Preventing Mother To Child Transmission (PMTCT) of HIV Infection

NOTE: Correction of error made to Appendix 2, page 36 in Feb 2012.

A practical guide to the management of the HIV positive pregnant woman and her infant

Also incorporating management of HBV, HCV and syphilis exposed infants

This document serves as a guideline for management.
Ultimately each pregnancy calls for an individualised care plan.

To replace all previous editions

Date: Feb 2012
Review date: June 2013

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Table of Contents

Appendices

Acknowledgements:
The staff of the Rainbow Clinic would like to thank everyone who contributed to the development and review of this document, in particular Dr Fiona Lyons SJH and colleagues in the adult HIV and obstetric services.

National guidelines are available and are currently under review. They can be viewed on the website www.ssstdi.ie/guidelines

Snapshot of Changes to PMTCT HIV Guidelines 2011

Antenatal

Late Bookers (ie. after fetal viability): please request URGENT HIV testing and organise a quick turn around with the relevant testing facility. Results should be available within 2 working days.

Women refusing AN testing: Strong recommendation to test the baby ASAP after birth. Results should be available within 48 hours of birth to facilitate urgent commencement of neonatal post exposure prophylaxis if needed.

Starting (anti-retroviral) ARV treatment in pregnancy
There has been a move towards earlier initiation of ARV to approximately 20/40 gestation to maximise the reduction of mother-to-child transmission (MTCT) risk

Changing ARV treatment
In general, for women stable on ARV, conception is not an indication to change treatment choice.

Intra-Partum

Intra-partum zidovudine is no longer considered necessary for women who are stably suppressed on ARVs and for whom no additional risk factors for HIV transmission have been identified, i.e. where the following apply:

- Maternal ARV for > 4 weeks with an HIV viral load at 36 weeks of <40 copies/ml AND
- No concerns about maternal adherence to antiretroviral therapy
- No spontaneous pre-labour or preterm (≤37 weeks) rupture of membranes
- No premature labour

Intra-partum ZDV is indicated for:

- All women on ZDV monotherapy
- All women with a 36 week viral load of >40 copies/ml and/or <4 weeks ARVs
- Any women who is non-adherent to treatment
- Late presenters
- Women with planned C/Section where primary indication for C/sectionis prevention of HIV transmission

Mode of Delivery

Vaginal delivery is recommended for women with a 36 week HIV viral load of <400copies/ml., however, this decision will also be influenced by:

- Duration of ARVs
- Adherence to ARVs
- Viral load trends
- Obstetric and fetal considerations

Elective C/section is recommended for women with an HIV viral load of >400 copies/ml at 36 weeks gestation and all women in receipt of zidovudine monotherapy.

Background

In 1994, the administration of zidovudine to pregnant women was shown to reduce mother to child transmission (MTCT) of HIV infection by 67%.[1] Since then strategies have evolved to reduce transmission rates to ~1%. Current approaches include diagnosis of HIV infection in pregnancy through antenatal screening, antenatal antiretroviral therapy (ARV), selective use of c/section, neonatal ARV; and in the Irish setting, avoidance of breastfeeding. Success in achieving low transmission rates requires the formation of a partnership between HIV infected women and their health care providers. Ideally, antenatal care of these women includes input from obstetric, adult, paediatric services and primary care givers.

General Considerations

Confidentiality

Receiving a diagnosis of HIV in pregnancy is traumatic and extremely difficult. It takes time to adjust to the diagnosis. Patient confidentiality must be respected at all times, however, the implications for partners and children must also be addressed. Disclosure to, and testing of those at risk must be considered. The health care worker (HCW) plays an important role in supporting the woman through this time. Guidance can be sought from any of the HIV specialist services.

Health care providers cannot assume that partners, parents, relatives, friends or even other health care workers are informed of the woman's HIV status. All discussions of her condition, management, test results and care of the infant must be undertaken in confidence[2]. There are situations where an HIV positive woman refuses to disclose to her sexual partner. This can potentially give rise to legal, ethical and moral issues and is best tackled by the multidisciplinary team. Breaking confidence should be a last resort[3]. In general it is usually possible to achieve disclosure through supportive counselling. The Irish Medical Council has issued guidance for doctors in this regard[4].

Infection Control

Standard precautions should be used for everyone[5]. There is no need for elaborate infection control measures or single rooms where the woman, or child, has either been exposed to, or has HIV, Hepatitis B or C infection. In the event of occupational exposure, please contact your Occupational Health Department or the nearest infectious diseases physician promptly for advice. For any issues relating to infection control please speak to your infection control team.

Care of the pregnant woman

Antenatal care

The HIV test

Any woman who is pregnant deserves to be offered an HIV test. An 'opt-out' approach to antenatal screening, whereby all women are offered routine testing but can elect to decline the offer, has been adopted in Ireland. The success of this over other strategies is now proven[6,7].

Women booking for antenatal care after fetal viability (late bookers) should have an urgent HIV test. Make direct contact with the laboratory where the test is performed. Explain the urgency of the situation and arrange for delivery of test result to the physician in charge of the patient within 2 working days. In the event of a positive test make urgent referral to adult HIV services **without** waiting for the results of a second HIV test.

Response to the test

Ensure that there is a failsafe mechanism in place to obtain HIV test results in a timely manner and to communicate those results to the patient and their relevant care providers

Women identified with or known to be HIV positive and pregnant

- Inform the woman of her diagnosis
- Prompt referral to Adult HIV Service
- Referral to Paediatric HIV Service

Women identified as HIV positive and pregnant who refuse to attend an adult HIV clinic

- Discuss with adult HIV care providers
- Clinical evaluation
- Investigations as per recommendations of adult HIV service
- Discuss with the Paediatric HIV Service

Women who decline testing

- Women who refuse testing when first offered, should be counselled and testing re-offered. Women should be encouraged to avail of testing at each antenatal visit.
- Testing women without consent where the woman has explicitly refused is **not** advocated
- Women who have refused testing throughout pregnancy may consent to testing the infant in the neonatal period. This is strongly recommended.

Women who present in labour

Women presenting unbooked in labour should have an urgent HIV test. Seek a rapid turn around of the HIV antibody test by making direct contact with the laboratory where the test is performed. Explain the urgency of the situation and arrange for delivery of test result to the physician in charge of the patient.

Women without an antenatal HIV test

It is strongly recommended that infants of women without an antenatal test in pregnancy be tested as soon as possible such that results can be available within 48 hours to enable use of neonatal post exposure prophylaxis.

HIV negative women who are pregnant and at continued risk

HIV seroconversion in pregnancy is emerging as a significant source of paediatric HIV infection. A single negative HIV test in pregnancy test does not always exclude HIV infection. Cost effectiveness of a 2nd routine test is under evaluation in Ireland.

- Women with recent risk exposures or who continue to be at risk of exposure during pregnancy (e.g. active injecting drug use; known HIV infected partner; partner from high prevalence country or partner with identified risks for HIV infection and unknown status) should have tests repeated later in pregnancy.
- Women with repeatedly negative tests in pregnancy, with on-going exposure risk should be offered repeat testing postnatally.

Risk factors for Vertical Transmission of HIV

HIV can be transmitted from an HIV infected woman to her infant during pregnancy, during labour and delivery, or through breastfeeding. Available data suggest that up to 25% to 30% of perinatal HIV transmission may occur in utero, and up to 70%-75% intrapartum. The overall risk of transmission in untreated women varies from 20-40% compared with <1-8% in treated women.

The use of antiretroviral treatment, antenatally and for the infant, is the single most effective way to reduce transmission risk. In selected cases elective c/section delivery is beneficial. Breastfeeding is also associated with a significant increased risk of transmission and should be avoided. In Ireland, HIV infected women are advised to bottle feed their infants with formula milk.

Factors that increase risk

- High maternal viral burden (e.g. seroconversion during pregnancy or advanced disease)
- Low maternal CD4 count
- Maternal co-infections (e.g. sexually transmitted infections)
- Prolonged rupture of membranes
- Use of invasive devices during labour (e.g. fetal scalp electrodes)
- Breastfeeding
- Prematurity

Factors that may decrease risk

- Identification of HIV +ve women antenatally
- ARV in pregnancy
- In some instances, elective caesarean section
- Avoidance of invasive monitoring of infant during labour
- Bottle-feeding with formula milk
- Anteretroviral therapy to the infant for 4 weeks

For Women Co-Infected with HIV and Hepatitis C

The exact mechanism(s) and timing of MTCT of hepatitis C are not known. Reports of hepatitis C RNA in umbilical cord blood and within the first six days of life suggest that in-utero transmission occurs and the appearance of hepatitis C RNA between birth and three months of age suggests that intrapartum/peripartum transmission can also occur.

Reported maternal risk factors include active Hepatitis C infection; HIV co-infection; higher hepatitis C viral loads, elevated maternal serum transaminases[8,9]. There are inconsistent data around the potential risk associated with vaginal delivery and potential benefit associated with delivery by elective c/section in both mono and HIV co-infected women[10]. The use of antenatal maternal antiretroviral therapy in HIV/Hepatitis C co-infected women may reduce the risk of hepatitis C transmission[11]. Whilst there is an absence of clear data, in Ireland HIV/Hepatitis C co-infected women with on-going hepatitis C viral replication are generally offered triple antiretroviral therapy and an ELCS to reduce the risk of hepatitis C transmission.

