplating pregnancy or seeking antenatal care should be made aware of the benefits of diagnosis of HIV Infection and management, and prevention strategies available for both the mother and the infant.
- Women with limited literacy, or for whom English is a second language, require appropriate educational resources. Material using other media (video, audio, multimedia) and in languages other than English may be necessary.
- Women with a first language other than English should be offered access to accredited interpreting services.

II. MTCT HIV RISK FACTORS

Factors associated with a higher risk of MTCT of HIV include:[4-6]

- High maternal viral load
- Low maternal CD4 count
- Lack of HAART in pMTCT[5]
- Breast feeding[7]
- Mixed feeding (breast feeding + solids)[8]
- Prolonged rupture of membranes> 4 hours[9]
- Some obstetric interventions such as fetal blood sampling or fetal scalp clips
- Mode of delivery (vaginal versus caesarean section) [6, 10]

A high maternal viral load or low CD4 count (both of which indicate either advanced HIV infection or high HIV viral activity) are most significantly associated with transmission of HIV.

III. STRATEGIES TO REDUCE MTCT HIV

Extensive and significant advances in the area of prevention of MTCT have been made. The most significant advance has been the use of 'highly active antiretroviral therapy' (HAART) during pregnancy, intrapartum zidovudine (AZT) during labour and post exposure prophylaxis to the newborn[5]. Effective HAART (where viral loads become undetectable) in pregnant women, combined with strategies that include planned (elective) caesarean section, avoidance of invasive obstetric procedures and formula feeding of infants (in developed countries) has reduced the risk of perinatal HIV transmission to 1-2%.[1-2]

The key intervention strategies for MTCT are listed below, and discussed further in individual sections. It has to be stressed that for interventions to be implemented, maternal HIV status needs to be first determined, underscoring the importance of antenatal testing if the woman's HIV status is not already known.

- Maternal viral load suppression by effective antiretroviral (ARV) therapy antenatally (HAART)
- Mode of delivery: elective caesarean section versus vaginal delivery
- Minimising use of Obstetric/Perinatal interventions (e.g. scalp electrodes, scalp blood sampling)

- Post exposure prophylaxis (PEP) to the infant – antiretroviral regimen
- Mode of feeding: Avoidance of breast feeding and only formula feeding
- Other measures suggested but not established include vaginal douching prior to delivery, gentle oral suction immediately after delivery

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A. ANTIRETROVIRAL (ARV) THERAPY DURING PREGNANCY AND FOR THE INFANT.

The first study on the use of ARVs was the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (ACTG) 076 study which demonstrated a significant decrease in perinatal HIV transmission (~ 70% reduction from 25% to 8%) when pregnant women and their babies received a 3 part zidovudine (AZT) regimen i.e. AZT during pregnancy (after the 14th week of gestation), intrapartum intravenous AZT and then 6 weeks of AZT to the infant.[11] The rate is now as low as 1-2% if elective caesarean section, or vaginal delivery if undetectable viral load, is undertaken together with an antiretroviral regimens containing AZT. Rates as low as 0.1% are achieved with HAART regimens where viral suppression to undetectable levels are achieved in non-breast fed babies.[2]

Prophylactic ARV regimens are now widely accepted and are used in Australia with success. However AZT monotherapy for mothers is no longer the standard of care and most mothers will receive HAART. Discussion on HAART regimens and the risks and benefits should be included in the counselling of all HIV positive women contemplating pregnancy or who are pregnant. Decisions regarding the use of HAART should be made in conjunction with the woman (and her partner if present).

General principles

- Combination antiretroviral (ARV) regimens (HAART) are more effective than single-drug regimens in reducing MTCT
- Longer durations of ARV are more effective than shorter duration
- If a woman does not need ARVs for her HIV health, HAART should be commenced after the first trimester and not later than 28 weeks of gestation
- If not already on ARVs, the preference is for avoidance of d4T and efavirenz as part of the starting regimen
- Nevirapine must not be commenced as part of ARV therapy in women with CD4 counts > 250 c/ml (increased risk of hepatotoxity)
- ARV drug resistance studies should be performed before starting ARV combinations or modifying ARV regimens in women where RNA levels are detectable and above the threshold for resistance testing (criteria is dependent on laboratory performing the testing but is generally > 500 copies/ml)

Most women who are receiving ARV's will be on a combination of therapy, which may or may not include AZT. In some instances the infant may need to receive additional ARV's in combination with AZT particularly if the mother has a detectable viral load close to or at delivery time. This decision should be discussed in detail with the woman during the pregnancy and will be reviewed at the time of delivery, as this will be influenced by the most recent maternal viral load available at time of delivery. A "Care Plan" incorporating infant ARV recommendations will be drawn up by the paediatric team and forwarded to the referring obstetrician and the physician involved in the management of the mother with the mother's consent.

