



Preventing Perinatal Transmission:

A practical guide to the antenatal and perinatal management of

HIV

Hepatitis B

Hepatitis C

Herpes Simplex

&

Syphilis

Ultimately each pregnancy calls for an individualised care plan.

To replace all previous editions

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The Rainbow Clinic

**Our Lady's Children's Hospital, Crumlin, &
The Children's University Hospital, Temple Street.
Dublin, Ireland**

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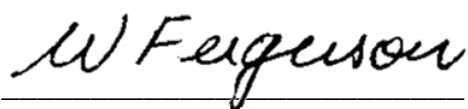
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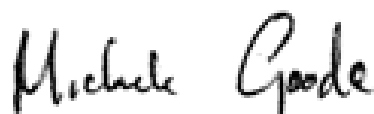
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Glossary

ABC	Abacavir
ACV	Acyclovir
ARV	Antiretroviral
ART	Antiretroviral therapy
cART	Combination antiretroviral therapy
GRT	Genotypic resistance testing
NVP	Nevirapine
RAL	Raltegravir
SD-NVP	Single dose nevirapine
TDF	Tenofovir
T20	Enfuvirtide
ZDV	Zidovudine
3TC	Lamivudine
ARM	Artificial rupture of membranes
ELCS	Elective Caesarean Section
EMCS	Emergency Caesarean Section
PROM	Prolonged Rupture of membranes
ROM	Rupture of membranes
SOL	Spontaneous onset of labour
HIV	Human immunodeficiency virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HSV	Herpes simplex virus
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
HBcAb	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody or antibody to hepatitis B surface antigen (also written as HBsAb)
Anti-HBe	Hepatitis B e antibody or antibody to hepatitis B e antigen (also written as HBeAb)
Anti-HBc	Hepatitis B core antibody or antibody to hepatitis B core antigen (also written as HBcAb)
HBIG	Hepatitis B immune globulin (Preparation currently available in Ireland is Hepatect CP [®])

Scope and purpose of this document

- To provide guidance on best clinical practice in preventing perinatal transmission and management of antenatal and perinatal exposure to HIV, HBV, HCV, HSV and syphilis
- The document is aimed at clinical professionals directly involved in the care of pregnant women and their infants and is designed to be clinically and practically relevant
- Information relating to management of HIV was prepared, revised and updated by the HIV in Pregnancy Network Committee who meet monthly to discuss individual treatment and care plans of HIV positive pregnant women currently in their care and for their infants when born
- The committee is comprised of experts in the field of obstetrics, midwifery, adult HIV physicians & nurses and paediatric ID physicians & nurses
- Recommendations are proposed by the committee based on current literature and best international clinical practice
- The draft document was disseminated to relevant stakeholders for review and comment prior to its ratification
- Recommendations will be updated in 2018, however if, in the interim, clinically important information becomes available, amendments to the current recommendations will be made before the next revision date
- This document is available on line: at www.ssstdi.ie/guidelines

Key Points HIV

In Ireland, HIV positive women of known status in pregnancy who receive timely antenatal antiretroviral therapy, are adherent to therapy, and are virally suppressed at delivery have a less than 1 in 1,000 chance of having an HIV infected infant

Antenatal Management

- Ensure failsafe mechanism in place to obtain antenatal HIV test results in a timely manner
- In the event of a positive test result contact an adult HIV service for advice as soon as the 1st result is available
- **DO NOT** wait for the results of confirmatory repeat testing before contacting adult services
- Assess for co-infections including STI screen
- For various scenarios see Appendix 1

Late Bookers (i.e. after fetal viability):

- Request **URGENT HIV** testing and organise a quick turnaround of results with the relevant testing facility

Starting antiretroviral (ARV) treatment in pregnancy

- ARV therapy should be started as soon as possible after the first trimester

Continuing ARV treatment in pregnancy

- In general, for women virally suppressed and stable on ARVs, conception is not an indication to change treatment choice

Intrapartum Management

- Where possible avoid artificial rupture of membranes (ARM)
- Avoid fetal scalp electrodes or fetal blood sampling
- Limit duration of rupture of membranes

Intra-Partum ARVs

- Oral ARVs should be continued in labour
- Intra-partum zidovudine (ZDV), see Appendix 2
 - Intra-partum ZDV is no longer considered necessary for
 - Women who are stably virally suppressed on ARVs and for whom no additional risk factors for HIV transmission have been identified
 - Intra-partum intravenous ZDV is indicated for:
 - Women in premature labour and/or with preterm ROM (< 37 weeks)
 - Women receiving ZDV monotherapy, (with exception of elite controllers)
 - Women with a 36 week viral load of >40 copies per millilitre (c/ml) (excludes women fully suppressed with a single unanticipated low level blip (i.e. to ≤ 400 c/ml)
 - Any woman who has received <4 weeks ARVs
 - Any woman who is non-adherent to treatment
 - Women scheduled for elective Caesarean section (ELCS) for the prevention of HIV transmission

- Other ARVs.
 - In certain situations mothers may be given single dose nevirapine, raltegravir, double dose tenofovir or other agents to rapidly reduce maternal viral load and preload the infant e.g. for late presenting ARV naïve women or those with a high viral load despite treatment.

Mode of Delivery

Viral load at ~36/40

- **≤40 copies/ml**
 - **Vaginal delivery** is recommended for women whose 36 week HIV viral load is ≤40 copies/ml, who have received 4 weeks ARVs and in whom there are no concerns regarding adherence or poor virological response.
- **>40 but ≤400 copies/ml**
 - For women with a viral load between 40 and ≤400 copies/ml the recommendation regarding mode of delivery will be guided by factors including duration of antenatal ARVs, trajectory of viral load response to ARVs, maternal adherence to ARVs.
- **>400 copies/ml**
 - **ELCS** at 38-39 weeks gestation is recommended for women whose HIV viral load late in the third trimester is >400 c/ml and for those receiving ZDV monotherapy with the exception of 'elite controllers'. Elite controllers, even those on ZDV monotherapy, can aim for a vaginal delivery.

Neonatal Management

- Minimise direct infant exposure to maternal blood (avoidance of scalp electrodes, bathe infant after delivery, clean eyes with saline)
- **ARV neonatal prophylaxis**
 - A four week neonatal ZDV regimen is standard for infants of women who received ARVs in pregnancy, are stably virally suppressed and there are no concerns re maternal adherence
 - A four week triple therapy regimen (4 weeks ZDV and lamivudine (3TC) coupled with 2 doses of nevirapine (NVP) within the first 48 – 72 hours) is used in Ireland for all other infants
 - Alternative combination ARV regimens may be occasionally used as directed by the paediatric HIV specialist
- Continuation of maternal ARVs post-delivery can significantly reduce, but does not eliminate the risk of HIV transmission through breast milk. In Ireland, as safe alternatives exist, breast feeding should be avoided
- All HIV exposed neonates should receive hepatitis B virus (HBV) vaccine prior to hospital discharge, even if mother is HBsAg negative
- For monitoring and follow-up of the exposed infant see Appendix 2

Key Points Hepatitis B

All women should be offered testing for HBV in pregnancy

Appropriate intervention can prevent vertical transmission in 90 – 95% cases

Antenatal Management

- Refer all newly diagnosed women to adult HBV services
- Where transmission risk is high, maternal antiviral medication may be used to reduce maternal Hepatitis B viral load and thus reduce transmission risk

Intrapartum Management

- Minimise direct infant exposure to maternal blood (avoid invasive fetal monitoring).

Mode of Delivery

- Maternal HBV infection does not alter decisions regarding mode of delivery

Neonatal Management

- Bathe infants and clean eyes as soon as possible following delivery
- Immunisation post delivery
 - Mother Hepatitis B surface antigen (HBsAg) positive:
 - Give hepatitis B immunoglobulin AND hepatitis B vaccine as soon as possible and within 12 hours of delivery
 - Mother HBsAg negative and core Antibody (HBcAb) positive or known family member with hepatitis B infection i.e. HBcAb positive:
 - Give neonate first dose of HBV vaccine prior to hospital discharge
- Maternal HBV infection is not a contraindication to breastfeeding which can be initiated in the usual way following delivery
- HIV/HBV co-infected women in Ireland should not breastfeed their infants because of the risk of HIV transmission.
- Infants who receive Hepatitis B Immunoglobulin can receive neonatal BCG vaccination.
- Ensure defined pathway for infants of HBsAg positive women to complete infant HBV vaccination (usually as part of primary immunisation programme) and have follow up serology testing.
- For follow up of the exposed infant see Appendix 6

Key Points Hepatitis C

HCV testing in pregnancy is not universally offered

HCV testing is indicated for women with HIV or HBV infection or other HCV risk factors e.g. recreational drug use, tattoos, or a partner with either HCV or history of recreational drug use

Antenatal Management

- Refer women with newly diagnosed HCV to adult HCV services
- Current HCV treatments are not recommended for use in pregnancy

Intrapartum Management

- Minimise direct infant exposure to maternal blood (avoid invasive fetal monitoring).