The evidence is not yet strong enough to routinely recommend ELCS or exclusive formula feeding for hepatitis C mono-infected women.

Mother to Child Transmission of Hepatitis B Virus (HBV)

Maternal infection with HBV is associated with a high incidence of transmission to their infants. Transmission can be effectively prevented by immunisation of the infant shortly after birth (Appendix 7). Antenatal treatment of women co-infected with Hepatitis B and HIV will likely include antiretroviral agents that are active against both HBV and HIV. This decision will be made by the adult HIV physician.

Antiretroviral therapy for HIV positive pregnant women

A decision to use potent antiretroviral agents in pregnancy must be balanced against the potential for toxicity to the mother and the developing fetus. In the non-pregnant population the need for ARV is determined by the status of the immune system which is reflected by the CD4 count, normally 400 -1400 x 10^6/L. Current international guidelines recommend ARV for most persons with a CD4 count of ≤ 350 - 500 x 10^6/L depending on individual circumstances[12].

Generally:

- For women with a CD4 count <350 x 10^6/L at presentation, ARV for maternal health is warranted and should be initiated as soon as possible and treatment should be continued post partum. Women in the first trimester may consider delaying treatment until after the first trimester.
- Women with CD4 counts of <200 x 10^6/L will require prophylaxis for pneumocystis carinii pneumonia (PCP) and the first line preventative therapy is co-trimoxazole, a folate antagonist. In addition to neural tube defects, first trimester exposure to folate antagonists has been associated with increased frequency of cardiac and renal tract malformations[13]. Regular administration of even small doses of folic acid appears to negate this additional risk[14].
- For women with a CD4 count of ≥350 10^6/L the primary indication for ARV is reduction of vertical transmission risk. The ideal time for initiation of antenatal ARV is not known, however, earlier initiation is associated with reduced transmission risk[15]. This together with the accumulating safety data has resulted in a move towards earlier initiation of ARV in pregnancy. Early initiation is of particular importance where there is a history of prematurity. The choice of antiretroviral regimen will be determined by the woman's HIV physician. In this group, ARVs are not always continued post-partum.
- In certain circumstances (i.e. high CD4 counts and low level HIV viremia and absence of hepatitis C co-infection) zidovudine monotherapy may be considered and when used, intra-partum IV zidovudine, elective c/section and neonatal zidovudine is also recommended.

Zidovudine has traditionally been the cornerstone of regimens to prevent vertical transmission because of its ability to cross the placenta (and thus acts as pre and post exposure prophylaxis for the infant). In addition experience and safety data with zidovudine is greatest although experience with other agents is increasing. Thus, a number of ARV options are available and are selected based on maternal need, treatment history and resistance patterns. Women prescribed ARVs in pregnancy are appraised of the rationale for their use and the potential for toxicities, both known and as yet unanticipated.

Current standard treatment for women for PMTCT usually includes 2 nucleoside reverse transcriptase inhibitors and a boosted protease inhibitor. Depending on maternal immunological status, non-nucleoside reverse transcriptase inhibitor containing regimens may be used. In general for women who are stable on treatment, conception is not an indication to change ARV.

The management of pregnant HIV positive women is decided in consultation with adult and obstetric services. The management of the infant is decided by the paediatric team towards the end of the pregnancy when the mother's response to treatment becomes apparent. These recommendations will be communicated, in writing, to the obstetrician. Sometimes these recommendations are updated and revised as new maternal results come to light. Every effort should be made to ensure the most recent correspondence is placed in the medical file.

Labour and Delivery

Peripartum IV Zidovudine:

Previous guidelines have recommended IV zidovudine (ZDV) for all women in labour. Now, because of the potency of current ARV regimens, IV ZDV is no longer recommended for all women. ***The indications for use of IV ZDV are:***

- All women on ZDV monotherapy
- All women with <4 weeks ARVs
- All women with a 36 week viral load of >40 copies/ml
- Any women who is non-adherent to treatment
- Late presenters
- Women with planned C/Section to prevent HIV transmission

Women with detectable viral load at 36 weeks:

Commence IV zidovudine infusion at onset of labour or 4 hours prior to elective c/section. **2mg/kg loading dose over 1 hour followed by 1mg/kg/hr until delivery is complete*. (Appendix 2)***

Single dose Nevirapine

Nevirapine is an oral antiretroviral that has rapid onset of action, crosses the placenta efficiently, and achieves good levels in the infant. Used as a single dose at labour onset, it is extremely safe and can have an important additive benefit when trying to prevent transmission in both contributing to viral suppression in the mother and prophylaxis in the infant. However, monotherapy using single dose nevirapine has been associated with a significant risk for development of antiretroviral resistance[15,16]. Therefore this strategy is reserved for and only considered in the following situations:

- Women who have refused ARV in pregnancy may accept SD-NVP at labour onset
- Mothers diagnosed in labour should be given single dose Nevirapine in addition to existing ARV
- Mothers who are not, or are anticipated not to be virally suppressed at labour onset may be prescribed SD-NVP in addition to their existing ARV regimen both for its effect on maternal viraemia and prophylaxis for the infant

- Mothers who labour prematurely may also be prescribed SD-NVP. In this case the aim is to achieve prophylactic levels in an infant who may not be able to tolerate oral medications in the immediate postnatal period.
- When single dose nevirapine is used, the women will be offered combination antiretroviral therapy for a period following the single dose with a view to reducing the risk of developing nevirapine resistance. The adult HIV physician will make recommendations in this regard.

Delivery

In a 10 year audit of PMTCT in Ireland, (Jan 1999 to December 2008 inclusive), of 964 live births, the overall transmission rate for infants born to women in receipt of ≥4 ARV was 0.4%. 56% were delivered vaginally, 24% by emergency c/section and 20% by planned C/section delivery[17].

Elective C section is proven to reduce the risk of transmission in women who have not received any ARV; those in receipt of zidovudine monotherapy and those failing combination ARV. In those failing combination ARV the viral load threshold above which an ELCS is necessary is not precisely known. Previously a threshold of 1000 copies/ml was suggested[18]. While two studies have shown potential benefit of C/section in reducing transmission even in women with VL <1000cpm, one was in the pre triple combination era and the second lacked sufficient power to permit adjustment for HAART treatment[19]. However in a French cohort study of women with a delivery viral load <400 cpm the transmission rate was 0.4% for ELCS vs 0.5% for all other modes of delivery[20]. In Ireland, c/section is currently recommended for women with a viral load of > 400 cpm. The decision regarding mode of delivery for women with viral load <400cpm will be influenced by duration of ARV, adherence to ARV, trends in viral load, obstetric & fetal considerations.

The role of ELCS in women on suppressive combination ARV has not been determined in a RCT but recent data from the UK and Ireland of over 4000 mother-infant pairs did not demonstrate a difference between women on combination ARV who were delivered vaginally or by c/section delivery supporting the recommendation to allow women who are stable on a suppressive regimen to proceed to routine vaginal delivery[21].

Minimise exposure of HIV to the infant by:

- ***Where possible avoid artificial rupture of membranes (ARM)
- Avoid fetal scalp electrodes or fetal blood sampling
- Clamp cord ASAP to minimise the risk of maternal-fetal micro transfusions
- Avoid nasopharyngeal suction.
- Clean eyes and towel dry baby and bath ASAP.
- Clean skin thoroughly before any infusions or injections. Ensure this is done prior to any vaccinations e.g. Hepatitis B vaccine or immunoglobulin administration.

*HIV transmission risk correlates with the duration of labour and ROM. Every effort should be made to safely minimise this risk. Decisions to expedite delivery, through induction or c/section delivery in women with pre-labour ROM will be made balancing potential risks and benefits[22].

Post Partum

Women taking ARV for PMTCT will discontinue therapy postpartum. Recommendations for continuing or discontinuing maternal treatment post partum will be made by the adult HIV team and will be communicated by letter.

After delivery, communication with the adult HIV service to arrange an appointment for maternal resistance testing within 3-6 weeks of delivery is recommended for women who discontinue therapy post partum. This test will provide important information for their future antiretroviral options.

Neonatal Care

Antenatal discussion with the Paediatric service is recommended. Topics covered by the paediatric team during consultation include:

- Vertical transmission of HIV, risks, rates and timing of transmission
- Interventions to reduce risk
- ARV in pregnancy; benefits and possible infant toxicities
- Avoidance of breastfeeding
- Monitoring and treatment of infant
- Infant outcome

Recommendations are communicated in writing to the Obstetric team.

Infant Feeding

In Ireland breastfeeding is not recommended for HIV exposed infants. Formula feeding should be used. Maternal and infant HAART continued through the breastfeeding period has been shown to protect against HIV transmission and may be an appropriate choice in areas of the world where safe formula feeding can not be achieved[23].