The **pharmacy** should be notified in advance and alerted that AZT +/- additional antiretrovirals will be needed for the baby. A "starter pack" of the recommended ARVs should be kept in Delivery Suite before the expected delivery date. If care is shared with a regional centre, a starter pack should also be available 6 weeks before expected date of delivery (EDD) in the event of premature delivery at the regional centre.

Additional Note - There is no data to suggest that a mother on triple combination therapy should cease current therapy pre-pregnancy of in the first trimester to avoid fetal abnormalities. It may be prudent to delay starting new drugs until the second trimester (but preferably no later than the beginning of the third trimester), unless the

delay is likely to disadvantage the mother. The risk of fetal malformations are not believed to be significantly higher than "baseline" fetal anomaly risks. The Antiretroviral Pregnancy Registry maintains a registry of pregnancy exposures to ARVs http://www.apregistry.com/. MotherSafe provides a comprehensive counselling service for women and their healthcare providers concerned about exposures during pregnancy and breastfeeding. Further information can be obtained from MotherSafe. (http://www.mothersafe.org.au)

B. ELECTIVE CAESAREAN SECTION VERSUS VAGINAL DELIVERY

Elective caesarean section (ie. performed before the onset of labour) reduces the risk of MTCT.[12] The mode of delivery is dependent on the estimated risk of perinatal transmission, which will include maternal viral load and the health status of the mother. The additional advantage of caesarean section in women already on HAART and with effective viral control e.g. viral load <1000 copies/ ml or even "undetectable" viral load is yet to be determined. Note there is no "safe cut off viral load" viz. there is no demarcated viral load below which transmission does not occur.[9]

General principles

- Delivery plans should be made in advance, prior to the pregnant woman going into labour. The mode of delivery should be discussed and planned by the obstetric team

The additional benefit of caesarean section to reduce MTCT is uncertain if there is effective viral suppression. If the woman has an undetectable viral load due to effective HAART, the discussion should include the risks vs benefits of caesarean section and the uncertain extra benefit conferred by this mode of delivery.[2, 13] NOTE: the definition of **"undetectable viral load"** varies according to literature sources, era of HIV or origins of HIV guidelines. For our purposes, this is defined as **"< 50 copies/ml"** [as per BHIVA 2012 and current literature].

- **Undetectable maternal viral load:** Women with optimal viral suppression [BHIVA, 2012]
  - If maternal viral load (VL) is **'undetectable'** (by 36 weeks of gestation: vaginal delivery is an option
  - Women with **undetectable** viral load (< 50 copies/ml) by 36 weeks of gestation with a previous caesarean section may also opt for a 'trial of labour' [vaginal birth after caesarean section (VBAC)] after discussion with her obstetric team, if there are no obstetric contraindications

- **Detectable viral load**: Women with detectable viral load [BHIVA 2012]
  - If VL is **50 – 399 copies/ml**: caesarean section should be considered
  - If VL is ≥ **400 copies/ml**: caesarean section is recommended

- Planned delivery by elective LSCS (PCS) should be undertaken at 38 - 39 weeks gestation depending on the viral load and obstetric indications
- If planned caesarean section (PCS) has been elected, the woman should be asked to present ASAP for assessment to confirm labour onset.
- If labour is confirmed, intrapartum IV zidovudine (AZT, **if in the plan – see next section**) should commence during the preparations for a semi-urgent LSCS. PLSCS should not be delayed to complete the intravenous induction course of AZT. (IV AZT regimen: see section on "Intrapartum zidovudine", table on "Intrapartum zidovuine regimen")
- **Premature rupture of membranes**: If there is premature rupture of membrane with or without labour, an assessment will have to be made as to the risk of HIV transmission compared to the risk of premature delivery.
- If steroids for lung maturity are needed: there are no known contraindications to the use of short-term steroids to promote fetal lung maturity in women with HIV.

C. INTRAPARTUM ZIDOVUDINE (AZT)

There is no universal consensus as to whether the "intrapartum" AZT is now needed in women who have been on effective HAART and who have achieved effective viral suppression i.e. "undetectable" viral load

- **Undetectable maternal viral load:** (Low risk MTCT): We are currently recommending that intrapartum AZT can be omitted in cases with "low risk" for MTCT i.e. the woman has been on HAART for > 4 weeks and has achieved "undetectable" viral load (< 50 copies/ml)

- **Detectable viral load:** Women with detectable viral load
  - If VL is **50 – 399 copies/ml**: intrapartum zidvudine (AZT) is to be considered
  - If VL is **> 400 copies/ml:** intrapartum zidovudine (AZT) is recommended [USA guidelines]