Mode of Delivery

- To date, no obstetric intervention has been proven to reduce the risk of HCV transmission.
- ELCS is no longer recommended for the prevention of HCV transmission in HIV/HCV co-infected women.

Neonatal Management

- Bathe infants and clean eyes with saline as soon as possible following delivery
- Breastfeeding is not contraindicated for HCV mono-infected women
- HIV/HCV co-infected women in Ireland should not breastfeed their infants because of the risk of HIV transmission.
- For follow up of the exposed infant see Appendix 6

Key Points Herpes Simplex Virus

Awareness of maternal genital HSV infection in pregnancy is important in order to ensure that a plan is in place to minimize the risk of neonatal HSV

Primary maternal HSV infection in the third trimester represents the greatest risk for neonatal disease

Antenatal Management

- All women with genital ulceration in pregnancy should have history of genital herpes or history of prior episodes of genital ulceration sought, lesions swabbed for HSV PCR, and blood taken for HSV type specific antibodies. Repeat syphilis and HIV serology.
- Women who experience a **first episode genital herpes in the first or second trimester** should receive prophylactic antiviral medication throughout the third trimester (e.g. prophylactic dose - acyclovir 400mg BD or valacyclovir 500mg once daily).
- Treat women with a **first episode of genital herpes in the third trimester** with antiviral medication (e.g. treatment dose - acyclovir 400mg TDS for 5 days or valacyclovir 500mg BD for 5 days) and continue prophylactic antiviral medication until delivery.
- In women with a history of **recurrent genital herpes**, treat episode(s) with acyclovir 400mg TDS for 5 days or valacyclovir 500 mg BD for 3 – 5 days. Prophylactic antiviral medication in the third trimester is recommended (eg. acyclovir 400mg BD or valacyclovir 500mg once daily).
- Consultation with or referral to an adult STI service is recommended, particularly if there is any doubt regarding management
- See HSV algorithms Appendix 7

Intrapartum Management and Mode of Delivery

- Vaginal delivery can be anticipated in women with a history of **recurrent genital herpes** or with **first episode genital herpes in the first or second trimester**, provided it is at least six weeks since the episode and there are no visible genital lesions at labour onset
- Delivery by caesarean section should be offered to all women with visible genital herpetic lesions at presentation in labour (includes all women with a history of **recurrent genital herpes** or with **first episode genital herpes in the first or second trimester**, or with **first episode genital herpes in labour**)
- Delivery by ELCS is recommended in women with **first episode genital herpes in the third trimester when the episode occurs within 6 weeks of estimated delivery date**
- Individualised care plans with multidisciplinary input to evaluate the competing risks are required in the event of premature labour or preterm prolonged rupture of membranes

Neonatal Management

Management of symptomatic infants

- Any infant with signs or symptoms suggestive of HSV or with positive HSV PCR from any site should be treated with intravenous acyclovir.

Management of asymptomatic infants (Appendix 8, HSV scenarios I – IV)

- Asymptomatic infants delivered vaginally or by caesarean section to women with suspected first episode of infection at or within six weeks of delivery should be managed as **high risk** infants

- Asymptomatic infants delivered vaginally **or** by caesarean section to mothers with a history of recurrent HSV or with a first episode more than 6 weeks prior to delivery but **with** visible lesions should be managed as **intermediate risk** infants
- Infants born to mothers with a history of recurrent HSV or with first episode more than six weeks prior to delivery **without** visible lesions at delivery should be managed as **low risk** infants
- Direct contact between neonates and active HSV skin lesions in health care workers or other family members should be avoided

Key Points Syphilis

Women testing positive for syphilis must be evaluated for previous syphilis treatment, risk of re-infection and response to treatment

Clear documentation of maternal treatment and maternal response to treatment is essential in order to avoid unnecessary neonatal investigation and treatment

Antenatal Management

- All women should have antenatal syphilis screening
- Robust local mechanisms should be in place to ensure results are checked, appropriate action taken and a neonatal management plan in place prior to delivery
- Women with newly diagnosed syphilis in pregnancy should be referred to adult Genitourinary or Infectious Diseases services for treatment and partner notification
- Women with a history of previously treated syphilis should have previous treatment and treatment response confirmed and risk for re-infection assessed. Where there is any doubt about previous treatment, treatment response or risk of re-infection, referral to adult Genitourinary or Infectious Diseases services is recommended.

Intrapartum Management and Mode of Delivery

- Maternal syphilis infection does not alter decisions regarding mode of delivery
- Post delivery, histopathological examination of the placenta should be performed on all cases

Neonatal Management

- For management of the exposed infant see Appendix 9, Syphilis 2013 algorithm

Human Immunodeficiency Virus (HIV)

Background

In 1994, the administration of ZDV to pregnant women was shown to reduce mother to child transmission (MTCT) of human immunodeficiency virus (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 caesarean 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.

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% peripartum. The overall risk of transmission in untreated women varies from 20-40% compared with <0.1% in treated women who are adherent to management recommendations.

The use of antiretroviral treatment, antenatally and for the infant, is the single most effective way to reduce transmission risk. In selected cases elective caesarean section delivery is beneficial. Breastfeeding is also associated with a significantly increased risk of transmission and should be avoided where safe alternative feeding is available. Both suppressive maternal ARV therapy and extended neonatal PEP can significantly reduce the risk of transmission through breast feeding. Nonetheless there remains a level of transmission risk that cannot be precisely quantified even for fully virally suppressed woman, thus where safe formula feeds are available breast feeding is strongly discouraged for this group. In Ireland, all HIV infected women are advised to exclusively bottle feed their infants with formula milk.

Avoidance of breastfeeding is culturally challenging for some women, particularly those from Sub Saharan Africa. Their natural reluctance to formula feed may also be increased by the knowledge that in their home countries, because of the increased morbidity and mortality associated with formula feeding in that environment, exclusive breast feeding for the first six months of life with concurrent use of ARVs is recommended. This is an area that must be sensitively explored with the woman and explanations for the difference in approach given. All practical support should be offered as necessary including possibility of lactation suppression. Should a fully informed woman insist on breastfeeding, full discussion with adult and paediatric services is essential so that maternal therapy and infant prophylaxis can be planned. This strategy will only be entertained in exceptional cases and only if a mother is fully virally suppressed with an excellent adherence record. For women who are not ARV suppressed and/or not virally suppressed, breastfeeding cannot be permitted and has on occasion required extended infant hospitalisation or other interventions to ensure that such does not happen.

The transmission of HIV from mother to infant in association with maternal pre-mastication of solid food that is then given to very young infants has been reported. Parents should be advised against such practices.

Risk Factors for HIV Transmission

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 can decrease risk

- Knowledge of maternal status antenatally
- ARVs in pregnancy
- Elective caesarean section
- Avoidance of invasive monitoring of infant during labour
- Bottle-feeding with formula milk
- Neonatal post exposure prophylaxis i.e. antiretroviral therapy to the infant for the first 4 weeks of life

Care of the HIV+ Pregnant Woman

General Considerations

Confidentiality

Receiving a diagnosis of HIV in pregnancy can be traumatic. It takes time to adjust to the diagnosis. Patient confidentiality must be respected at all time, 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.^{2,3} 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. 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. **There is no need for additional infection control measures or single rooms where a 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 adult HIV physician promptly for advice. For any issues relating to infection control please speak to your infection control team.

Antenatal Care

The HIV test

Any woman who is pregnant deserves to be offered an HIV test. 'Opt-out' antenatal screening, whereby all women are offered routine testing but can elect to decline the offer, is of proven benefit and used in Ireland.^{5,6} 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 an urgent referral to adult HIV services **without waiting for the results of a second confirmatory HIV test**.

Women who decline testing

- Women who decline testing when first offered, should be counselled and testing re-offered. Such 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 declined testing throughout pregnancy may consent to testing the infant in the neonatal period. This is strongly recommended

Response to the test result

Ensure that there is a failsafe mechanism in place to obtain HIV test results in a timely manner. Contact an adult HIV service for advice as soon as a 1st positive result is available.

DO NOT wait for the results of a second confirmatory HIV test

Women identified with or known to be HIV positive and pregnant

- Inform the woman of her diagnosis
- Refer promptly to adult HIV service. If the woman presents at or after fetal viability make contact with adult HIV services within 1-3 working days, depending on the gestational age. (Contact details for relevant services are listed in Appendix 11)
- Refer to paediatric HIV service

Paediatric service referral

Antenatal discussion between the expectant mother and 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
- Infant feeding
- Monitoring and treatment of infant
- Infant outcome

Recommendations are communicated in writing to the Obstetric team.