Antiretroviral therapy for the baby

Choice of post exposure prophylaxis for the infant will depend on both the timing of maternal diagnosis of HIV, maternal adherence, the level of maternal viraemia at/near delivery, maternal resistance patterns and the duration of rupture of membranes. Treatment is commenced as soon as possible after delivery and will continue for 4 weeks. Treatment choices are as follows:

Infants of mothers who have received at least 4 weeks ARV <u>and</u> who have a viral load < 40 copies per ml <u>and</u> who have rupture of membranes for <12hours (I.e. lowest risk for transmission) will receive:

ZDV (AZT/Retrovir) 4mg/kg/dose 12 hourly

All other infants receive

- **Zidovudine** (ZDV /AZT/Retrovir) 4mg/kg/dose 12 hourly ***and***
- **Lamivudine** (3TC/Epivir) 2mg/kg/dose 12 hourly ***and***
- **Nevirapine** 2mg/kg/dose. **Two doses only. The timing is as follows:**

Mother treatment history	Timing of Nevirapine to infant
If the mother has **never** taken Nevirapine as part of her ARV in pregnancy	***Two doses of Nevirapine***, one as soon as possible after delivery (preferably within 4 hours) and a second dose at 48-72 hours age
If the mother has taken a single dose of Nevirapine at labour onset ***but delivery occurs within 2 hours of maternal ingestion***	***Two doses of Nevirapine***, one as soon as possible after delivery (preferably within 4 hours) and a second dose at 48-72 hours age
If the mother **has** taken Nevirapine as part of her ARV in pregnancy	***Two doses of Nevirapine,*** one at 24 hours and one at 48-72 hours of age.
If the mother has taken a single dose of Nevirapine at labour onset and there is at least a ***two hour delay before delivery***	***Two doses of Nevirapine***, one at 24 hours age and a second at 48-72 hours age

If the neonate is unable to take oral Zidovudine, an IV preparation is available *(see appendix 3)* Lamivudine (3TC, epivir) and Nevirapine (Viramune) are not available in IV formulation.

Diagnosis of the neonate

All infants born to HIV positive mothers will have passively acquired, transplacental IgG antibodies to HIV, i.e. they will have a positive HIV antibody test. The median time to loss of antibody (i.e. seroreversion) is 10 months, but it may be as long as 18 months. New generation HIV antibody tests are now so sensitive that trace amounts of residual maternal antibody can sometimes be detected up to 20 – 24 mos. However, with the use of HIV PCR (polymerase chain reaction) testing, infection can be diagnosed in more than 95% of infants by 6 weeks of age and an infant determined to be not infected by 3 months of age. A positive HIV PCR result within 72 hours of birth has been taken as evidence of intra-uterine transmission. Infants who are not breastfed and who have serial HIV PCR tests that are negative up to and including the 3 month test are not HIV infected.

Infant Monitoring (appendix 4)

Infants are generally seen in the Rainbow clinic, however, where distance is a problem alternative arrangements can be made on an individual basis. Arrangements are in place for infants born in Galway and Cork to be reviewed locally. ***As soon as the infant has been delivered please contact a member of the Rainbow Clinic.*** (Please see contacts at the back of this document).

- **HIV PCR** is taken at day 1 and repeated at 2 weeks of age. A copy of the results should be sent to the Rainbow Clinic.

  PLEASE REQUEST '*HIV PCR ULTRA SENSITIVE ASSAY'*. Please send two filled paediatric EDTA tubes for this.

  CORD BLOODS MUST NOT BE SENT (Obtaining cord blood represents an unnecessary hazard to Health Care Staff and is subject to false positive results due to the potential for contamination with maternal blood**)**
- Side effects of ZDV include bone marrow suppression therefore in addition to the HIV PCR; the **FBC** should be checked at 2 weeks of age. Please arrange for results to be copied to the Rainbow Clinic.
- Further Paediatric review should be carried out at intervals indicated on appendix 4***.***

Baby with a positive HIV PCR result

Please contact the Rainbow Team at Our Lady's Children's Hospital Crumlin, immediately. Any child with a positive HIV PCR result should have a repeat sample for HIV RNA and DNA PCR testing. ARV will be continued beyond 4 weeks of age. The early diagnosis of HIV infection is critical for optimum management. More rapid disease progression is observed in vertically transmitted infants. Twenty five percent will develop symptoms within the first year of life. Potent combination ARV must be initiated early in the course of infection to control viral replication and preserve immune function.

Management of the exposed infant

Pneumocystis jiroveci (carinii) Pneumonia (PJP/PCP) Prophylaxis

In HIV infected children, PCP occurs most frequently at 3-6 months of age. At the 6 week check, co-trimoxazole is commenced for infants perinatally exposed to HIV where the risk of infection is high (ie. on a practical basis this means that infants who were prescribed triple therapy in the postnatal period should be considered for co-trimoxazole). If the HIV PCR at 3 months is negative PCP prophylaxis is discontinued as these infants are unlikely to be HIV infected. ***(Appendix 5)***

Immunisations

HIV exposed infants should receive all the normal childhood immunisations. **BCG** vaccination at birth is deferred until the HIV PCR at 6 weeks is confirmed negative. All children, infected and exposed, should receive MMR vaccine ***(Appendix 6).***

Infants of women who are HBsAg positive should receive hepatitis B immune globulin, in addition to hepatitis B vaccine, as soon as possible following delivery ***(appendix 7).*** Completion of HBV vaccination will be carried out as part of the National Immunisation Programme as hepatitis B vaccination is now an integral part of the routine immunisation schedule.

Screening for other infections

Infants at risk of HIV may also be at risk of other infections. If the mother is found to have Hepatitis B virus (HBV) and Hepatitis C Virus (HCV) or Syphilis then the infant will need appropriate evaluation and monitoring. ***(Appendix 7 and 8)***

Mitochondrial toxicity

ARV's (including zidovudine and lamivudine) have the potential to cause mitochondrial toxicity through inhibition of mitochondrial DNA polymerase-γ. HIV per se is also associated with inhibition of mitochondrial DNA. One study where antenatal zidovudine and lamivudine were used to prevent vertical transmission, highlighted concerns when 2 of 200 infants studied developed an extremely rare and fatal neurological disease, related to mitochondrial toxicity[24]. A review of over 20,000 ARV exposed infants in North America has not shown an increased risk of mitochondrial dysfunction[25]. Nonetheless the possibility of mitochondrial toxicity must

be considered in infants exposed to ARV who present unwell to your service. Infant manifestations of mitochondrial dysfunction include lactic acidosis, elevated liver transaminases and disturbed neurological function.

Long term follow up

Once the HIV Ab test becomes negative, it is recommended that all infants exposed to ARV are maintained in long term follow up until aged 5 years. The monitoring schedule adopted at the Rainbow clinic includes visits at 2, 3, and 5 years of age. More frequent visits are arranged if clinically indicated. Particular areas for attention include growth and development, especially speech and language and vaccination history **(*Appendix 13*).**

Maternal refusal of treatment/care recommendations

In the event of a HIV positive woman refusing to link with specialist services or refusing management to reduce mother to infant transmission, the following considerations may be helpful during your consultation;

Antenatal care

- Discuss the benefits and risks of potential interventions.

Peripartum care

- A woman, who refuses ARV in pregnancy, might be willing to take a single dose of nevirapine at labour onset. Please contact the adult ID team as soon as possible as additional ARV therapy may also be recommended to reduce the risk of development of treatment resistant virus.
- A woman might also accept an elective c/section with peripartum intravenous Zidovudine

Treatment and care of baby

- For infants of women who refuse ARV during pregnancy, post exposure prophylaxis of the infant with triple therapy and bottle feeding is strongly recommended

Guidance must be sought from specialist services, on each individual situation, to determine the best strategy. In rare cases where a woman still refuses intervention against advice and extensive counselling, discussion with social services is recommended pre delivery so that a strategy can be developed. The mother should be informed that court permission will be sought to treat the infant. The Irish courts have previously supported physicians in providing HIV exposed infants the benefit of ARV where parents have refused.

CONTACTS

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Or contact any of the above through switch on 01 410 3000

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Attending pre-conception on antiretroviral therapy			**RECOMMENDATIONS**				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
Virally suppressed throughout pregnancy Continue PCP prophylaxis if CD4 <200		<40	In general continue ARVs Substituting efavirenz for alternative may not be of benefit depending on gestational age when presents	If HIV VL <40 @36/40 **NOT** for IV ZDV Continue oral ARVs in labour	Continue	If HIV VL <400 @36/40 await SOL	If HIV VL <40 @36/40 and ROM <12hrs, ZDV x 4/52
Failing therapy anytime Continue PCP prophylaxis if CD4 <200		>40	Optimise HAART with guidance of GRT and previous ARV history	If HIV VL >40 @36/40 IV ZDV as per protocol	Case by case	If HIV VL >400 at 36/40 ELCS @39/40	If HIV VL >40 @36/40 or ROM >12 hrs Triple ARV x 4/52
				If HIV VL <40 @36/40 **NOT** for IV ZDV Continue oral ARVs in labour		If HIV VL <400 @36/40 await SOL	If HIV VL <40 @36/40 and ROM <12hrs, ZDV x 4/52