INTRAPARTUM ZIDOVUDINE (AZT) REGIMEN Recommended only if maternal viral load is detectable (> 400 copies/ ml) and considered if b/w 50 to 399 copies per ml	
ELECTIVE LSCS	Commence IV infusion of zidovudine (AZT) 3 hours prior to elective caesarean Section **Loading dose:** Zidovudine (AZT) 2 mg/kg IV over 1 hour (dilution = 2 mg/ ml) diluted in normal saline (**refer to Appendix 2**) **Maintenance dose:** Continuous infusion AZT 1 mg/kg/hr until delivery. NOTE: If the maternal HAART regimen contains D4T, then intrapartum AZT is contraindicated and should not be commenced.
WITH ONSET OF LABOUR This is applicable in the following scenarios: The chosen mode of delivery is for a vaginal delivery or The chosen mode of delivery is elective caesarean section but spontaneous labour occurs before the date of elective LSCS. AZT should commence in the time interval during the preparation for the semi-urgent caesarean section *(LSCS should not be delayed to complete the IV induction course of AZT)*	**Loading dose:** AZT 2 mg/kg IV over 1 hour (dilution – 2 mg/ ml) **Maintenance dose:** AZT 1 mg/kg/hr continuous infusion until delivery. NOTE: If the maternal HAART regimen contains D4T, then intrapartum AZT is contraindicated and should not be commenced.

D. OBSTETRIC/PERINATAL INTERVENTIONS

Obstetric/perinatal interventions also influence the risk of HIV transmission from mother to child. For this reason, specific recommendations are made in relation to this to minimise those risks. These are listed below:

- Avoid early artificial rupture of membranes (ARM). Studies (pre-HAARTT have shown that there is an increased vertical transmission rate in those women with rupture of membranes for more than 4 hours[9] It is not known if the risk is associated with the conditions causing premature membrane rupture or the

actual duration of membrane rupture. This causation is therefore a conservative interpretation of the available data.

- If artificial rupture of membrane (ARM) is undertaken, careful use of the amnihook is necessary so that scalp integrity is maintained.
- Assess fetal well being using non-invasive methods - avoid the use of fetal scalp electrodes and fetal blood sampling. An open wound may allow direct entry of HIV from mother to infant.
- The use of forceps or ventouse extraction may cause a loss of skin integrity increasing the risk of transmission. However this does not preclude their use as required.
- On delivery of the head, gently wipe the baby's eyes free of secretions.
- Suction is not generally required, but if it is, be gentle to avoid damage to mucous membranes.
- Clamp the cord as soon as possible, milking between the clamps in a direction away from the baby. Place a sponge over the cord before cutting to prevent spurting of blood and in accordance with the NSW Department of Health policy.
- Once born, towel-dry the baby. Wash the baby as soon as possible, following the hospital policy.
- Prior to any procedures on the neonate that will disrupt skin or mucous membrane integrity, ensure the area is thoroughly cleaned.
- Follow the hospital's policy for cleaning up blood/body fluid spillage
- There are no contraindications to intramuscular (IM) vitamin K (*Kanakion*) or the routine newborn hepatitis B immunisation being administered following delivery. Skin cleansing is recommended prior to IM injections
- Blunt needles have been shown to reduce the risk of care giver needle stick injuries. These should be considered when caesarean section or perineal repair is undertaken[14]

Pre-term labour rupture of membranes

- Recommend immediate delivery when preterm labour rupture of membranes occurs between 34 to 37 weeks gestation with either caesarean section or vaginal delivery. Consideration should be given to starting broad-spectrum intravenous antibiotics

Pre-labour rupture of the membranes (term)

- Expedite delivery in all cases of term pre-labour spontaneous rupture of the membranes
    - If maternal HIV viral load is <50 HIV RNA copies/mL immediate induction of labour is recommended, with a low threshold for treatment of intrapartum pyrexia
    - Consider immediate caesarean section for women with a last measured plasma viral load of 50–999 HIV RNA copies/mL, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's wishes
    - Recommend immediate caesarean section if maternal HIV viral load is ≥1000 RNA copies/mL plasma

E. MODE OF FEEDING AND THE ROLE OF BREAST MILK IN HIV TRANSMISSION

Breastfeeding by mothers with HIV infection is associated with an increase in the rate of transmission of HIV from mother to infant. The benefits of breastfeeding are recognised. However, the mother should be advised of the risks of HIV transmission from breastfeeding, such that the decision is informed. The only way to reduce this risk completely is to **avoid exposing the infant to breast milk**. (note: in resource limted settings, the World health Organisation (WHO) recommendations are 'when replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected women is recommended'. [WHO 2010 http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf]

Whist recent studies from resource limited settings (where breast feeding is important for infant survival) demonstrate a reduction in MTCT if mothers are on ART for 6 months and exclusively breast feed in that time +/- infant prophylaxis of varying duration (never > 6 weeks), the risks of transmission are still present and range from

2 – 5%.[15-17] Thus, breast feeding whilst on HAART cannot be recommended as a **safe** option in a setting like Australia where formula feeding is feasible, affordable and sustainable.

Skin-to-skin contact between mother and baby however should still be encouraged. All infant formula available in Australia meets strict Australian standards. It is recommended a standard cow's milk protein based formula is used. This should be discussed with the family prior to delivery.