Pregnant HIV+ women who refuse to attend an adult HIV clinic

- Encourage attendance and explore reasons for refusal with the woman.
- Discuss with adult HIV care providers
- Clinical evaluation
- Investigations as per recommendations of adult HIV service
- Discuss with the paediatric HIV service to enable development of a neonatal management plan

Unbooked women who present in labour

- Women presenting unbooked in labour should have an urgent HIV test
- Make direct contact with the testing laboratory to ensure a rapid test turn around
- Explain the urgency of the situation and arrange for delivery of the test result to the treating physician
- In the event of a positive result please contact adult and paediatric HIV services as soon as possible
- Follow recommendations as detailed in Appendix 1
- Rapid point of care testing can be used if available but does not replace the need for laboratory test. If a woman presenting in labour has a reactive point of care test, contact adult and paediatric services as soon as possible and arrange urgent referral, see Appendix 11 for contact details

Women without an antenatal HIV test

It is strongly recommended that infants of women without an antenatal HIV test be tested as soon as possible following delivery and results available within 48 hours to enable use of neonatal post exposure prophylaxis (PEP) and consideration of infant feeding.

HIV negative women who are pregnant and at continued risk

HIV seroconversion in pregnancy remains a residual source of paediatric HIV infection.^{7, 8, 9} A single negative HIV test in pregnancy does not always exclude HIV infection. The cost effectiveness of a routine second HIV test in pregnancy was examined in the Irish context in 2011 and was not cost effective <http://www.higa.ie/publications>. Thus, as repeat testing in pregnancy is not routine it is important to keep the possibility of HIV acquisition during pregnancy under consideration and to request repeat testing if there are concerns. Such cases should be discussed with HIV services who will make recommendations regarding timing of repeat testing and where indicated, use of HIV post exposure prophylaxis.

Repeat testing in pregnancy and/or postnatally

- 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
- Please liaise with adult HIV services on timing of repeat test

Antiretroviral therapy for HIV+ 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. There is accumulating safety data and international experience that overwhelmingly favours the use of ARVs in pregnancy to reduce MTCT of HIV. In general, for women stable on effective ARVs, conception is not an indication to change treatment choice.

For women initiating or reinitiating ARVs in pregnancy, therapy should start as soon as possible after the first trimester and definitely before fetal viability. Observational data has demonstrated an association between duration of maternal ARVs and risk of HIV transmission; the lowest transmission being observed in those on ARVs pre conception.¹⁰

In the non-pregnant HIV infected population the need for ARVs is determined by the status of the immune system which is reflected by the CD4 count, normally 400 -1400 x 10⁶/L. Current international guidelines strongly recommend ARVs for anyone who is symptomatic, for all with a

CD4 count of $\leq 350 \times 10^6/\text{L}$ and for those with $CD4 >350 - 500 \times 10^6/\text{L}$ depending on individual circumstances,^{11,12} with some recommending consideration of treatment for all who are HIV-1 positive.¹³

Generally:

- For women with a CD4 count $\leq 350 \times 10^6/\text{L}$ at presentation, ARV therapy for maternal health is warranted and should be initiated as soon as possible and continued post partum. It is reasonable to wait until after the first trimester in women with CD4 counts $\geq 200 \times 10^6/\text{L}$
- Women with CD4 counts of $<200 \times 10^6/\text{L}$ require *Pneumocystis carinii* pneumonia (PCP) prophylaxis in addition to ARVs. First line PCP prophylaxis 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. Regular administration of even small doses of folic acid appears to negate this additional risk.¹⁴
- For women with CD4 count $>350 \times 10^6/\text{L}$ but $\leq 500 \times 10^6/\text{L}$, ARVs are indicated for maternal health in certain circumstances (e.g. coinfection with HBV or HCV) and should be initiated as soon as possible
- For women with a CD4 count of $>500 \times 10^6/\text{L}$ 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.^{10,15} This together with the accumulating safety data has resulted in a move towards earlier initiation of ARVs in pregnancy. Early initiation is of particular importance where there are risk factors for prematurity, (e.g. previous premature delivery, twin and higher order pregnancy). The woman's HIV physician will determine the choice of ARV regimen. In this group of women ARVs may be discontinued post partum. The decision is made by the adult HIV physician in conjunction with the woman. Factors that favour continuing ARVs post partum in women with a presenting CD4 of $>350 - 500 \times 10^6/\text{L}$ include: HCV/HBV co-infection, HIV negative partner and likelihood of future pregnancies
- In certain circumstances (i.e. high CD4 counts, low level HIV viremia, and absence of hepatitis B/C co-infection) ZDV monotherapy may be considered for the prevention of perinatal transmission. In general, if ZDV monotherapy is used intra-partum IV ZDV, ELCS and neonatal ZDV are also recommended. (Worldwide production of ZDV 250mg and 300mg tablets has ceased which may make ZDV monotherapy less feasible)
- Elite controllers are a small subset of HIV infected individuals who without ARVs have undetectable HIV RNA in plasma as assessed by more than one assay on more than one occasion and maintain CD4 counts $>350 \times 10^6/\text{L}$. For these, ZDV monotherapy or combination ARV therapy can be used to prevent perinatal transmission. Regardless of ARV type selected a normal delivery can be anticipated.

ZDV was traditionally the cornerstone of therapy to prevent vertical transmission because of its ability to cross the placenta (and thus acts as pre and post exposure prophylaxis for the infant), experience with other agents has steadily increased. 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.

Treatment of women to prevent perinatal transmission usually includes 3 active antiviral agents, often 2 nucleoside reverse transcriptase inhibitors and a boosted protease inhibitor. NNRTI and integrase inhibitor regimens can also 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 paediatric team, towards the end of the pregnancy, decides the

management of the infant 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

Intra-Partum ARV's

Oral antenatal ARVs should be continued in labour

Intravenous Zidovudine (ZDV)

- Intra-partum intravenous ZDV is no longer considered necessary for women who are stably suppressed on ARVs¹⁶
- Intra-partum intravenous ZDV is indicated for:
 - Premature labour and/or preterm ROM (<37 weeks)
 - Women receiving ZDV monotherapy, (exception may be made for elite controllers)
 - All women with a 36 week viral load of >40 copies/ml
 - Any women who has received <4 weeks ARVs
 - Any women who is non-adherent to treatment
 - Women undergoing ELCS for the prevention of HIV transmission
- When to start IV ZDV:
 - Commence IV ZDV infusion when labour is diagnosed or 3 hours prior to elective caesarean section.
- Duration & Dose IV ZDV
 - 2mg/kg loading dose over 1 hour followed by 1mg/kg/hr until delivery is complete. (Appendix 3).
- In situations of emergency delivery for the purpose of preventing HIV transmission, completion of the 1 hour loading dose (where obstetrically feasible) prior to delivery is recommended

Oral ARV's for intrapartum use

In certain situations, oral antiretroviral agents may be used to rapidly reduce viral load and to preload the infant as prophylaxis. Because of their good oral bioavailability, rapid onset of action and ability to cross the placenta, raltegravir (RAL), nevirapine (NVP) and tenofovir (TDF) can be useful where there is urgency in bringing about a rapid reduction in viral load and to preload the infant. Maternal administration of single dose nevirapine (200mg stat dose) has been associated with the development of resistance to this agent and other agents in this class. When a decision to use SD NVP is made, this risk must be recognised. The administration of other oral ARVs at the same time may reduce this risk and the adult HIV physician will make recommendations in this regard.

These agents may be useful in the following situations:

- Mothers who are not, or are not anticipated to be virally suppressed at labour onset may be prescribed SD-NVP (200mg single dose) or RAL (400mg stat dose) in addition to their existing ARV regimen, both for its effect on maternal viraemia and by virtue of their ability to cross the placenta, provides pre exposure prophylaxis for the infant.
- Mothers who labour prematurely may also be prescribed SD-NVP, RAL or a double dose of TDF (may be administered as tenofovir 245mg, 2 tablets **or** Truvada[®] 2 tablets) in order to achieve prophylactic levels in an infant who may not be able to tolerate oral medications in the immediate postnatal period.
- Mothers diagnosed in labour.

Delivery

The success of antenatal ARVs in reducing perinatal transmission of HIV means that for the majority of HIV infected women on suppressive ART before delivery, labour can be managed more like the general obstetric population. 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 weeks ARV therapy was 0.4%. 56% were delivered vaginally, 24% by emergency caesarean section and 20% by planned caesarean section delivery.⁸

It remains prudent to:

- Where possible avoid artificial rupture of membranes (ARM)
- Avoid fetal scalp electrodes or fetal blood sampling

Management of pre-labour spontaneous rupture of membranes

A meta-analysis of HIV infected women, most of who were receiving ZDV monotherapy or no therapy, showed an incremental increase in risk of HIV transmission with duration of membrane rupture. It is not clear how soon after rupture of membranes the benefit of ELCS to reduce this risk is lost. It is also not clear whether a similar increase in risk occurs in women who are on combination therapy and virally suppressed. Two recent studies have explored this issue. Of 210 women in Canada on ARVs with VL <1000 copies/ml (c/ml), 80% were <50 c/ml. The median duration of ROM was short at 0.63 hours but ranged up to 77.8 hours, yet no transmissions were identified, thus no incremental increase risk by duration of ROM could be identified, however the numbers are relatively small with only 59 women having ROM > 4 hours.¹⁷ A US study of a prospective cohort of 707 women found transmission rates of 1% and 1.9% for ROM less than and more than 4 hours overall, with no difference for the subgroup of 493 women with delivery VL <1000c/ml. The duration of membrane rupture >4 hours did not appear to be a risk factor for transmission in women on combination ARVs with a viral load <1000 c/ml.¹⁸

Thus while every effort should be made to safely minimise this risk, decisions whether to expedite delivery, through induction or caesarean section delivery in women with pre-labour ROM must be individualised balancing potential risks and benefits.