Not on treatment or new HIV diagnosis in pregnancy **Gestation at presentation:** <20/40			**RECOMMENDATIONS**				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
Because of ↓ baseline CD4, mother requires ARVs for own health	<350		Send baseline GRT prior to commencing ARV Commence ARVs ASAP after 1st trimester. No later than 20/40 NB - Commence PCP prophylaxis ASAP if CD4 <200	If HIV VL >40 @36/40 IV ZDV as per protocol	Continue	If HIV VL >400 at 36/40 ELCS @39/40	If HIV VL >40 @36/40 or ROM >12 hrs Triple ARV x 4/52
				If HIV VL <40 @36/40 **NOT** for IV ZDV Continue oral ARVs in labour		If HIV VL <400 @36/40 await SOL	If HIV VL <40 @36/40 and ROM <12hrs, ZDV x 4/52
Antenatal ARV primarily for PMTCT	>350		Send baseline GRT prior to commencing ARVs Commence ARVs in the second trimester. No later than 20/40.	If HIV VL >40 @36/40 IV ZDV as per protocol	discontinue ARVs post-partum and see for GRT at ~6 weeks	If HIV VL >400 at 36/40 ELCS @39/40	If HIV VL >40 @36/40 or ROM >12 hrs Triple ARV x 4/52
				If HIV VL <40 @36/40 **NOT** for IV ZDV Continue oral ARVs in labour		If HIV VL <400 @36/40 await SOL	If HIV VL <40 @36/40 and ROM <12hrs, ZDV x 4/52

Not on treatment or new HIV diagnosis in pregnancy **Gestation at presentation:** >20/40			**RECOMMENDATIONS**				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
Because of ↓ baseline CD4, mother requires ARVs for own health	<350		Send GRT but commence ARVs asap If CD4 <250 consider nevirapine based regimen Consider raltegravir based regimen if presents in third trimester or baseline HIV VL >100,000	If HIV VL >40 @36/40 or mother on ARVs x <4/52 IV ZDV as per protocol	Continue ARVs	If HIV VL >400 @ 36/40 or <4/52 maternal ARVs: ELCS @ 39/40	If HIV VL >40 @36/40 or ROM >12hrs or <4/52 maternal ARVs: Triple ARVs x 4/52
				If HIV VL <40 @36/40 and mother on ARVs x ≥4/52 **NOT** for IV ZDV Continue oral ARVs in labour		If HIV VL <400 @ 36/40 and mother on ARVs x ≥4/52: await SOL	If HIV VL <40 @36/40 +ROM <12hrs + mother on ARVs x ≥4/52: ZDV X 4/52
Antenatal ARV primarily for PMTCT	>350		Send GRT but commence ARVs asap Consider raltegravir based regimen if presents in third trimester or baseline HIV VL >100,000	If HIV VL >40 @36/40 or mother on ARVs x <4/52 IV ZDV as per protocol	Discontinue ARVs and see for GRT at ~6 weeks	If HIV VL >400 @ 36/40 or <4/52 maternal ARVs: ELCS @ 39/40	If HIV VL >40 @36/40 or ROM >12hrs or <4/52 maternal ARVs: Triple ARVs x 4/52
				If HIV VL <40 @36/40 and mother on ARVs x ≥4/52 **NOT** for IV ZDV Continue oral ARVs in labour		If HIV VL <400 @ 36/40 and mother on ARVs x ≥4/52: await SOL	If HIV VL <40 @36/40 +ROM <12hrs + mother on ARVs x ≥4/52: ZDV X 4/52

Premature labour on effective HAART			**RECOMMENDATIONS**				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
<34/40		<40	Steroids and tocolysis if obstetrically indicated Continue HAART	IV ZDV as per protocol	Continue	Consider CS after steroids	If ROM >12 hours Triple ARVs x 4/52 where possible
>34/40			Continue HAART	IV ZDV as per protocol	Continue	Consider CS if delivery not imminent	If ROM >12 hours Triple ARVs x 4/52 where possible

<table>
<tr><td colspan="3">Premature labour failing HAART</td><td colspan="5">RECOMMENDATIONS</td></tr>
<tr><td>Clinical</td><td>CD4</td><td>HIV VL</td><td>Antepartum</td><td>Intrapartum or prior to CS</td><td>Postpartum mother</td><td>Mode of delivery</td><td>Postpartum infant*</td></tr>
<tr><td><34/40</td><td rowspan="2"></td><td rowspan="2">>40</td><td>GRT
Steroids and tocolysis if obstetrically indicated
Consider raltegravir or nevirapine (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay</td><td rowspan="2">IV ZDV as per protocol</td><td rowspan="2">Continue if indicated for maternal health

Discontinue if not indicated for maternal health. Staggered stop if NVP based.
GRT at ~6 weeks</td><td>Consider CS after steroids</td><td rowspan="2">Triple ARVs x 4/52where possible</td></tr>
<tr><td>>34/40</td><td>GRT
Consider raltegravir or nevirapine (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay</td><td>Consider CS if delivery not imminent</td></tr>
</table>

Premature labour not on HAART	**RECOMMENDATIONS**						
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
<34/40		>40	GRT Steroids and tocolysis if obstetrically indicated Consider raltegravir or nevirapine (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay	IV ZDV as per protocol	Continue if indicated for maternal health Discontinue if not indicated for maternal health. Staggered stop if NVP based. GRT at ~6 weeks	Consider CS after steroids	Triple ARVs x 4/52where possible
>34/40			GRT Consider raltegravir or nevirapine (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay			Consider CS if delivery not imminent	

<table>
<tr><td colspan="2">Prelabour ruptured membranes at term</td><td colspan="6">RECOMMENDATIONS</td></tr>
<tr><td>Clinical</td><td>CD4</td><td>HIV VL</td><td>Antepartum</td><td>Intrapartum or prior to CS</td><td>Postpartum mother</td><td>Mode of delivery</td><td>Postpartum infant*</td></tr>
<tr><td rowspan="2">On effective HAART</td><td rowspan="3"></td><td rowspan="2"><40</td><td rowspan="2">Continue HAART</td><td rowspan="3">IV ZDV as per protocol</td><td rowspan="2">Continue</td><td rowspan="3">Expedite delivery, aim for shortest duration of ROM</td><td>If ROM <12 hours ZDV x 4/52</td></tr>
<tr><td>If ROM >12 hours triple ARVs x 4/52</td></tr>
<tr><td>Failing HAART</td><td>>40</td><td>Optimise ARVs with clinical and resistance data
Consider raltegravir based regimen to facilitate rapid virological decay</td><td rowspan="2">Continue if indicated for maternal health

Discontinue if not indicated for maternal health.
Staggered stop if NVP based.
GRT at ~6 weeks</td><td>Triple ARVs x 4/52</td></tr>
<tr><td>Not on HAART</td><td>>40</td><td>Consider raltegravir based regimen to facilitate rapid virological decay</td><td></td></tr>
</table>

Prelabour ruptured membranes pre term			**RECOMMENDATIONS**				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
On effective HAART		<40	Steroids if obstetrically indicated Continue HAART Urgent VL Consider sdNVP to mother to pre load infant	IV ZDV as per protocol	Continue if on effective HAART	<34/40 consider CS once steroids effective	Triple ARVs where possible if ROM >12 hours or mother on failing regimen
Failing HAART		>40	Steroids if obstetrically indicated Optimise ARVs with clinical and resistance data Consider raltegravir or nevirapine (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay		Optimise HAART if failing therapy	>34/40 expedite delivery aiming for shortest duration of ROM	
Not on HAART		>40	Steroids if obstetrically indicated Consider raltegravir or nevirapine (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay				

Diagnosed in labour			RECOMMENDATIONS				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
				IV ZDV as per protocol where possible Consider sdNVP (NB – risk for NNRTI resistance, consider temporary triple ARVs or NRTI tail)	Urgent confirmation of HIV status Assessment at adult HIV service post partum	Expedite delivery	Urgent initiation of triple ARVs and urgent confirmation of maternal HIV Ensure not breastfeeding

Diagnosed </= 72 hours post partum			**RECOMMENDATIONS**				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
					Assessment at adult HIV service post partum		Urgent initiation of triple ARV and urgent confirmation of maternal HIV Ensure not breastfeeding

Refusing interventions to reduce MTCT			**RECOMMENDATIONS**				
Clinical	**CD4**	**HIV VL**	**Antepartum**	**Intrapartum or prior to CS**	**Postpartum mother**	**Mode of delivery**	**Postpartum infant***
				Offer IV ZDV +/- sdNVP	Offer adult HIV service assessment	Offer ELCS	Triple ART, infant to be made ward of court if required Ensure not breastfeeding

ART: Antiretroviral therapy
ELCS: Elective caesarean section
sdNVP: single dose nevirapine
VL: viral load
HIV VL measured in copies per ml
GRT: genotypic resistance testing
SOL: Spontaneous onset of labour
ZDV: Zidovudine or AZT or Retrovir
C.S: Caesarean Section
NVP: Nevirapine
Rx: therapy
CD4 units = x 10^6/L
Triple ART to baby = ZDV + 3TC x 4/52 + stat NVP

INSTRUCTIONS FOR ADMINISTRATION OF ZIDOVUDINE (RETROVIR FOR INFUSION) TO AN HIV POSITIVE WOMAN INTRAPARTUM*:*

Presentation: Zidovudine 200mg/20ml

Use: Indicated for use in HIV positive pregnant women (over 14 weeks of gestation) and their newborn infants for primary prophylaxis of maternal fetal HIV-1 transmission.