F. POSTNATAL ARV PROPHYLAXIS FOR THE BABY

General principles of prophylaxis for the baby

- Postnatal ARV should commence within 6 – 12 hours of birth
- **In low risk MTCT:** (< 2%, maternal VL < 50 copies / ml and pMTCT strategies in place)
    - monotherapy with AZT is the ARV regimen of choice
    - the duration of therapy is **4 weeks**
    - **Maternal zidovudine resistance**: Where the mother has had a previously documented zidovudine resistant strain but has an undetectable HIV viral load (< 50 copies/ml), **monotherapy** with AZT for the baby remains the regimen of choice. Available data suggests very low risk of transmission and preferential transmission of wild-type over zidovudine-resistant virus when a mixed population of virions are present[18]

- **Where MTCT risks are deemed to be higher** (>2 %, maternal VL > 50 c/ml, inadequate pMTCT strategies**):** neonatal PEP regimens should be discussed and decided by the paediatric HIV team
    a. In general, if maternal viral load is detectable, additional ARVs to AZT is recommended for the baby
    b. The ARV regimen of choice should be discussed and decision made by the paediatric team. There are 2 regimens proffered.

        Approach 1 is the BHIVA 2012 preference. **This is our preferred regimen.**

        Approach 2 is the USA approach[19] . Approach 2 is less complex, is associated with less neutropenic events. However, nevirapine resistance is a potential concern. In this study, equivalence of pMTCT efficacy cp to 3 drug regimen was demonstrated when used with other pMTCT strategies (~ 2%). Nevirapine resistance was not a feature (however, small numbers). We will consider this regimen in some circumstances (e.g. maternal viral load detectable but "low"). Decisomp ,made after discussion with paediatric HIV team.

    c. See Table 1 information on drug doses/concentrations of drug

APPROACH 1: Three drug regimen: zidovudine + lamivudine + nevirapine
This is our preferred regimen

Zidovudine = 4 mg/kg/dose, BD (term baby) – for 4 weeks
Lamivudine = 2 mg/kg/dose, BD (term baby) – for 4 weeks

Nevirapine dosing

If mother had not had NVP or had received NVP < 3 days

i. 2 mg/kg/dose, daily for 1st week
ii. Then 4 mg/kg/dose, daily for 2nd week, then **stop**

If mother had received NVP ≥ 3 days

iii. 4 mg/kg/dose, daily for 2 weeks, then **stop**

APPROACH 2: Two drug regimen: zidovudine (4 weeks) + nevirapine as a 3 dose regimen[14]

This regimen will only be adopted in some circumstances and only after discussion

Zidovudine = 4 mg/kg/dose, BD (term baby) - for 4 weeks

Nevirapine

Dosing (by birth weight):

i. if birth weight 1.5 - 2 kg: nevirapine, 8 mg orally, each dose (total 3 doses)
ii. if birth weight > 2 kg: 12 mg orally, each dose (total 3 doses)

Dosing frequency

i. 1st dose: within 48 hours of birth
ii. 2nd dose 48 after the first dose
iii. 3rd dose, 48 hour after the 2nd dose

d. Note: Lopinavir/ritonavir (Kaletra) is **contraindicated** in term newborns ≤ 14 days old or in premature babies till ≥ 14 days past their due date (reports of adrenal dysfunction) and so must not be part of neonatal PEP regimen

G. INSTANCES WHERE MTCT RISKS ARE CONSIDERED HIGH (> 2%):

MATERNAL RECOMMENDATIONS FOR LATE PRESENTER NOT ON HAART (BHIVA 2012)

This section is added for information only. **These are complex decisions,** made in conjunction with the woman's treating HIV physician and obstetric team. Scenarios provided are not exhaustive. Nb: The ARV recommendations below pertain to maternal ARV (not to baby)

a. NOT IN LABOUR > 28 weeks
   - Assessment by the relevant adult services (HIV, Obstetrics team), followed by recommendation for HAART for mother as soon as possible
   - Intrapartum zidovudine (AZT) and caesarean section if viral load detectable at 36 weeks

b. NOT IN LABOUR , VL UNKNOWN OR > 100 000 COPIES/ML
   - Assessment by the relevant adult services (HIV, Obstetrics team) , followed by recommendation for HAART for mother as soon as possible
   - Raltegravir* may be ***included*** in the regimen
   - Intrapartum zidovudine and caesarean section: if viral suppression is not achieved by 36 weeks (if applicable) or by delivery

c. IN LABOUR: Term baby, mother not on ARV
   - Stat dose of nevirapine (200 mg) to the mother* (must be followed by combination ARV as below, and HAART reviewed after the delivery of baby)
   - Start zidovudine/lamivudine (fixed dose tablet, *Combivir*) + Raltegravir*
   - Intrapartum zidovudine for the duration of labour and delivery
   - Mode of delivery: Caesarean section ≥ 4 hours after onset of labour / rupture of membrane may not be of benefit. The decision is best made after discussions (HIV physician, obstetric team ad paediatric team)
   - HAART to be reviewed by HIV physician after delivery

d. IN LABOUR: pre-term baby, mother not on ARV
   - Stat dose of nevirapine (200 mg) to the mother*
   - Use double dose tenofovir* (as baby may not be able to take oral medications in early period post birth)
   - Add raltegravir to regimen*
   - Then start HAART regimen of choice (as per HIV physician recommendation)
   - Intrapartum zidovudine for the duration of labour and delivery