Management of term, pre-labour ROM

- In all cases of **term** pre-labour ROM delivery should be expedited
- If maternal VL is suppressed (≤ 40 c/ml) immediate induction of labour is recommended
- In women with a detected VL >40 to 999 c/ml when last measured, caesarean section delivery should be considered taking into account the actual VL, the trajectory of the VL, length of time on treatment, adherence issues, obstetric factors and the woman's views. If VL is stably ≤ 400 c/ml and there are no additional risk factors for transmission, vaginal delivery is a potential option
- If maternal VL >999 c/ml, immediate caesarean section following IV ZDV loading i.e. 2mg/kg over 1 hour, is recommended

Management of pre-term, pre-labour ROM

- In pre-term (<37 weeks), pre-labour ROM, delivery decisions must be based on best obstetric practices and are dependent on degree of prematurity and HIV transmission risk.
- Steroids should be given, if appropriate, to accelerate lung maturity in accordance with normal obstetric practice.

Elective Caesarean Section

The role of elective caesarean section (ELCS) in reducing the risk of mother to child transmission of HIV has been established in women who have not received any ARVs.^{19,20,21} and in those in receipt of ZDV monotherapy¹ (with the exception of elite controllers). Therefore,

in Ireland, for HIV infected women who have not received antenatal antiretroviral therapy and for those in receipt of zidovudine monotherapy the recommendation is for delivery by elective caesarean section.

In women on antenatal ARVs without complete virological suppression (viral load >40 c/ml) the viral load threshold above which an ELCS is necessary is not precisely known. Data from the French antenatal cohort study demonstrated that in women on ARVs with a delivery viral load ≤ 400 c/ml, the transmission rate was 0.4% for ELCS versus 0.5% for all other modes of delivery suggesting that for women in receipt of ARVs with a HIV VL ≤ 400 c/ml, ELCS may not provide any additional benefit in terms of averting transmission.¹⁰ In contrast, the data from the European Collaborative Study demonstrated an 80% reduction in transmission risk for women on ARVs with HIV viral load <400 c/ml, AOR 0.20 [0.05-0.65].²² Based on the available data in Ireland, ELCS to prevent HIV transmission is recommended for women with a 36 week viral load of >400 c/ml. In women with a 36 week HIV viral load between 40 and 400 c/ml, recommendations regarding the mode of delivery will be influenced by duration of antenatal ARVs, trajectory of viral load response to ARVs and maternal adherence to ARVs.

The role of ELCS in women on suppressive combination ARVs has not been determined in a randomised controlled trial, but recent data from the UK and Ireland of over 4000 mother–infant pairs did not demonstrate a difference in transmission rates between vaginal and caesarean section delivery in those on ARVs (median HIV viral load <50 c/ml).²³ Therefore, in Ireland, for HIV infected women on antiretroviral therapy with a HIV viral load of ≤ 40 c/ml, the recommendation is for vaginal delivery (where obstetrically appropriate).

Post Partum

Maternal care

Some women taking ARV solely to prevent perinatal transmission may 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

Minimise exposure of HIV to the infant by:

- Clamp cord ASAP to minimise the risk of maternal-fetal micro transfusions
- Avoid nasopharyngeal suction
- Clean eyes with saline 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.

Neonatal antiretroviral prophylaxis

Choice of post exposure prophylaxis for the infant will depend on both the timing of maternal diagnosis of HIV, maternal adherence, maternal ARV history, 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. **Dose modification for prematurity may be required – see Appendix 3.**

Neonatal Prophylaxis:

- ZDV (AZT/Retrovir) monotherapy for first four weeks of life where the risk of transmission is lowest - i.e. women consistently virally suppressed on ARVs. Confirm that:
 - Mother received at least 4 weeks antenatal ARV
 - Maternal HIV Viral load ≤ 40 c/ml at 36 weeks, or thereafter, prior to delivery
 - Rupture of membranes <12 hours

- *All other infants receive triple therapy -*
 - Zidovudine (ZDV /AZT/Retrovir) for four weeks *and*
 - Lamivudine (3TC/Epivir) for four weeks *and*
 - Nevirapine. (Viramune) **Two doses only.**

If the neonate is unable to take oral ZDV, an IV preparation is available (see Appendix 3). Lamivudine and NVP are not available in IV formulations.

In the event that a premature delivery is anticipated such that the infant might not be expected to tolerate oral medications, preloading the infant through the administration of a double dose of TDF to the mother together with either NVP or RAL in addition to the IV ZDV can result in good infant ARV levels during the critical time of delivery. For high risk situations intravenous infant T20, an HIV fusion inhibitor, can be also be used in addition to IV ZDV where oral therapy is precluded.

Determining Infant status

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. 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 uninfected 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, are off ARVs, have never had a positive HIV PCR test and who have serial negative HIV PCR tests up to and including at ≥3 months of age are not HIV infected. Infants will continue in follow-up until seroreversion is confirmed at 24 months of age.

It is important to note that **infected** infants who receive suppressive early treatment, commencing in the first days of life, may fail to develop an antibody response and test HIV antibody negative while on ARVs and, in exceptional instances, for some limited period thereafter.^{24, 25}

Maternal Refusal of Treatment/Care Recommendations

In the event of an HIV positive woman refusing to link with specialist services or refusing management to reduce mother to infant transmission, guidance must be sought from specialist services, on each individual situation, to determine the best strategy.

Antenatal care of women who refuse treatment

Discuss the benefits and risks of potential interventions.

Peripartum care of women who refuse treatment

A woman, who refuses ARV in pregnancy, might be willing to take a single dose of nevirapine or raltegravir at labour onset and accept an ELCS with peripartum intravenous ZDV. Please contact the adult HIV team as soon as possible as additional ARV therapy may also be recommended to reduce the risk of development of resistant virus.

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. 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.

HIV positive mothers who insist on breast feeding

Ensure the woman is making a fully informed decision. Although the transmission risks are reduced, women virologically suppressed on ARVs, can still transmit HIV through breast feeding.

IF and only if the mother adamantly refuses bottle feeding, breast feeding could be considered provided:

- the mother remains on combination ARVs
- is reliably adherent
- has an undetectable viral load and
- is willing to attend for monthly viral load assessment
- is willing to exclusively breast feed (mixed feeding is associated with transmission risk).
- Breast-feeding should not be entertained once solid feeds are introduced

In all other situations a care order may be sought for the infant if the mother persists in wishing to breast-feed. Discuss all such cases with the Rainbow team.

Neonatal Management

Infants are generally seen in the Rainbow clinic however, where distance is problematic, 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 Team.*** (Contacts: Appendix 11).

HIV RNA PCR testing

- Obtain blood for HIV RNA PCR testing on day 1 and repeat at 2 weeks of age
- Please send **TWO** filled paediatric EDTA tubes and request '**HIV PCR ULTRA SENSITIVE ASSAY**'
- **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)
- Request a copy of results to be sent to the Rainbow Clinic
- Further paediatric review should be carried out at intervals indicated in appendix 2

HIV RNA PCR testing is routine for HIV exposed infants. In selected situations, HIV DNA PCR testing may also be required. The Rainbow team will advise in this regard. As HIV DNA PCR testing is not locally available special arrangements for shipping of samples must be made.

Infant with a positive HIV PCR result

- Please contact the Rainbow Team at Our Lady's Children's Hospital Crumlin, within one working day.
- Any child with a positive HIV PCR result should have a repeat sample for HIV RNA and DNA PCR testing.
- ARV doses will be adjusted to therapeutic doses and continued beyond 4 weeks of age and for those on ZDV monotherapy treatment will be intensified with addition of three additional agents (e.g with 3TC, abacavir (ABC) and NVP i.e. quadruple therapy).

The early diagnosis of HIV infection is critical for optimum management. More rapid disease progression is observed in vertically transmitted infants than in adults. Twenty five percent of

untreated infants 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 HIV exposed infant

Infant Feeding

In Ireland all mothers known to be HIV positive, regardless of ART and infant post exposure prophylaxis should be advised to exclusively formula feed from birth. Maternal and infant cART continued through the breastfeeding period has been shown to significantly reduce the risk of HIV transmission to the infant and may be an appropriate choice in areas of the world where safe formula feeding cannot be achieved.²⁶

***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. If the HIV PCR at 3 months is negative PCP prophylaxis is discontinued as these infants are unlikely to be HIV infected (Appendix 4).

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 5).