Usual adult dose:

Spontaneous vaginal delivery:

Loading dose: 2mg/kg IV infusion over one hour **then give**

Maintenance dose: 1mg/kg/hour continued until the cord has been clamped.

Planned c/section:

Loading dose: 2mg/kg IV infusion over one hour starting 4hours before the operation

Maintenance dose: 1mg/kg/hour IV infusion continued until the cord has been clamped.

In the event of a false labour the infusion should be stopped and oral dosing restarted.

Administration Details:

Drug Name	***Route of Administration***	***Infusion Fluids***	***Final concentration***	***Notes***
Zidovudine	**Loading dose**: IV infusion over 60 minutes **Maintenance dose:** Continuous IV infusion	Glucose 5%w/v	2mg/ml or 4mg/ml of infusion fluid **Example**: to prepare a solution of concentration 2mg/ml, withdraw 100ml of fluid from a 500ml infusion bag, add the contents of 5 ampoules (1000mg = 100ml) to the infusion bag. Concentration is now 1000mg in 500ml or 2mg/ml.	**Must be diluted before use.** **Once diluted the infusion solution is stable for 24 hours. If any visible turbidity appears in the product either before or after dilution or during infusion, the preparation should be discarded.**

Notes:

- **Neutropenia/Anaemia:** Dosage adjustment is required in patients who develop neutropenia or anaemia – see information sheet for further details or consult pharmacy department.
- **Renal/Hepatic impairment:** Patients with advanced renal failure should receive zidovudine at the lower end of the dosage range. For dose management in patients with hepatic impairment contact the Pharmacy Department or see the information sheet.
- **Side effects:** include anaemia (usually not observed before 6 weeks of zidovudine therapy but occasionally occurring earlier), neutropenia (usually not observed before 4 weeks of zidovudine therapy but occasionally occurring earlier) and leucopenia (usually secondary to neutropenia). Other side effects include nausea, vomiting, anorexia, abdominal pain, headache, rash, fever, myalgia, paraesthesia, insomnia, malaise, asthenia and dyspepsia. Rare occurrences of lactic acidosis, in the absence of hypoxaemia, and severe hepatomegaly with steatosis have been reported in patients receiving zidovudine.
- **Potential drug interactions**: include phenytoin, paracetamol, aspirin, codeine, morphine, indomethacin, naproxen, lorazepam, cimetidine, dapsone, nephrotoxic or myelosuppressive medications, ribavirin and probenecid. For full details on all these interactions see the information sheet or consult the Pharmacy Department.

INSTRUCTIONS FOR ADMINISTRATION OF ZIDOVUDINE (RETROVIR) FOR INFUSION *TO HIV EXPOSED INFANTS UNABLE TO TAKE ORAL MEDICATIONS*

Date: April 2011

Review date: April 2013

The Rainbow Team, Our Lady's Children's Hospital, Crumlin and The Children's University Hospital, Temple Street

Presentation: Zidovudine 200mg/20ml

Use: Indicated in newborn infants of HIV positive mothers to reduce the rate of maternal-fetal transmission of HIV.

Dosage: **Patients should receive Zidovudine IV only until oral therapy can be administered.**

- Term neonates > 34 weeks 1.5mg/kg 6hrly IV infusion over 1 hour
- Preterm neonates < 34 weeks 1.5mg/kg/12hrly IV infusion over 1 hour

Dosage adjustment is required in patients who develop neutropenia or anaemia – see information sheet for further details or consults pharmacy Dept.

Administration Details:

Drug Name	***Route of Administration***	***Infusion Fluids***	***Final concentration***	***Notes***
Zidovudine	IV infusion over 1 hour	Glucose 5%w/v	2mg/ml or 4mg/ml	Must be diluted before use. If any visible turbidity appears in the product either before or after dilution or during infusion, the preparation should be discarded

Notes:

- Dosage adjustment is required in patients who develop neutropenia or anaemia – see information sheet for further details or consult Pharmacy Department.
- Patients with advanced renal failure should receive zidovudine at the lower end of the dosage range. For dose management in patients with hepatic impairment contact the Pharmacy Department or see the information sheet.
- Contraindicated in newborn infants with hyperbilirubinaemia requiring treatment other than phototherapy, or with increased transaminase levels of over five times the upper limit of normal.
- Side effects include anaemia, neutropenia and leucopenia (usually secondary to neutropenia). Other side effects include nausea, vomiting, anorexia, abdominal pain, headache, rash, fever, myalgia, paraesthesia, insomnia, malaise, asthenia and dyspepsia. Rare occurrences of lactic acidosis, in the absence of hypoxaemia, and severe hepatomegaly with steatosis have been reported in patients receiving zidovudine.
- Potential drug interactions include phenytoin, paracetamol, aspirin, codeine, morphine, indomethacin, naproxen, lorazepam, cimetidine, dapsone, nephrotoxic or myelosuppressive medications, ribavirin and probenecid. For full details on all these interactions see the information sheet or consult the Pharmacy Department.

If you require any further information please contact a member of The Rainbow Team 01 409 6338

Appendix 4

Management Guideline: Infants Born to HIV Positive Women

	Pregnant Mother	Day 1	2wk	4wk	6wk	3mth	6mth	18 months
HIV antibody	√	√						√
PCR	√	√	√		√	√	√	
T cell subsets*			*		*	*		
FBC		√	√		√	√		
LFT's		√						
CMV IgG, IgM	√#	Urine						
Toxoplasma	√#							
Hep BsAg	√#							
Hep C Ab	√#							
Haemaglobinopathy screen/G6PD (if indicated)					√			
Management considerations				Discontinue anti-retroviral agents	Commence TMP/SMX (Co-trimoxazole) in infants who received triple therapy. If PCR negative at day 1 and 6 weeks, refer for BCG	If PCR negative discontinue TMP/SMX (Co-trimoxazole)		

- **All HIV exposed infants should receive childhood immunisations as per National Guidelines. BCG vaccine should be deferred until 6 week PCR is confirmed negative. Additionally, infants born to HBsAg + mothers should receive HBIG and Hepatitis B Vaccine (HBV) (as per national guidelines).**
- ***T cell subsets should be taken in the event of a positive PCR result**
- **# If status unknown at time of delivery**
- **HIV PCR. Please fill 2 paediatric EDTA tubes (1.2ml) with blood. Plasma should be separated within 6 hrs and frozen at –70C. Send to Virus Reference Laboratory and ultrasensitive PCR assay requested.**
- **If the baby is born over a week/end or bank holiday, obtain PCR within 48hrs of delivery, spin down and freeze until it is possible to forward to Virus Reference Lab for analysis.**
- **If the mother is Hep C or Hep BsAg positive, please refer to appendices 7 & 8 .**

Appendix 5

Recommended chemoprophylaxis regimens for PCP

Co-trimoxazole: Suggested doses of trimethoprim/sulphamethoxazole (Co-trimoxazole) for prophylaxis of Pneumocystis Carinii Pneumonia (PCP), to be given once daily on three days a week (usually Monday, Wednesday and Friday). Dose is based on 900mg/m^2/dose.

Surface Area (m^2)	Dose of Co-trimoxazole
<0.25	120mg
0.25-0.39	240mg
0.4-0.49	360mg
0.5-0.75	480mg
0.76-1	720mg
>1	960mg (adult dose)

If for some reason e.g. adherence issues, administration three times weekly on Mondays, Wednesdays and Fridays is not appropriate then the above dose can be given on three consecutive days of the week e.g. Monday, Tuesday, Wednesday or the seven days of the week. The dose may be given as a single daily dose or divided 12 hourly.

Alternative therapies include:

Dapsone: PCP Prophylaxis: 2mg/kg/day (Maximum dose 100mg/day) – if the patient develops neutropenia then follow the guidelines for dosage adjustment for Co-trimoxazole.

Pentamidine: PCP Prophylaxis: <5years: 4mg/kg IV every 4weeks
>5years: 300mg aerosolised every 4weeks

Pentamadine injection is not licensed in Ireland but is available as an exempt medicinal product. Contact the Rainbow Team Pharmacist for more details.

If the infant/child/adolescent develops neutropenia while taking Co-trimoxazole then the following guidelines should be followed:

1. Stop Co-trimoxazole therapy for 5-7days.
2. Check FBC after the 5-7days stoppage period.
3. Depending on ANC the dose should be altered according to the table below:

Absolute Neutrophil Count (ANC)	What to do?
<0.8	If after stopping therapy for 5-7days the ANC remains less than <0.8, then the need to continue PCP prophylaxis should be discussed with the consultant in charge.
0.8-1.5	If the ANC improves to between 0.8-1.5 then Co-trimoxazole therapy should be restarted at one-third the normal dose. The FBC should be checked again after 5-7days and the dose adjusted accordingly.
>1.5	Restart Co-trimoxazole therapy at normal dose and recheck FBC after 5-7days. If the ANC has decreased for a second time then stop therapy for 5-7days, recheck FBC and discuss with consultant in charge.