- Timing and mode of delivery: The decisions should be made after a multidisciplinary discussion (HIV physician, obstetric team ad paediatric team)

*ARVs like (nevirapine (NVP), raltegravir or double dose tenofovir) readily cross the placenta and are added in situations such as these to "load" the fetus pre-delivery. NVP crosses placenta rapidly (achieves adequate neonatal concentrations within 2 hours)

IV. ADDITIONAL INFORMATION ON RISK TO INFANT AND MOTHER

There is no increase in risk of congenital abnormalities in babies born to women with HIV infection. There is some evidence to suggest that combination ARV's that include protease inhibitors may slightly increase the risk of premature birth. However mothers should be encouraged to stay on treatment with close monitoring throughout the pregnancy since evidence suggests that the mother's wellbeing and viraemic control have more significant effects on duration of gestation. The maternal use of protease inhibitors should be taken into account when assessing risk of premature delivery. Exposure to zidovudine *in utero* or in early life is associated with transient anaemia but not with significant adverse events in medium term follow-up of exposed, uninfected babies. [12]

Pregnancy is not believed to accelerate HIV disease progression unless the mother already has advanced HIV disease or AIDS related illness.

CARE AND MANAGEMENT OF THE INFANT

Whilst the diagnosis of HIV infection in adults is readily established by the detection of HIV antibodies, the situation is more complex in babies born to HIV positive women. Maternal HIV antibodies across the placenta such that the foetus passively acquires these antibodies. Thus, these babies will always test "HIV antibody positive" as the test will detect antibodies derived from the mother. Therefore, the HIV antibody test alone cannot be relied on in these babies as the presence of HIV antibodies reflects maternal HIV antibodies. It can take up to 12 -18 months for a baby to clear these maternal antibodies.

For this reason, the "PCR" (polymerase chain reaction), a sensitive nucleic based assay, is used for testing for the presence of HIV in babies. Both HIV DNA or RNA PCRs are now acceptable tests. The HIV DNA PCR remains the preferred test by our service. Multiple negative PCRs up to age 6 months are required to confirm an "uninfected" status in exposed infants. Testing 2 weeks (so at 6 weeks) and > 2 months (so at 3 , 4 and 6 months in our service) are required to exclude HIV.

A "final" HIV antibody test at 18 months to document "seroreversion" (clearance of maternal HIV antibodies) is recommended. Additionally this furthers confirms that the baby is not HIV infected. If a PCR is positive, the test is **always repeated** as soon as possible (on a new sample) before we confirm that the baby is infected. Ideally uninfected children should be followed-up long-term in view of the unknown long-term risks after exposure to antiretroviral therapy. Presently, we are only consistently following these "exposed, not infected" children in the first 2 years of life.

Table 2 summarises the testing and clinical follow-up schedule for perinatally exposed children

IV. TESTING REGIMEN FOR INFANTS AT RISK OF MTCT HIV

All babies who have been perinatally exposed to HIV should be followed closely with regular review by the Paediatric HIV Team. The table outlines the testing schedule for these infants.

- **HIV NUCLEIC ACID TESTING (Polymerase chin reaction (PCR):**

- DNA HIV PCR* is the recommended, and the preferred test at SCH. [*note: this is also called "HIV Proviral DNA PCR"]
- RNA PCR is acceptable (particularly outside the neonatal period) if HIV DNA PCR is not available. Both appear to be highly specific and of equivalent sensitivity (~ 60% at birth, 90% at 1 month and 100% at 1 and 6 months, with high concordance. [20] The theoretical concern with HIV RNA PCR Is the unknown effect of maternal or infant exposure to combination ARVs on the sensitivity of HIV RNA testing (may limit sensitivity of the test)
- It is recommended that testing occur at least 2 weeks and 2 months after postnatal ARV prophylaxis is stopped
- Schedule: Week 1, week 6 and 3 months of life
- Note: where MTCT risk is deemed to be greater than 2%, testing ASAP after birth and < 48 hours of age is recommended)

- **HIV Antibody**: Test at 18 months. > 98% of babies would be expected to clear maternal HIV antibodies by 18 months. If seroreversion has not occurred, re-test at 24 months

TESTING SCHEDULE, SCH (where MTCT risk is < 2%)

TIME OF TESTING	**TEST**	
	HIV Nucleic Acid Testing HIV (Proviral) DNA PCR (HIV RNA PCR can be used if HIV DNA PCR not available)	**HIV Antibody**
Week 1*	**YES**	No
Week 6	**YES**	NO
3 months	**YES**	NO
6 months	NO	NO
12 months	NO	NO
18 months	NO	**YES**

V. PNEUMOCYSTIS JIROVECI PNEUMONIA (PJP) PROPHYLAXIS

(previously known as pneumocytis carinii pneumonia (PCP)

PJP propyhlaxis is not indicated if the risk of MTCT is low (< 2 %). If PJP prophylaxis is indicated, it should start after neonatal PEP is completed (at 4 weeks). Sulfamethoxozole /Trimetoprim (Bactrim) is used. PJP prophylaxis is disctontinued once it is deemed that the baby is not infected (via testing).