Infants born to HIV/HBV co-infected women who are HBsAg positive should receive hepatitis B immune globulin in addition to hepatitis B vaccine as soon as possible following delivery. **In recognition of the higher prevalence of HBV infection in communities affected by HIV, all other HIV exposed infants should receive HBV vaccine prior to discharge to prevent early household acquisition of HBV.** Completion of HBV vaccination will be carried out as part of the National Immunisation Programme.

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 the infant will need appropriate evaluation and monitoring. (Appendices 6 and 9).

Mitochondrial toxicity

Nucleoside reverse transcriptase inhibitors (e.g ZDV 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 prospective study where antenatal ZDV 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.²⁷ A retrospective review of over 20,000 ARV exposed infants in North America has not shown an increased risk of mitochondrial dysfunction.²⁸ 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

HIV exposed, uninfected infants should be monitored until seroreversion with loss of maternal HIV antibodies is confirmed. This will usually have occurred by 18 – 24 months at which time they can be discharged from follow up unless otherwise clinically indicated.

Early suppressive treatment of HIV infected infants can inhibit HIV antibody development, thus infected infants on treatment may have both negative PCR and antibody tests. For final

confirmation as uninfected, an HIV exposed infant must never have had a positive HIV PCR test, had at least two negative HIV PCR tests off ARVs and test HIV antibody negative after 12 months of age (usually tested at 18 – 24 months).

Hepatitis B (HBV)

Background

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.

- 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 $\geq 90\%$ of cases by immunoprophylaxis i.e. active and passive immunisation

Vertical Transmission of HBV

Vertical transmission of HBV is increased if the mother has high level viremia and is e antigen (HBeAg) positive. Transmission can also take place from HBsAg positive but HBeAg 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. 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.

Antenatal Management

- All women should be offered testing for HBV in pregnancy
- Check HBV DNA (viral load) on all HBsAg positive women
- Refer all newly diagnosed women to adult services
- In selected situations, antenatal antiviral agents may be used to treat women with high levels of HBV viremia or with genotypes associated with higher risk of vertical transmission. It is likely that their use will increase in the future
- For HBV/HIV co-infected women antiretroviral agents with activity against HBV (lamivudine (3TC), tenofovir (TDF)) should be selected as part of the ARV regimen. The adult HIV physician will make this decision

Intrapartum Management and Mode of Delivery

- Maternal HBV does not impact mode of delivery
- Due care should be taken to avoid percutaneous exposure of the infant to maternal blood e.g. avoid scalp electrodes

Early Postnatal Management

- The infant should be bathed as soon as possible after delivery to remove any blood. (Wear plastic apron and gloves)
- Clean eyes
- Prior to administration of immunoprophylaxis clean skin carefully with an alcohol swab

- **Infants of Hepatitis B surface antigen (HBsAg) positive mothers:**
Give hepatitis B immunoglobulin AND hepatitis B vaccine as soon as possible after delivery
- **Infants of mothers who are Hepatitis B core Antibody (HBcAb) positive and HBsAg negative or where there is a family member with hepatitis B infection i.e HBcAb positive:**
Give first dose of HBV vaccine prior to hospital discharge
- Infants who receive Hepatitis B Immunoglobulin can receive BCG vaccination at the usual time

Hepatitis B Immunoglobulin (HBIG)

Infants born to HBsAg positive mothers should receive an intravenous infusion of HBIG, marketed as Hepatect CP®. This should be administered as soon as possible and within 12 hours of birth.

The dose for Hepatect CP® is 30 – 100 international units/kg (i.e. 0.6 – 2 ml/kg) given slowly intravenously. Please bring to room temperature before administration. 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'*. (SPC for Hepatect CP® www.hpra.ie Accessed 20/12/2014)

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

HBV vaccine

Intramuscular injection of 0.5ml HBV vaccine (Engerix B Paediatric® or HBvaxPro) should be given as soon as possible and within 12 hours of 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.

HBV immunisation in 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.

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. Hepatitis B infection is not a contraindication to breast-feeding that can be initiated at the usual time following delivery.

Neonatal Follow up of HBV Exposed 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
- Do not request HBV-PCR at this stage. Check HBV-PCR only if the infant tests HBsAg positive
- Arrangements for this follow up should be made locally either in the local paediatric clinic or with the family GP

Interpretation of HBV Serology Post Vaccination

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

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.

Hepatitis C (HCV)

Background

Hepatitis C virus (HCV) is a small, enveloped, single-stranded, RNA virus that was first identified in 1989. There are at least 6 distinct genotypes (1 – 6) with type 1 being most prevalent in Ireland, Europe and the US. HCV is generally acquired through exposure to contaminated blood or blood products. In Ireland the most common mode of acquisition of HCV is through injecting drug use, 82.5%, with 3% associated with receipt of contaminated blood products, 5.7% possibly the result of sexual transmission, 2.7% vertical transmission and in 5.9% no specific risk factor was identified (www.hpsc.ie, accessed 23.11.2014). The national prevalence of chronic hepatitis C is estimated to lie between 0.5-1.2%.

Risk factors for HCV infection include:

- Past and present intravenous drug use by the individual or their partners
- Percutaneous exposure to contaminated blood or blood products
- Hemodialysis
- Tattoos
- Coinfection with HIV
- Birth to an HCV infected mother

Most (60 – 70%) newly infected persons are asymptomatic or have a mild clinical illness. HCV RNA can be detected in blood within 1–3 weeks after exposure. The average time from exposure to antibody to HCV (anti-HCV) seroconversion is 8–9 weeks, and anti-HCV can be detected in > 97% within 6 months of exposure. Only a minority of infected persons will spontaneously clear infection. Most (70%–85%) become chronically infected. The majority of infected persons might not be aware of their infection because they are not clinically ill.

Heretofore, pegylated α -interferon combined with ribavirin has been the mainstay of therapy for those for whom treatment is indicated. Clearance of infection with this treatment is variable and viral genotype dependent. HCV genotypes 2 & 3 are three times more likely to respond to therapy than genotype 1. Advent of the directly acting antiviral agents has greatly improved the outlook for those infected with HCV with high clearance rates of genotype 1 achieved. As yet, none of these agents are recommended for use in pregnancy.

There are currently no interventions proven to reduce the risk of vertical transmission of HCV. Testing infants born to infected women permits early identification and linkage to medical services for infected children and reassurance to parents in the event that infection is excluded.

Vertical Transmission of HCV

Overall, HCV will be transmitted to 3 – 7% of infants born to mothers who are HCV antibody positive.^{29,30,31,32,33,34} The exact mechanism(s) and timing of perinatal transmission of hepatitis C are not known. Reports of hepatitis C RNA in umbilical cord blood and in infant peripheral blood samples in the first days of life indicate that in-utero transmission can occur. However, even in infected children HIV PCR tests can be negative in the first month of life³⁵ raising the possibility of intrapartum or peripartum transmission. The relative frequency of in-utero compared with intra/peripartum transmission has not been determined. Post natal transmission is considered less likely and may be a rare event. HCV RNA can be detected in breast milk but does not appear to be associated with transmission.^{32,36} Reported maternal risk factors for HCV vertical transmission include active hepatitis C infection, higher hepatitis C viral loads, elevated maternal serum transaminases and HIV co-infection.^{31,32} Invasive obstetric procedures, fetal scalp electrodes and prolonged rupture of membranes have also been associated with transmission.^{32,33,37} Transmission rates for women found to be stably PCR negative in

pregnancy, either through spontaneous clearance or treatment, is negligible.³⁴ The highest transmission rates are found in women who are co-infected with HIV with rates as high as 20% reported from co infected women in the pre HAART era.^{37,38,39,40} To date, no obstetric intervention has been proven to reduce the risk of vertical transmission and HCV infected women can aim for a normal delivery.^{32, 37,38,41,42}

Breastfeeding has not been identified as an important route of transmission for HCV and is not contraindicated for mono-infected women.^{32,38} Women may wish to abstain from breastfeeding while nipples are cracked or bleeding. Breastfeeding is contraindicated for HIV co-infected women.

Twenty percent of infants infected through vertical transmission clear HCV infection spontaneously, usually by 5 – 6 years of age. Most remain chronically infected. Symptomatic disease is rare in the first decade. As for adults, clearance rates for Genotype 3 infection using pegylated interferon and ribavirin are high (80 – 90%) but associated with potential for toxicity. The success rate is much lower for genotype 1 and progression with development of the directly acting antiviral agents for use in paediatrics is eagerly awaited.