Appendix 6

Immunisation Schedule for HIV exposed and infected infants

VACCINATION	HIV exposed infants	HIV infected CD4 >15%	HIV infected CD4 <15%	TIMING	COMMENTS
BCG	when 6 wk HIV PCR is negative	**NO**	**NO**	2-3 months of age in HIV exposed but uninfected infants.	Defer until HIV PCR tests taken at birth and 6 weeks of age are obtained and confirmed as negative.
DTaP/IPV/Hib/Hep B (6:1) (Infanrix-Hexa®)	YES	YES	YES*	2, 4, 6 months	
DTaP/IPV	YES	YES	YES*	4 – 5 years	
dTap	YES	YES	YES*	11 – 14 years.	
Meningococcal C	YES	Yes	YES*	<u>For infants < 12 months age:</u> 4, 6 and 13 months <u>For children >12 months age</u>: single dose only	The first dose should not be given earlier than 2 months of age and subsequent doses at interval of at least 1 month.
Prevenar 13 valent conjugate vaccine (PCV13)	YES	YES	YES*	<12 months (Minimum age for initiation 6 weeks) Doses 1&2 given 2 months apart. Dose 3 given at >12 months of age, at least 2 months after dose 2	Usually given as part of the national immunisation programme at 2,6 and 12 months of age
Pneumovax II 23 valent polysaccharide vaccine (PPVV 23)	Not routinely recommended	YES	YES*	Single dose given at >24 months of age at least 2 months after dose 3 PCV7 Booster doses of PPV23 A single booster dose should be given 5 years after the first dose. The need for repeated booster doses is not proven	This vaccine (Pneumovax) is licenced for use in children ≥2 years. Administer at a separate site to other childhood vaccines if given at same time.
MMR	YES	YES	**NO**	12-15 months and 4-5 years	

Influenza vaccine	Not routinely recommended but may be used if wish to decrease risk of influenza	YES	YES	For infants more than 6 months Yearly as appropriate	For children < 9 years who have not previously been vaccinated a second dose should be given after an interval of at least 4 weeks.
Varicella vaccine	Not routinely recommended but may be used if wish to decrease risk of Varicella	YES (if CDC class N, A or B and CD4 >25%)	**NO**	Children > 12months – 13 years Two doses 12- 15mos and 24 – 36 mos. Children >13 years 2 doses. 4 – 8 weeks apart	For asymptomatic children without history of chickenpox (negative varicella serology) and CD4>25% Children with no contraindications such as steroid therapy
Hepatitis A	Not routinely recommended but may be used if wish to decrease risk of Hep A	Yes	Yews	Mono component vaccine - Baseline and 6 months Combined with HBV - Baseline, 1 month and 6 months	
HPV Vaccine	Not routinely recommended	Not routinely recommended but may be used if wish to reduce risk of HPV infection	No	Baseline, 2 and 6 months	This vaccine may be considered for HIV infected girls greater than 9 years of age

* Children with severe immune deficiency (CD4<15%) are unlikely to generate a strong protective response to vaccination, if immune recovery is anticipated, may wish to defer vaccination until CD4 recovery.

Appendix 7

Guideline for the management of neonates born to HBsAg positive mother or to a mother who had acute hepatitis B infection during the pregnancy.

Prepared by Drs Mary Cafferkey, Niamh O'Sullivan and Karina Butler.

Updated by the Rainbow Team April 2011: Review date April 2013

Principle

Neonates born to mothers who have acute hepatitis B during pregnancy or who are chronic carriers are at increased risk of developing hepatitis B. Transmission of hepatitis B virus (HBV) from mother to baby occurs most often during delivery. It may also occur following delivery and there is some evidence that transplacental transmission may occur. HBV DNA has been demonstrated in breast milk but breast feeding has not been determined to be an important route of transmission for infants who have been immunised.

Vertical transmission of HBV is increased if the mother has a high titre of HBsAg and is e antigen (HBeAg) positive. Transmission can also take place from HBsAg positive but HBe Ag negative women who have detectable viremia. Thus early immunisation, active and passive, is recommended for infants of all HBsAg women regardless of HBeAg status. Early immunisation is also recommended for infants whose mothers are HBcAb positive but HBsAg negative to protect them against possible transmission from household contacts whose status is unknown.

- 80 - 90% of unimmunised neonates born to HBeAg-positive mothers become infected and most become chronic carriers.
- Transmission of HBV to the neonate will be prevented in ≥90% of cases by immunoprophylaxis i.e., active and passive immunisation.
- As HBV immunisation is now part of the National Immunisation programme, the course of HBV immunisation commenced in the maternity hospital will be completed by the child's GP as part of their routine 2, 4 and 6 month immunisations. Special arrangements may be required for children with no GP.

Immediate management

- Due care should be taken to avoid percutaneous exposure of the infant to maternal blood e.g. avoid scalp electrodes.
- The infant should be bathed as soon as possible after delivery to remove any blood. (Wear plastic apron and gloves).
- Prior to administration of immunoprophylaxis clean skin carefully with an alcohol swab.

Active Immunisation

Intramuscular injection of 0.5ml hepatitis B vaccine ("Engerix B Paediatric® or HBvaxPro) is given as soon as possible after birth. The anterolateral-thigh is the preferred site for injection.

Vaccine interchangeability

Hepatitis vaccines produced by different manufacturers are interchangeable. The Immune response following a course where product from more than one manufacturer has been used is comparable to that where just one brand of vaccine has been used.

Preterm Infants:

It is important that premature infants receive the full paediatric dose of HBV vaccine and HBIG where indicated. As premature infants, who are <2kg and <1month of age at time of vaccination may have a poorer response to HBV immunisation, a 4th dose is recommended. For premature infants born to HBsAg positive mothers, who receive the first dose of vaccine following delivery, the current schedule of vaccines given at birth, 2, 4 and 6 months, achieves this without adjustment for the normal schedule.

"Engerix B" Paediatric® and HBvaxPro is available from the Pharmacy.

Passive Immunisation

Infants born to mothers with hepatitis B infection (HBeAg or HBsAg positive) should receive an Intravenous infusion of hepatitis B immunoglobulin (HBIG), known as Hepatect CP ®. This should be administered as soon as possible after birth. Please bring to room temperature before administration.

HBIG is available from the Pharmacy.

The dose for Hepatect CP is 30 – 100 international units/kg (i.e. 0.6 – 2 ml/kg) given slowly intravenously. The SPC states that 'clinical experience in newborns of women with Hepatitis B has shown that Hepatect CP® intravenously used at an infusion rate of 2ml over 5 to 15 minutes has been well tolerated. (REF: SPC for Hepatect CP® www.imb.ie Accessed 14/03/2011)

Suggested doses of Hepatect CP based on body weight:

Body Weight	Total volume of Hepatect CP ® to be administered
<1.5 kg	1ml
1.5 – 3 kg	2mls
>3 – 5 kg	3mls

Follow Up of Infants

- Infants born to HBsAg+ mothers will receive the second, third and fourth dose of vaccine at 2, 4 and 6 months of age with their GP as part of the national immunisation schedule. Infants should have follow-up serologic testing carried out locally 2-4 months after completion of the vaccine course.

- Measure Hepatitis B surface Antibody (Anti-HBs), to check protective response, and Hepatitis B surface Antigen (HBsAg), to exclude infection, 2-4 months after the fourth dose of vaccine. Do not request Hepatitis B core Antibody (HBcAb) as the presence of core antibodies in this age group represents the presence of maternal antibody. Arrangements for this follow up should be made locally either in the local paediatric clinic or with the family GP.

Anti HBs Level	Action required
0 or <10 mIU/ml	**Non responder.** Check HBsAg result. If this is negative, repeat full course of hepatitis B vaccine (a different brand of vaccine is advised). Recheck anti-HBs at 2 months post completion. If anti-HBs remains <10 mIU/ml, person is susceptible to HBV.
10-99 mIU/ml	**Low response.** If low level anti-HBs is confirmed by 2 different assays, administer booster dose of vaccine but there is no need to retest for anti-HBs
100 mIU/ml or greater	**Good response** No need for further vaccination or anti-HBs investigations

Breast Feeding

HBV DNA has been demonstrated in breast milk, however breastfeeding of **immunised** infants does not significantly increase their risk of infection. Decisions regarding breast-feeding can be made in consultation with the mother. Currently, hepatitis B infection is not an accepted contraindication to breast-feeding.

Public Health Considerations

Hepatitis B infection is a statutorily notifiable disease. All newly diagnosed infections should be reported in accordance with standard procedures. Household contacts, including other children, should be screened for hepatitis B infection and if uninfected, should be immunised.