- Dose of sulfamethoxozole /trimetoprim for prophylaxis in babies < 6 month of age is **100 mg sulfamethoxozole / 20 mg trimetoprim once** daily (= 2.5 ml Bactrim syrup, once daily)
- Bactrim is 200 mg **s**ulfamethoxozole and 40 mg trimetoprim per 5 ml). Thus the daily dose of Bactrim (in babies < 6 months old) is **2.5 ml,** once a day

VI. IMMUNISATIONS

Routine childhood immunisations should be given to all babies according to the Australian immunisations schedule. This can be done either through follow-up visits at this hospital or through the family's local GP. Measles, Mumps, Rubella (MMR) and varicella vaccine is safe for infants exposed to, but not infected with HIV.

The use of these live attenuated viral vaccines is strongly recommended to reduce the likelihood of infecting the immunocompromised person in the household with wild-type measles or varicella.

Varicella vaccine is scheduled for 18 months. Vaccine related rash occurs in < 5% of vaccinees. If rash occurs in vaccinees, transmission to contacts (by direct contact, not air borne transmission) can occur but is of low risk. However, if parents/household contacts are severely immune-compromised, he/she should contact the HIV Service for advice should this occur (see contact list informaiton).

VII. SUPPORTS

This family should be well linked to supports that are available to them. Discharge planning is paramount and should include contact if appropriate to services available to all women such as GP, Child and Family Health Centres and community supports.

The Paediatric HIV Service provides clinical, practical and psychosocial supports to the family including

- Links to financial supports
- Family support group
- Counselling
- National HIV Camp, “Camp Goodtime” (for children with HIV and families)
- Camp for primary school aged infected children and “Teen” Camp for older HIV infected children
- Respite care arrangements

GLOSSARY

ARM	Artificial Rupture of Membranes
ARV	Antiretrovirals
AZT	Zidovudine
GP	General Practitioner
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
NVP	Nevirapine
MMR	Measles Mumps Rubella
MTCT	Mother-to-Child-Transmission (HIV)
pMTCT	Prevention of Mother-to-Child-Transmission
PCR	Polymerase Chain Reaction
3TC	Lamivudine
WHO	World Health Organisation

APPENDIX 1: SAMPLE CARE PLAN

A/Prof Pamela Palasanthiran, MB BS, MD, FRACP
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Provider No: 323004X
PHONE: : + 61 (2) 9382 1508
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Insert date

Dr X
XXX XXX

CARE PLAN: Insert patient name

Re: **Insert patient name** DOB: **xx/xx/xxxx** RHW MRN: **xxx xxx** XXX MRN**:** xxx xxx

Thank you for referring *Patient name* to our clinic for perinatal HIV counseling. She attended our clinic on the *insert date.* It is a pleasure to be involved in her care.

Patient name is currently in the XXX trimester of pregnancy. Her EDD is **xx/xx/xxxx**. Currently she is on *Insert patients antiretrovirals* for MTCT prevention during this pregnancy. She has had recent testing for HIV viral load which is XXXX and CD4+ve lymphocyte counts, which is XXX x 10^9 cells/L (XX%). She has been well from her HIV and is asymptomatic. I understand that you will remain involved for HIV care, and *that Insert obstetrician* will be her obstetrician. The midwife involved in her care is Insert/ delete if not applicable .

The risk of mother-to-child-transmission (MTCT) of HIV, prevention strategies and postnatal management of her baby were discussed. *Patient name* is familiar with these and is happy to adhere with prevention strategies discussed. Her risk of perinatal HIV transmission with all strategies in place (antenatal ARV, *caesarean section (*see next paragraph*), formula feeding and AZT to the infant for 4 weeks) with a good immune / clinical status and "undetectable viral load" is estimated to be in the order of ≤ **1-2%.**

Vaginal delivery is now considered a safe option if the mother's viral load is "undetectable". The risk of MTCT is expected to be extremely low provided all other preventions strategies are in place. Women with **undetectable** viral load (< 50 copies/ml) by 36 weeks of gestation with a previous caesarean section may also opt for a 'trial of labour' [vaginal birth after caesarean section (VBAC)] after discussion with her obstetric team, if there are no obstetric contraindications. Intrapartum zidovudine in only indicted if viral load is > 400 copies/ml. If VL is 50 – 399 copies/ml: intrapartum AZT should be considered. If used, intra-partum should be commenced at the start of labour or ruptured membranes (whichever is earlier) and continued for the duration of labour (stop after delivery).

I am including a "Care Plan" for her baby before, during and after delivery. Please do not hesitate to contact us should you require further information.