HIV and Hepatitis C co-infection

The highest rates for vertical transmission of HCV have been reported for HIV/HCV co-infected women.^{37, 38} The use of antenatal antiretroviral therapy in HIV/Hepatitis C co-infected women may reduce the risk of hepatitis C transmission.¹¹ Early reports suggested that, similar to HIV, prolonged rupture of membranes, exposure to maternal blood and amniocentesis increased the risk of HCV transmission³³ and that delivery by caesarean section might reduce that risk.³⁰ Subsequent studies^{34, 41} and systematic review^{38, 42} failed to confirm the benefit of ELCS in reducing HCV transmission. As clear data to support the use of caesarean section solely for the prevention of HCV transmission have not yet emerged and, as caesarean section is associated with small additional morbidity, it is no longer routinely recommended for this purpose. Breastfeeding is contra-indicated because of the presence of HIV infection

Antenatal Management of HCV Positive Women

- Women with risk factors for HCV infection should be offered HCV antibody testing
- Check HCV PCR status (viral load) on all HCV antibody positive women
- Newly diagnosed women should be referred to adult hepatitis services
- HCV infected women should be screened for co-infection with HBV or HIV

Delivery

- Presence of HCV does not impact mode of delivery
- Due care should be taken to avoid percutaneous exposure of the infant to maternal blood e.g. avoid scalp electrodes

Early Postnatal Management

- The infant should be bathed as soon as possible after delivery to remove any blood (wear plastic apron and gloves)
- Clean eyes with saline
- Breastfeeding is not contraindicated for mono-infected women
- Women with cracked or bleeding nipples may wish to temporarily abstain from breast feeding until the nipples are healed
- Breast feeding is contraindicated for women co-infected with HIV

Follow up of HCV Exposed Infants

- See table for testing schedule
- Infants who are HCR PCR positive at any time or who are HCV antibody positive at or after 18 months of age should be referred to the Rainbow clinic.

Maternal HCV Status	Test	6 Weeks in Maternity Hosp	6 Months Local Paed. Clinic	18 Months Local Paed. Clinic
Follow-up of infants where mother is both HCV Ab and PCR positive	<i>HCV Ab</i>	✓	✓	✓
	<i>HCV PCR</i>	✓	✓	
Follow-up of infants where mother is only HCV Ab (i.e. PCR negative)	<i>HCV Ab</i>			✓
	<i>HCV PCR</i>			✓

Herpes Simplex Virus (HSV)

Background

Herpes Simplex Virus is a double stranded DNA virus with 2 serotypes: herpes simplex type 1 (HSV-1) and herpes simplex type 2 (HSV-2). As with all human herpes viruses, after initial infection they establish latency and can reactivate at some future time.

Genital Herpes can be caused by either HSV-1 or HSV-2 resulting in a prodromal viral illness, genital itch, vesicles, painful ulceration with painful regional lymphadenopathy. The likelihood of recurrence is greater with HSV-2 than HSV-1 and the likelihood of recurrence reduces over time. The presence of antibodies to either serotype reduces the likelihood of genital infection with the other serotype and may ameliorate an attack. Disseminated maternal herpes in pregnancy is rare, but may be life-threatening. Acyclovir and its analogues used for treatment and prophylaxis can reduce risk of viral shedding at delivery and thus reduce transmission risk.⁴³ Experience and available data support the safety of this approach.⁴⁴

Neonatal HSV infection is rare, but can lead to potentially fatal disease in infants within the first 4-6 weeks of life. Transmission from mother to infant most commonly occurs due to exposure during delivery (85-90% cases).⁴⁵ Transmission may also occur due to early post natal exposure (5-10% cases) and rarely in utero (5%). Maternal HSV infection can be asymptomatic. 60-80% of women delivering an HSV infected infant have clinically inapparent infection and neither history of HSV infection, nor of a partner with HSV infection.⁴⁶

Neonatal HSV infection vs neonatal disease

Neonatal HSV **infection** occurs when viral replication has been established but is not causing illness. Neonatal HSV **disease** occurs when viral replication produces clinical signs of illness (e.g. skin lesions, encephalitis, hepatitis). Once an infant is infected with HSV, progression to neonatal HSV disease is virtually certain. In an effort to prevent progression, experts recommend that parenteral acyclovir be administered pre-emptively to HSV-infected neonates and that it is initiated for asymptomatic high risk exposed infants pending the results of their PCR tests.

Vertical Transmission of HSV

25 – 60% of women with first episode HSV infection and active lesions at delivery will transmit HSV to their infants (60% for those with first episode primary infection i.e. no prior HSV 1 or HSV 2 infection; 25% for those with first episode non-primary infection i.e. those who now have HSV 2 infection but who have had prior HSV 1 infection, or the converse situation). The risk of transmission from women with recurrent infection is significantly lower at 0 – 3%.⁴⁷ Characterisation of the episode by determining maternal type specific serology (i.e. does mother have antibodies to HSV1 or HSV 2) allows for more appropriate risk assessment, delivery planning and infant management. Current recommendations for infant management are based on expert opinion because of lack of randomised controlled trials in this area.^{46,48}

Factors known to influence transmission of HSV from mother to neonate

1. Type of maternal infection (primary vs non primary first episode vs recurrent)
2. Maternal HSV antibody status
3. Duration of rupture of membranes
4. Integrity of infant mucocutaneous barriers, e.g., use of fetal scalp electrodes
5. Mode of delivery, caesarean versus vaginal delivery
6. Presence of genital lesions during delivery (NB. transmission can occur in the absence of visible lesions)

Classification of Maternal Genital HSV Infection

Genital HSV infection can be clinically apparent with visible genital lesions, or inapparent with no visible lesions (asymptomatic or sub-clinical). Transmission to the neonate can occur with either presentation. The risk of transmission is high with first episode of infection and highest when that first episode is in an individual with no antibodies to HSV 1 or 2, i.e. first episode primary infection. Episodes are classified according to whether it is a first episode or a recurrence and whether maternal HSV antibodies are present (table below).

First episode primary infection

An individual with no HSV-1 or HSV-2 antibody who acquires either virus in the genital tract

First episode non-primary infection

Either

- a) an individual with pre-existing HSV-1 antibody who acquires HSV-2 genital infection or vice-versa

or

- b) an individual with pre-existing HSV-1 or HSV-2 antibody who develops a first episode of clinically apparent lesions

Recurrent infection

An individual with pre-existing HSV-1 or HSV-2 antibody and a history of one or more episodes of clinically apparent genital lesions

HSV Classification	HSV in Genital lesion	Maternal IgG Antibodies to:	
		HSV -1	HSV -2
Primary HSV 1	HSV 1	Negative	Negative
Primary HSV 2	HSV 2	Negative	Negative
First episode non primary HSV 1 ^a	HSV 1	Negative	Positive
First episode non primary HSV 2	HSV 2	Positive	Negative
Recurrent HSV 1 ^b	HSV 1	Positive	Positive or Negative
Recurrent HSV 2 ^c	HSV 2	Positive or Negative	Positive

^a Most adults have had childhood HSV 1 exposure, thus first episode non primary HSV 1 is rare.

^b HSV 1 has a much lower propensity for recurrence than HSV 2.

^c Most with recurrent HSV 2 will have evidence of prior exposure to HSV 1 and HSV 2.

Antenatal Management

- Ask pregnant women if they have had any episode of genital ulceration or genital herpes
- Anyone with a genital ulcer should have lesions swabbed for HSV PCR and blood taken for HSV type specific antibodies and repeat syphilis and HIV serology
- Women who experience a **first episode genital herpes in the first or second trimester** should receive prophylactic antiviral medication throughout the third trimester (eg. prophylactic dose - acyclovir 400mg BD or valacyclovir 500mg once daily)
- Treat women with a **first episode of genital herpes in the third trimester** with antiviral medication (eg treatment dose - acyclovir 400mg TDS for 5 days or valacyclovir 500mg BD for 5 days) and continue prophylactic antiviral medication until delivery
- Treat women with a history of **recurrent genital herpes** with acyclovir 400mg TDS for 5 days or valacyclovir 500 mg BD for 3 – 5 days. Prophylactic antiviral medication in the third trimester is recommended (e.g. acyclovir 400mg BD or valacyclovir 500mg once daily)
- Consultation with or referral to an adult STI service is recommended, particularly if there is any doubt regarding management
- See HSV algorithms (Appendix 7)

Intrapartum Management and Mode of Delivery

- Vaginal delivery can be anticipated in women with a history of **recurrent genital herpes provided there are no visible lesions at labour onset**
- Women with **first episode genital herpes in the first or second trimester** can anticipate a normal delivery provided it is at least six weeks since the episode and there are no visible genital lesions at labour onset
- Delivery by caesarean section should be offered to all women with visible herpetic genital lesions at presentation in labour (includes women with a history of recurrent genital herpes, or with first episode genital herpes in the first or second trimester, or with first episode genital herpes in labour)
- Delivery by ELCS is recommended for women with **first episode genital herpes in the third trimester when the episode occurs within 6 weeks of estimated delivery date**
- Individualised care plans with multidisciplinary input to evaluate the competing risks are required in the event of premature labour or preterm prolonged rupture of membranes.