Abbreviations:

HBsAg: 'Hepatitis B surface antigen' **HBeAg:** 'Hepatitis B e antigen'
Anti-HBs (also written as HBsAb): 'Hepatitis B surface antibody' or 'antibody to hepatitis B surface antigen'
Anti-HBe (also written as HBeAb): 'Hepatitis B e antibody' or 'antibody to hepatitis B e antigen'
Anti-HBc (also written as HBcAb): 'Hepatitis B core antibody' or 'antibody to hepatitis B core antigen'
HBIG: Hepatitis B immune globulin (Preparation currently available in Ireland is Hepatect CP®)

Appendix 8

Follow-up of Infants where mother is Hepatitis C Ab positive

	Pregnant mother	6 Weeks in Maternity Hosp	6 Months Local Paediatric Clinic	18 Months Local Paediatric Clinic
AST / ALT	√			
HCV Antibody	√	√	√	√
HCV PCR	√	√**	√**	
FBC				
Genotype	√*			
Quantitative PCR	√*			

* If not previously determined
** If PCR is positive, please schedule an appointment at The Rainbow Clinic (see under 'Contacts' for further details)

Follow-up of infants where mother is HBsAg positive

Mother	Birth	2 months	4months	6 months	8 months	
HBsAg+	Vaccinate with: HBIG (Hepatect CP®) **and** HBV	HBV (Given as part of 6:1)	HBV (given as part of the 6:1)	HBV (Given as part of the 6:1)	Blood for HBsAb and HBsAg	HBsAb ≥100 mIU = satisfactory HBsAb ≥10mIU and <100 by 2 assays. Give booster dose. HbsAb <10 mIU Check HbsAg result. If negative, reimmunise
HBcAb+ HBsAg-	Vaccinate with HBV	HBV (Given as part of 6:1)	HBV (given as part of the 6:1)	HBV (Given as part of the 6:1)	Blood for HBsAb and HBsAg	HBsAb ≥100 mIU = satisfactory HBsAb ≥10mIU and <100 by 2 assays. Give booster dose. HbsAb <10 mIU Check HbsAg result. If negative, reimmunise

HBsAg: Hepatitis B surface antigen HBcAb: Hepatitis B core antibody HBsAb : Hepatitis B surface antibody HBV: Hepatitis B Vaccine

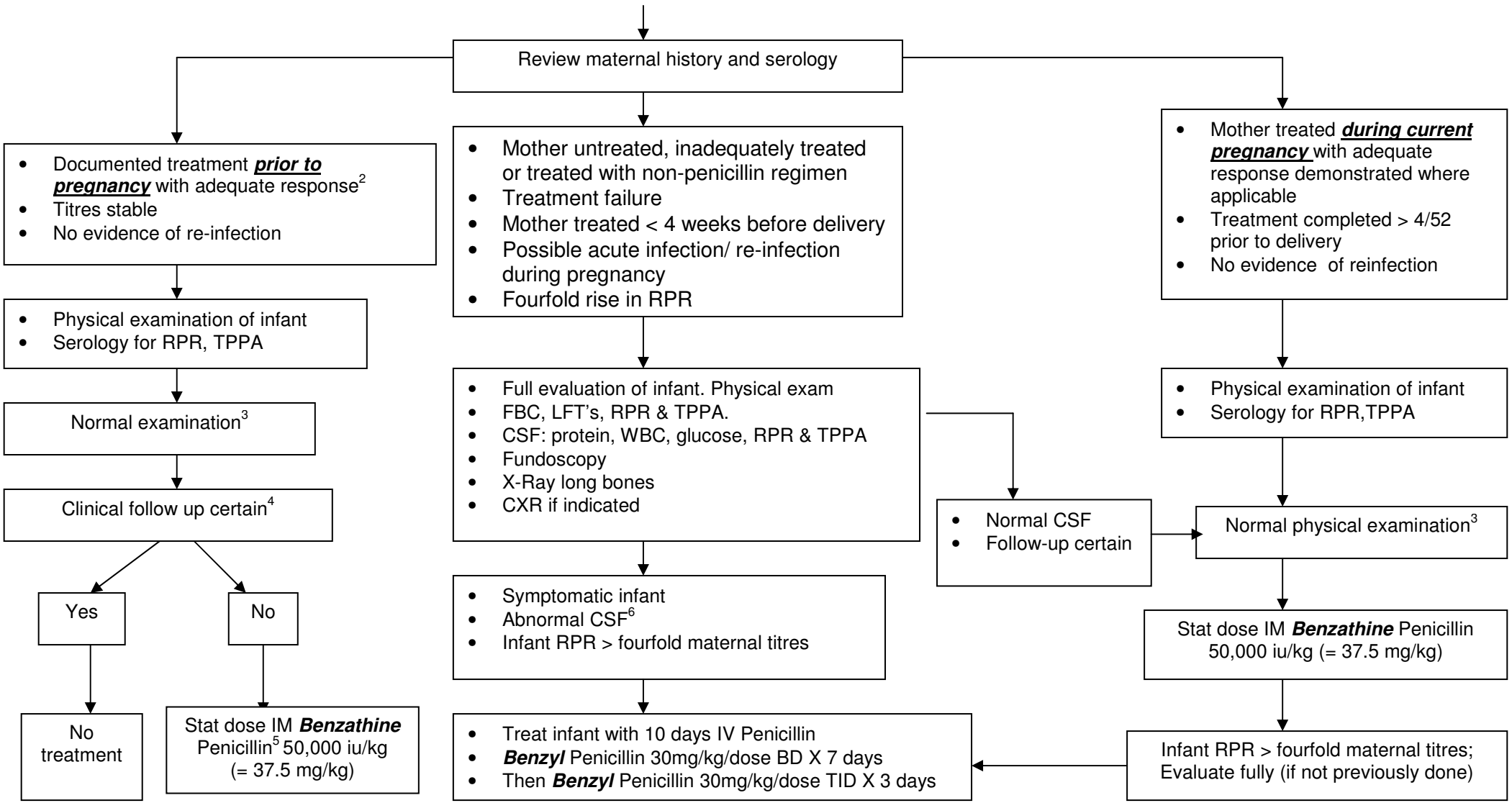
Notes: Infants who receive HBIG can also receive BCG vaccination at the usual time.

Review Date: April 2013

Appendix 9

Maternal Syphilis Serology Reactive & Confirmed Positive (RPR,TPPA)[1]

Ref: CDC 2006 Sexually Transmitted Diseases Treatment Guidelines. Congenital Syphilis



1. Maternal TPPA positive; RPR positive, neat or negative.
2. Maternal treatment prior to pregnancy with Penicillin regimen confirmed by adult services with serology post treatment documented.
3. No evidence of congenital infection at birth. Any infant with signs of congenital syphilis should receive full evaluation and treatment regardless of maternal treatment history.
4. Follow up clinical evaluation and RPR @ 6 weeks, 3, 6, 12 months or until 2 consecutive negative RPR's then discharge. In general if follow up uncertain infant should receive treatment with single dose Benzathine Penicillin.
5. **Procaine Penicillin is not a substitute for Benzathine Penicillin.**
6. CSF, WBC >5, protein >0.4g/l, Normal CSF does not exclude neurosyphilis. Interpret with clinical findings and serology.[In this context there is little evidence and expert opinion differs as to the appropriate CSF WBC threshold that requires treatment for neurosyphilis. Some experts accept up to 25 WBC, whereas others recommend treatment for neurosyphilis in infants at risk if CSF WBC is > 5. MMWR]
7. if > 1 day of therapy is missed, the entire course should be re-started.

Zidovudine (Retrovir)
Prescribing Information for Doctors Treating HIV Exposed Infants
Date: April 2011. Review Date: April 2013

Zidovudine is a Nucleoside Analogue used in newborn infants to reduce the incidence of HIV transmission from mother to infant. It is used alone or in combination with Lamivudine + Nevirapine.

Availability: Zidovudine (Retrovir) Syrup 10mg/ml
Zidovudine IV infusion 200mg/20ml

Dosing of Zidovudine for HIV exposed infants:

- ***Fullterm neonate:*** 4mg/kg 12hrly PO for 4 weeks.
- ***Preterm neonate:***
  (≤ 30 weeks gestation) 2mg/kg/dose 12hrly PO for 4 weeks
  (> 30 – 34 weeks gestation) 2mg/kg/dose 12hrly PO for 2 weeks ***then increase to*** 2mg/kg/dose 8hrly PO for a further 2 weeks
- ***Sick infants:*** Unable to take oral medications:
  Fullterm infant (≥34 weeks) IV dose: 1.5mg/kg 6hrly IV infusion
  Preterm infant (<34 weeks) IV dose: 1.5mg/kg 12hrly IV infusion

Therapy should be initiated as soon as possible following delivery, preferably within four hours.

- Zidovudine should preferably be administered 30 minutes before a feed, though this is not critical.
- Discontinue therapy after 4 weeks
- If the infant cannot tolerate PO then Zidovudine may be administered intravenously

Side effects:
Neutropenia and anaemia. Check FBC two weeks after initiating therapy or sooner if clinically indicated. Other potential side effects include nausea and vomiting, skin rash, headache, muscle pain and lack of energy or sleep disturbances.

If the infant develops neutropenia (ANC <0.8 x 10^9/l confirmed on 2 occasions) while taking Zidovudine, the following guidelines should be followed:

- Stop Zidovudine therapy for 3-5days.
- Repeat the FBC after the 3-5day-stoppage period.
- Reintroduce therapy depending on the ANC - the dose should be adjusted according to the table below.

Absolute Neutrophil Count (ANC x 10^9/l)	**What to do?**
<0.8	If after stopping therapy for 3-5days the ANC remains less than <0.8, **discuss with the Rainbow Team.**
0.8-1.5	If the ANC improves to between 0.8-1.5, Zidovudine should be restarted at two-thirds the normal dose. Check FBC again after 3-5days. Dose adjustments will depend on ANC result. If the ANC is >1.5 return to full dosage.
>1.5	If the ANC improves to greater than 1.5, restart Zidovudine therapy at normal dose and recheck FBC after 3-5days. If the ANC has decreased for a second time, stop therapy for 3-5days, recheck FBC and discuss with The Rainbow Team

Other information:

- Zidovudine is contraindicated in newborn infants with hyperbilirubinaemia requiring treatment other than phototherapy, or with increased transaminase levels of over five times the upper limit of normal.
- The infant should be clinically monitored for signs of mitochondrial toxicity.