CARE PLAN: Patient name

1. **ARV Cover and Mode of delivery**

   The baby is due ***Insert due date.*** *Patient name* informs us that she plans to have a normal vaginal delivery or caesarean section Delivery*[Insert option]*

   In the case of planned vaginal delivery (undetectable viral load): Xxx should be advised to present to delivery suite as soon as possible if there is ruptured membranes (ROM) or as soon as labour / contractions begin. Intrapartum IV AZT is no longer indicated if maternal viral load is undetectable at 36 weeks gestation.

   In case of elective caesarean delivery: IV zidovudine is indicated if the maternal viral load is > 400 copies/ml at 36 weeks gestation, and is to be commenced 3 hours prior to delivery and ceased after delivery. In the meantime maternal ARV will remain unchanged and managed by her own HIV care team. [for viral load 50 – 399 copies/ml, a decision for IV zidovudine will be discussed abd decided prior to delivery]

   Dose of intrapartum IV zidovudine: (if detectable viral load pre-delivery) **2 mg/kg/hr** for the first hour, then **1 mg/kg/hr** till delivery

2. **Baby**

   The baby's eyes should be cleaned at birth. The baby should be washed as soon as it is practical, prior to administering any intramuscular injection e.g. vitamin K

   If maternal viral load is undetectable: The baby should be commenced on oral **zidovudine (AZT) 4mg/kg/dose, twice daily** within 6-12 hours after birth and should be continued for **4 weeks**. The above dose should be rounded up to the closest figure to make dispensing easier. If the baby is 'nil by mouth', the recommended IV **zidovudine** (**AZT)** at 1.5mg/kg 6 every 6 hours. These doses are for term babies. For preterm babies, dose recommendations will be made in consultation with our service

   If delivery is complicated or if maternal viral load is "detectable": If the delivery is complicated or if XXX does not have an "undetectable viral load" at or around the time of delivery, postnatal ARV to the baby will need to be reviewed. Please contact us to assist with this; dose recommendations will be made in consultation with our service. Contact the ID consultant on-call via switchboard (9382 1111).

3. **Mode of feeding**

   The baby will be formula fed.

4. **Postnatal Management of baby**

   XXX will attend clinic here with her baby for infant follow-up. The following is our guide to the follow up of the infant. Please note that if maternal viral load is still detectable at or around the time of delivery, the prophylactic ARV regimen for the baby may be amended. In this situation, please discuss with us for further guidance (contact ID consultant on-call via switchboard).

Postnatal schedule for follow-up of infants at risk of perinatal HIV infection (mother "undetectable viral load")

Time	TEST	CLINICAL CARE
Week 1 (anytime in the week while in hospital)	HIV DNA PCR	• Clinical review • **AZT** syrup (**4 mg/kg per dose, BD**) for **4 weeks** (start within 6 - 12 hours of birth) • Neonatal hepatitis B vaccine as per Australian Immunisation Schedule
Week 6	HIV DNA PCR	• Clinical review • Ensure stop AZT syrup was stopped at **WEEK 4** • Infant vaccines as per Australian Immunisation Schedule (*Infanrix-hexa* + 13vPCV + Rotavirus vaccine (*Rotarix*)
3 months	HIV DNA PCR	• Clinical review • Infant vaccines as per Australian Immunisation Schedule (*Infanrix-hexa* + 13vPCV + Rotavirus vaccine (*Rotarix*)
6 months	No test Clinical review	• Clinical review • Infant vaccines as per Australian Immunisation Schedule (*Infanrix-hexa* + 13vPCV)
12 months	No tests Clinical review	• Clinical review • Infant vaccines as per Australian Immunisation Schedule (MMR, HiB-MenC)
18 months	HIV antibody	• Clinical review • Infant vaccine as per Australian Immunisation Schedule (MMRV)

The family should be given enough anti-retrovirals (AZT syrup in this case) at discharge as they are S100 drugs and not available from local chemists. Follow up appointment for the baby will be arranged by the Paediatric HIV team on discussion with the parents.

If you have any question or require further information please do not hesitate to contact us.

Regards

XXXXXXXXX

Insert cc list

APPENDIX 2: CALCULATION FOR INTRAVENOUS ZIDOVUDINE (AZT) INFUSION FOR MATERNAL INTRA-PARTUM REGIMEN (IF INDICATED)

DOSE OF ZIDOVUDINE (AZT) REQUIRED

Loading dose: first hour **= 2 mg/kg**
Maintenance dose: second and subsequent hours until delivery = **1 mg/kg/hr**

TO CALCULATE APPROPRIATE CONCENTRATION OF ZIDOVUDINE (AZT)

To make up the appropriate concentration of zidovudine (AZT)

- One ampoule zidovudine (AZT) contains **200 mg zidovudine**
- Dilute content of one ampoule in 1000 ml of Normal Saline
    - **200 mg** zidovudine (AZT) in **1000** ml Normal Saline
    - **2 mg** zidovudine (AZT) in 1**0 ml** Normal Saline
    - **1 mg** zidovudine (AZT) in 5 **ml** Normal Saline

CALCULATE RATE OF FIRST HOUR:

Patient's weight _____kg x 10 = _____ml per hour

CALCULATE RATE FOR SECOND AND SUBSEQUENT HOURS UNTIL DELIVERY:

Patient's weight_____kg x 5 =_____ml per hour

Divide the above formula by 60 to give rate of infusion in ml per minute.