Neonatal Management

General considerations

The risk of transmitting HSV to the newborn infant during delivery is influenced directly by the mother's previous immunity to HSV. Women with primary genital HSV infection who are shedding HSV at delivery are 10 to 30 times more likely to transmit virus to their infant than women with recurrent infection. The increased risk is attributable to lower concentrations of transplacental HSV-specific antibodies in women with primary infection and to the higher quantities of HSV that are shed for a longer period of time in the maternal genital tract compared with women who have recurrent genital HSV infection. However, a substantial percentage of women with a first **clinical** episode of genital herpes are experiencing reactivation of a previously unrecognised genital herpetic infection. Management of the exposed neonates is based on their risk. Maternal history does not reliably distinguish primary from recurrent infection. To accurately determine the infants risk, typing of HSV from the maternal lesions coupled with maternal type specific serology is necessary.

Neonatal HSV infection and disease can also arise as a result of horizontal transmission, either in the nursery environment or from close contacts at home. Avoid direct contact between neonates and active HSV skin lesions in health care workers or other family members

Clinical Manifestations of Neonatal HSV Disease

HSV infection, acquired either intrapartum or postpartum, can manifest as:

- Mucocutaneous disease limited to the skin, eyes, and/or mouth [SEM]
- Central nervous system (CNS) disease, with or without skin lesions
- Disseminated disease involving multiple visceral organs, including lung, liver, adrenal glands, skin, eye, and/or brain

Neonates with disseminated and SEM HSV disease typically present for medical attention at 10 to 12 days of age. Infants with CNS disease typically present at 17 to 19 days of age. Overall, approximately half of all infants with neonatal HSV disease will have CNS involvement or disseminated disease with CNS involvement, and approximately 70% will have characteristic vesicular skin lesions (SEM disease 83%; CNS disease 63%; disseminated disease 58%).

Diagnosis of Neonatal HSV

HSV PCR testing is now the standard technique for diagnosis allowing for a faster time to diagnosis than traditional culture techniques.

- Sites from which specimens (viral swabs) should be routinely obtained from all exposed infants include the conjunctivae, mouth, nasopharynx, and rectum i.e. mucocutaneous or surface swabs
- If skin or mucosal lesions are present, the lesion should be punctured and a viral swab taken from the base of the lesion for HSV PCR assay
- Obtain an EDTA blood sample for HSV PCR
- CSF should be obtained from any symptomatic neonate, any neonate where there is a high level of suspicion regarding HSV and any neonate with a positive HSV PCR test result from any site. Full CSF analysis and HSV PCR testing is indicated. The sensitivity of CSF PCR testing in neonatal HSV disease ranges from 75-100%
- Ensure specimens reach the diagnostic virology laboratory in a timely fashion

Management of Symptomatic Infants

- Any infant with signs or symptoms suggestive of HSV or with positive HSV PCR from any site should be treated with acyclovir.

Management of Asymptomatic Infants

- High Risk Infants
 - Suspected 1st episode maternal HSV infection at or within 6 weeks of delivery. (transmission risk ~ 40-60%) (Appendix 8, Scenario 1).
 - First episode maternal HSV, confirmed as non - primary infection (transmission risk ~ 25%)(Appendix 8, Scenario 2).
- Intermediate Risk Infants
 - History of first HSV occurrence greater than 6 week prior to delivery or history of recurrent HSV lesions during or prior to pregnancy (Appendix 8, Scenario 3).
 - Recurrent Infection – visible lesions at labour onset (transmission risk ~< 2- 3%) (Appendix 8, Scenario 3).
- Low Risk Infants
 - History of first infection > 6 weeks prior to delivery or history of recurrent HSV lesions during or prior to pregnancy. Recurrent infection – no visible lesions (transmission risk ~ 0 - <1%) (Appendix 8, Scenario 4)

Treatment of Proven Infant HSV Infection and/or Disease

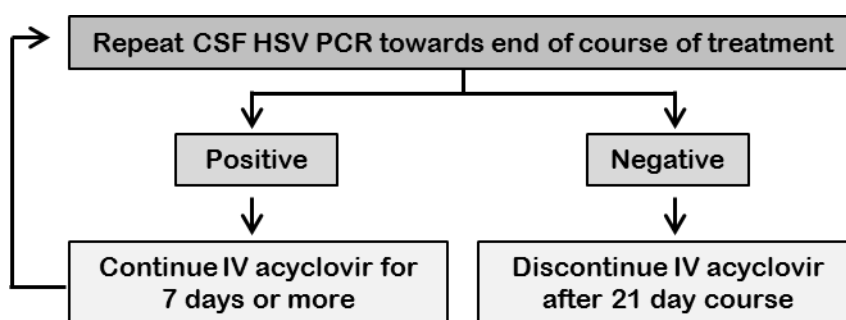
See Appendix 8, Scenario 1

Asymptomatic infant, proven HSV infection, no evidence HSV disease

- No clinical symptoms and surface and/or blood PCR positive with normal CSF, LFTs and Coags
- Rx IV acyclovir 60 mg/kg/day in 3 divided doses for 10 days
- If CSF or LFTs are abnormal treat as for infant with proven HSV disease

Symptomatic infant and/ or proven neonatal HSV disease

- Clinical symptoms or abnormal LFTs, coags, CSF, or CSF PCR positive
- Rx IV acyclovir 60 mg/kg/day in 3 divided doses
 - 14 days for skin/eye/ mouth disease
 - 21 days minimum if CSF PCR positive or evidence of CNS or disseminated disease and follow algorithm below
- Infants with neonatal HSV disease should receive suppressive therapy with oral acyclovir for 6 months after completion of intravenous acyclovir and regular clinical follow up



Prevention of postnatal HSV transmission

- Ten percent of neonatal HSV cases are attributed to postnatal transmission
- Horizontal transmission of either HSV 1 or 2 can occur, usually through contact with contaminated hands or other fomites
- All individuals, including health care workers, with oral or genital HSV lesions in close contact with the neonate, should practice strict hand hygiene
- The importance of prevention of postnatal transmission of HSV to the neonate should be stressed and advice given to parents and care givers

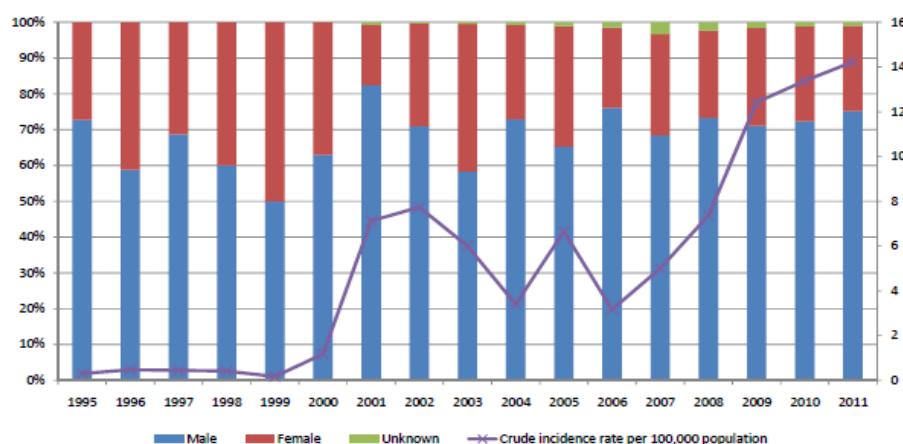
Syphilis

Background

Syphilis infection is caused by the spirochete *Treponema pallidum* (*T. pallidum*). They appear as motile thin helical rods on dark field microscopy. They survive only briefly outside the host but remain motile in specific enriched media for several days at 35°C. In Ireland there was a low incidence of syphilis throughout the 1990's, in 1999 the lowest incidence was reported in 10 years. Since January 2000 there has been an increase in the incidence of syphilis across Ireland amongst heterosexuals.

Rates of infection remain disproportionately high among men who have sex with men (MSM) and HIV infected adults. Syphilis is commonly transmitted through sexual contact, but can also be transmitted by direct vascular inoculation (IVDU, rarely transfusions), direct cutaneous contact with infectious lesions or vertically from mother to infant either in utero or in the peripartum period (congenital syphilis).

Percentage of syphilis notifications by gender and crude incidence rate* per 100,000 population, 1995-2011



*Rates calculated using Census 1996 (1995-1999), Census 2002 (2000-2003), Census 2006 (2004-2008) and Census 2011 (2009-2011)

accessed at www.hpsc.ie

Acquired Syphilis – Stages of Infection

Infection can be classified into 2 main stages: a) early or b) late. Neurosyphilis refers to specific clinical manifestations which can occur in early and late syphilis infection.

Early Syphilis

Early syphilis encompasses three stages: primary syphilis, secondary syphilis and early latent syphilis, a period of time extending to one year after acquisition of infection.

Primary syphilis

After an incubation period of 10 – 90 days (typically 3 weeks) one or more painless indurated ulcers (chancres), often unrecognised, at the inoculation site on the genitalia or mucous membranes develop. These heal spontaneously after 1-2 months.

Secondary stage syphilis

Occurs 1-6 months following primary exposure. This is the systemic phase of syphilis where there has been widespread dissemination of treponemes/chancres organisms with or without CNS involvement. Typical presentation includes a generalised polymorphic maculopapular rash involving palms and soles. Other features include mucocutaneous lesions, snail track mouth ulcers and in moist skin fold/genital/perineal/ areas hypertrophic papular lesions (condylomata lata); often confused with HPV related condylomata acuminata. Lymphadenopathy, fever,

malaise, splenomegaly, headache, arthralgia, may also be present. Uveitis or iritis occur in 10% of cases.