References:

(1) Glaxowellcome Medical Information Department, 2000
(2) Neofax 2009 edition
(3) British HIV Association and Children's HIV Association Guidelines for the management of HIV infection in pregnant women. 2008 HIV medicine (2008), 9, 452-502

FOR FURTHER INFORMATION PLEASE CONTACT A MEMBER OF THE RAINBOW TEAM 01 409 6338

APPENDIX 11

LAMIVUDINE (EPIVIR, 3TC)
PRESCRIBING INFORMATION FOR DOCTORS TREATING HIV EXPOSED INFANTS

Date: April 2011 Review date: April 2013

The Rainbow Clinic
Our Lady's Children's Hospital Crumlin and
The Children's University Hospital, Temple Street

Lamivudine is a Nucleoside Analogue used in newborn infants to reduce the incidence of HIV transmission from mother to infant. It is used in combination with Zidovudine +/- Nevirapine

Availability: Lamivudine (Epivir, 3TC) Oral Solution 10mg/ml

Dosing:

Full term neonate: 2mg/kg/dose 12hrly PO for four weeks[1,2].
Discontinue therapy after four weeks.

- **Initiate treatment as soon as possible following delivery, preferably within 4hrs.**
- Lamivudine may be administered with or without a feed.

Side effects of Lamivudine:

Lamivudine is generally well tolerated, but some patients may experience neutropenia and anaemia. Check FBC two weeks after initiating therapy or sooner if indicated. Other potential side effects include diarrhoea, nausea and vomiting, abdominal pain, cramps, headache, rash, fatigue, malaise, cough and nasal symptoms, numbness, tingling sensation or a sensation of weakness in limbs. Pancreatitis has been reported. Stop therapy immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

If the infant develops neutropenia (ANC <0.8) while taking Lamivudine, the following guidelines should be followed:

4. Stop Lamivudine therapy for 3-5days.
5. Repeat the FBC after the 3-5day-stoppage period.
6. Reintroduce therapy depending on the ANC – dose adjustments are as follows::

Absolute Neutrophil Count (ANC x 10^9/l)	**What to do?**
<0.8	If after stopping therapy for 3-5days the ANC remains less than <0.8, the need to continue Lamivudine prophylaxis should be discussed with a member of the Rainbow Team.
0.8-1.5	If the ANC improves to between 0.8-1.5, Lamivudine therapy should be restarted at two-thirds the normal dose. FBC should be checked again after 3-5days and the dose adjusted accordingly. If the ANC at this time is >1.5 return to full dosage.
>1.5	Restart Lamivudine therapy at normal dose and recheck FBC after 3-5days. If the ANC has decreased for a second time, stop therapy for 3-5days, recheck FBC and discuss with Rainbow Team

Other information:

- Dosage reduction required in infants with renal impairment.
- The infant should be clinically monitored for signs of mitochondrial toxicity.

Reference:

(1) The Sanford Guide to HIV/AIDS Therapy 2004 (Moodley et al, Journal of Infectious Diseases 1998: 178; 1327-33)
(2) PENTA 2009 Guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. HIV Medicine (2009) 10, 591-613
(3) British HIV Association and Childrens HIV Association Guidelines for the management of HIV infection in pregnant women 2008. HIV Medicine (2008) 9, 452-502

FOR FURTHER INFORMATION PLEASE CONTACT A MEMBER OF THE RAINBOW TEAM 01 409 6338

Appendix 12

NEVIRAPINE (VIRAMUNE)
PRESCRIBING INFORMATION FOR DOCTORS TREATING HIV EXPOSED INFANTS

Reviewed April 2010
Review date: April 2013

The Rainbow Clinic

Nevirapine is a Non Nucleoside Analogue used in newborn infants to reduce the incidence of HIV transmission from mother to infant. It is used in combination with Zidovudine + / - Lamivudine.

Availability: Nevirapine (Viramune) Liquid 10mg/ml

Dosing of Nevirapine for HIV exposed infants:

- **Dose to be prescribed: 2mg/kg/dose PO(1) 2 doses only as outlined below.**

Management of Mother	**Infant should receive**
If the mother has never taken Nevirapine	***Two doses of Nevirapine***, one as soon as possible after delivery (preferably within 4 hours) and a second at 48-72 hours age
If Nevirapine is taken by mother throughout pregnancy	***Two doses of Nevirapine***, one at 24 hours age and one at 48-72 hours of age.
If just a single dose of Nevirapine is taken at onset of labour and there is at least **a 2 hour delay to delivery**	***Two doses of Nevirapine***, one at 24 hours age and one at 48-72 hours of age.
If just a single dose of Nevirapine is taken at onset of labour **but delivery occurs within 2 hours of maternal ingestion**	***Two doses of Nevirapine***, one as soon as possible after delivery (preferably within 4 hours) and a second at 48-72 hours age

- Nevirapine may be administered with or without food.

Side effects
Nevirapine is generally well tolerated, but some patients may develop rash, allergic reactions, vomiting, diarrhoea, and stomach cramps, headache, sleepiness and muscle pain. However, there are generally no side effects attributable to Nevirapine using just one or two doses as per this schedule.

Other information:

- This dosing schedule for nevirapine has been associated with the emergence of viral resistance the clinical significance of which remains to be determined.

Reference:

(1) The Sanford Guide to HIV/AIDS Therapy 2004 (Musoke et al, AIDS 1999, 13: 479-86 & HIV NET 006)
(2) WHO Consultative Meeting on the Use of NVP for the Prevention of Mother to Child Transmission in Women of Unknown Serostatus. Safety/Toxicity and Drug resistance Issues Related to Single Dose NVP Prophylaxis. (Lynne Mofenson 2003)
(3) Predose infant nevirapine concentration with the two dose intrapartum neonatal Nevirapine regimen: association with the timing of maternal intrapartum Nevirapine dose. Mirochnick et al. JAIDS 33:153-156, 2003

FOR FURTHER INFORMATION PLEASE CONTACT A MEMBER OF THE RAINBOW TEAM
01 409 6338

Appendix 13

DEVELOPMENTAL ASSESSMENT CHEKLIST Attach addressograph here

				Red Flags
Age 6 Weeks: Date:	***Doctor's name:***			
GM	Raising head from prone	**Y**	**N**	
FM	Tight grasp, hands fisted	**Y**	**N**	
LS	Alert to sound	**Y**	**N**	
SA	Fixes and follows to midline	**Y**	**N**	
Age: 2 months: ***Date***	***Doctor's name***			
GM	Chest up in prone	**Y**	**N**	*rolling before three months*
FM	Retains rattle	**Y**	**N**	*might indicate hypertonia*
LS	Coos, regards speaker	**Y**	**N**	
SA	Smiles socially, follows past midline	**Y**	**N**	
Age: 4 months: ***Date***	***Doctor's name***			
GM	Up on hands in prone, rolls front to back	**Y**	**N**	*head lag, poor head control*
FM	Reaches, obtains and retains rattle, bring hands to midline	**Y**	**N**	
LS	Laughs, orients to voice	**Y**	**N**	
SA	Recognises mother	**Y**	**N**	
Age: 6 months: ***Date:***	***Doctor's name***			
GM	Sits unsupported, puts feet in mouth	**Y**	**N**	
FM	Transfer objects hand to hand, raking grasp	**Y**	**N**	
LS	Babbles "baba" "gaga", lateral orientation	**Y**	**N**	*absent babbling may indicate*
SA	Recognises strangers	**Y**	**N**	*hearing deficit*
Age: 18 months: ***Date***	***Doctor's name***			
GM	Runs, throws objects from standing without falling	**Y**	**N**	*If not walking - refer hand dominance prior to 18 mnths*
FM	Tower 3-4 cubes, scribbling, turns 2-3 pages at a time	**Y**	**N**	*points to contra lateral weakness*
LS	Points to 3 body parts, points to self, 7-10 words	**Y**	**N**	*lack of social relatedness may*
SA	Plays with other children, feeds with spoon, imitates parents	**Y**	**N**	*indicate autism*
Age: 2 years: ***Date***	***Doctor's name***			
GM	Walks up and down steps without help	**Y**	**N**	
FM	Tower 7 blocks, turns page one at a time, removes shoes/socks	**Y**	**N**	
LS	Uses I, you, me. 40 word vocabulary. 2 word sentences	**Y**	**N**	
SA	Parallel play	**Y**	**N**	
Age: 5 years: ***Date***	***Doctor's name***			
GM	Skips alternate feet, jumps over low obstacles	**Y**	**N**	
FM	Copies triangle, ties shoes, spreads with knife	**Y**	**N**	
LS	Ask what a word means, repeats story	**Y**	**N**	
SA	Plays competitive games, understands rules	**Y**	**N**	

GM: Gross Motor. FM: Fine Motor. LS: Language Skills. SA: Social/Adaptive