Examples

i. For a 60 kg patient

1) Rate for first hour = 60 kg x 10 = 600 ml per hour

2) Divide the above by 60 = **10 ml per minute**

3) **Half** the above rate for the second and subsequent hours until delivery (= **5 ml per minute**)

ii. For 84 kg patient

1) Rate for first hour = 84 kg x 10 = 840 ml per hour

2) Divide the above by 60 = **14 ml per minute**

3) **Half** the above rate for the second and subsequent hour until delivery (= **7 ml per minute**)

TABLE 1: ARV DOSING RECOMMENDATIONS (POSTNATAL PROPHYLAXIS)[17,18]

Drug Name	Dosages		Duration
Zidovudine (AZT) Syrup concentration: 10 mg/ml	**ORAL** <u>TERM INFANT</u> • 4mg/kg per dose, BD • Give 12 hourly <u>PREMATURE INFANT</u> **30 – 34 weeks** • 2 mg/kg, 12 hourly for 2 weeks • Then 2 mg/kg, 8 hourly for 2 we**eks** **< 30 weeks** • 2 mg/kg, 12 hourly (for 4 weeks)	**IV (IF NEEDED)** (concentration: 10 mg/ml) <u>TERM INFANT</u> • 3.0 mg/kg per dose * • Give 12 hourly <u>PREMATURE INFANT</u> • 1.5 mg/kg per dose • Give 12 hourly	Zidovudine (AZT) should be given for total of **4 weeks** Cease IV once infant is established on oral feeding and commence oral
Lamivudine (3TC) Oral solution concentration: 10 mg/ml	• 2mg/kg per dose, BD		**4 weeks**
Nevirapine (NVP) Oral suspension concentration: 10 mg/ml	**<u>No maternal nevirapine in the peripartum period</u>** • 2 mg/kg/dose, once daily for <u>first week</u> • 4 mg/kg/dose, once daily for <u>second week</u> • **Stop after week 2** (nb: "tail" of AZT +3TC needs to continue after for 2 weeks) **<u>If mother has had > 3 days of nevirapine (antenatal):</u>** • 4 mg/kg/dose, once daily for <u>2 weeks</u> (nb: "tail" of AZT +3TC needs to continue after for 2 weeks) Nevirapine has a long half life. This regimen allows for a 2 week "tail" cover with the other 2 ARVs (AZT + 3TC)		**2 weeks**

NOTE: The dosing for zidovudine differs in the BHIVA and USA guidelines. We have used the BHIVA recommendations with the exception of * (IV dosing) which is from the USA Perinatal Guidelines

NOTE:Lopinavir/ritonavir *(Kaletra)* is contraindicated in term newborns ≤ 14 days old or in premature babies till ≥ 14 days past their due date (reports of adrenal dysfunction)

TABLE 2: TESTING AND CLINICAL FOLLOW UP OF THE INFANT

Note: testing schedules where MTCT risk low < 2% (ie: mother had "undetectable" viral load at 36 weeks and pMTCT in place))

Time	TEST*	CLINICAL CARE
Week 1 (anytime in the week while in hospital)	HIV DNA PCR	• Clinical review • **Zidovudine (AZT**) syrup (**4 mg/kg per dose, BD**) for **4 weeks** (start within 6 - 12 hours of birth) • Neonatal hepatitis B vaccine as per Australian Immunisation Schedule
Week 6	HIV DNA PCR	• Clinical review • Ensure zidovudine (AZT) syrup was stopped at **WEEK 4** • Infant vaccines as per Australian Immunisation Schedule (*Infanrix-hexa* + 13vPCV + Rotavirus vaccine (*Rotarix*)
3 months	HIV DNA PCR	• Clinical review • Infant vaccines as per Australian Immunisation Schedule (*Infanrix-hexa* + 13vPCV + Rotavirus vaccine (*Rotarix*)
6 months	No tests Clinical review	• Clinical review • Infant vaccines as per Australian Immunisation Schedule (*Infanrix-hexa* + 13vPCV)
12 months	No tests Clinical review	• Clinical review • Infant vaccines as per Australian Immunisation Schedule (MMR, HiB-MenC)
18 months	HIV antibody	• Clinical review • Infant vaccine as per Australian Immunisation Schedule (MMRV)

*Note: HIV DNA PCR is the recommended test. However, HIV RNA PCR is acceptable if HIV DNA PCR is not available. It is recommended that testing occur at least 2 weeks and 2 months after postnatal ARV prophylaxis is stopped

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