Early Latent Syphilis

Latent syphilis is when patients are seroreactive without clinical manifestations. It can follow unrecognised primary infection or spontaneous resolution of symptomatic secondary infection. The period of latency is variable and can be interrupted by recurrences of symptoms of secondary syphilis. The early latent period refers to infections acquired during the preceding year.

Late Syphilis

Late syphilis encompasses both late latent syphilis (latency more than 1 year after acquisition) and tertiary syphilis.

Late latent syphilis or syphilis of unknown duration

Latent infection of unknown duration is the commonest diagnosis in women who present with positive syphilis serology in pregnancy. The duration of infection is not known because the infected person is asymptomatic and has no previous history of syphilis serology.

Tertiary stage syphilis (Occurs years to decades after primary infection)

Manifestations include gummatous changes of skin, bone, viscera or organs, aortitis, aneurysm formation, and left ventricular failure

Neurosyphilis

Neurosyphilis can occur during early or late syphilis. Early neurosyphilis may present with uveitis, meningitis, cranial nerve palsies, seizures, hemiplegia, limb paralysis, and or stroke. Features of late neurosyphilis include general paresis of the insane, Argyll-Robertson pupils, and tabes dorsalis

Congenital Syphilis

Congenital syphilis is a preventable disease. Untreated or inadequately treated syphilis can result in the transmission of *T. pallidum* from a pregnant woman to her fetus at anytime during pregnancy or delivery. During the first year of infection in an untreated woman, there is an 80-90% risk of transmission to the fetus. If early syphilis is not treated, 25-30% of fetuses die in utero, 25-30% die postnatally and 40% of surviving infants will develop symptomatic syphilis with symptoms typically appearing after the third week of life. The risk of congenital infection is 50% with maternal secondary syphilis, 40% in latent syphilis and 10% in tertiary syphilis. Intrauterine infection can result in preterm delivery, stillbirth, non-immune hydrops and IUGR. Syphilis remains an important cause of infant mortality.⁴⁹

Clinical Manifestations of Congenital Syphilis

Congenital syphilis is classified as early or late.

Early congenital syphilis (manifests in the newborn or < 2 years)

- IUGR, hydrops, jaundice, anemia, hepatosplenomegaly, generalized lymphadenopathy, pyrexia
- Skin manifestations; maculo-papular, petechial or any form of rash, palms and soles may be red, mottled and swollen; vesicles or bullae may be present
- Ulceration of nasal mucosa, rhinitis ('snuffles' usually after the first week of life)

- Pneumonia Alba (white pneumonia) is caused by inflammatory cells and fibrosis in the alveolar septa. Spirochetes are demonstrable in lung tissue sections
- Osteochondritis, periosteitis (humerus, femur, tibia)
- Parrot Pseudoparalysis (painful epiphysitis) - failure to move an extremity
- Neurosyphilis signs: bulging fontanelle, seizures, cranial nerve deficit
- **Normal physical examination does not exclude the possibility of neonatal syphilis**

Late congenital syphilis (manifests > 2years, usually near puberty)

- Hutchinson's teeth (peg shaped incisors), mulberry molars (molars with extra cusps)
- Interstitial keratitis, chorioretinitis
- Eighth nerve deafness, cranial nerve palsies, general paresis, learning disability
- Hutchinson's triad = Hutchinson's teeth + Interstitial keratitis + Eighth nerve deafness
- Facial bone abnormalities; frontal bossing, saddle nose deformity secondary to nasal cartilage destruction
- Saber shins (tibial bowing)
- Clutton's joints (sterile effusions of large joints)
- Unilateral clavicular enlargement

Diagnostic Tests

Treponemal specific tests

- **Treponemal Enzyme immunoassay (EIA) or chemiluminescent microparticle assay**
 - Most assays detect both IgM and IgG treponemal antibody
 - This test is used for antenatal screening and is reported as positive or negative
 - This blood test checks for antibodies to the bacteria that cause syphilis
 - A positive test will prompt further testing in the laboratory
- **TPPA (*Treponema pallidum* particle agglutination)**
 - Represents antibody directed against *T. pallidum*; Poor correlation with disease activity and response to treatment
 - False positive: other spirochetal disease; e.g. leptospirosis, Lyme disease, yaws
 - Infected individuals usually remain reactive for life even after successful treatment
- ***Treponema pallidum* IgM**
 - High titres of IgM can be detected during acute primary infection
 - However, weak "false positive" can be generated which may confuse the diagnosis
 - Therefore IgM should only be requested if there is a clinical suspicion of recent infection
 - Interpret with follow up tests where applicable
- **PCR**
 - PCR based tests are used for samples taken from muco-cutaneous lesions. This test is rarely used in Ireland and its use is currently for study/research purposes

Non -Treponemal specific tests

- **VDRL (Venereal disease research laboratory, no longer used in Ireland)**

- **RPR (Rapid Plasma Reagin)**
 - **RPR** does not detect specific treponemal antibody but antibody directed against cardiolipin which is present in many patients with syphilis
 - **RPR** correlates with disease activity e.g., RPR positive at 1:64 suggests active or early infection versus an RPR that is negative or positive at 1:2 or a neat dilution
 - **RPR** assay can be used to monitor treatment response, titres usually decrease after treatment
 - This test can generate “false positive” results due to a number of infections e.g EBV, VZV, and other conditions such as TB, malaria, lymphoma, connective tissue disease, pregnancy, drug abuse
 - False negative results can occur during early primary syphilis, late latent syphilis, late congenital syphilis
 - **RPR** may become non reactive (i.e. negative) over time or persist at low titres for life with or without treatment
- **Microscopy –**
 - Dark field or immunofluorescent microscopy of samples taken from mucocutaneous lesions and other tissue samples e.g., placenta, organs at post mortem

Antenatal Management

- All women offered syphilis testing at first antenatal visit
- Refer to adult GU/ID services in the event of a positive test result
- All women with positive syphilis serology should have an STI screen to include HIV, Chlamydia and gonorrhoea
- If treated in the past for syphilis, obtain clear history and where possible documentation of adequate treatment and of serologic response to treatment.
- Where possible treatment of syphilis is with parenteral penicillin. The duration and dose of parenteral penicillin will be determined by the stage and clinical manifestation of infection. Decisions regarding maternal treatment are made by an adult GU/ID physician.
- Oral doxycycline is an effective treatment option for syphilis in the non pregnant population, where penicillin is contraindicated but is NOT used in pregnancy
- Infants born to women who have been treated in pregnancy with erythromycin, regardless of the timing of maternal treatment, cannot be considered treated as erythromycin does not cross the placenta.
- Partners should be referred to GU/ID for testing.

Intrapartum Management and Mode of Delivery

- Maternal syphilis infection does not alter decisions regarding mode of delivery
- Post delivery, pathology examination of the placenta should be performed on all cases

Neonatal Management

- Determine maternal risk category according to algorithm (Appendix 9) and assign infant management accordingly
- Infants with congenital infection are highly infectious as treponemes are present in mucosal secretions and skin lesions if present

- Gloves should be worn when handling infants with signs of congenital syphilis or infants in whom infection is highly likely or suspected. Such infants should be placed in contact isolation for the first 24 hours or until one day of treatment with IV Penicillin is completed
- All infants born to mothers with positive syphilis serology should have blood for RPR taken at birth or day 1 of life
- High risk infants should be commenced on 10 days IV benzylpenicillin until CSF results are available. If CSF analysis is normal and infant follow up certain, discontinue IV Penicillin; administer stat dose IM Benzathine Penicillin and discharge.
- High risk infants for whom follow up cannot be guaranteed should be treated with a full course of 10 days IV benzylpenicillin even if CSF results normal
- All infants with an abnormal CSF in the newborn period require repeat CSF analysis at age 6 months
- Low risk infants for whom follow up cannot be guaranteed should be treated with a stat dose of IM Benzathine Penicillin
- All syphilis exposed infants require clinical and serological follow up
- Infants may be discharged from hospital pending results but ensure infant follow up with a paediatrician or the paediatric ID service
- See Appendix 9 for details of infant management

Guide for Interpretation of Infant Syphilis Results

Serological tests should be performed on infant's blood, not cord blood.

RPR

- An infant RPR titre four-fold or greater than that of the mother (e.g. mother 1: 4, infant 1:16) supports a diagnosis of congenital syphilis
- Interpret infant serology with most recent maternal serology
- Passive trans-placental transfer of maternal IgG antibodies may cause a false positive RPR test in the newborn but these usually revert to negative by 6 months
- A positive RPR beyond the age of 6 months also supports a diagnosis of congenital syphilis
- Two consecutive negative RPR tests documented in infancy suggests congenital syphilis is very unlikely
- **A neonatal RPR titre less than four-fold that of the mother's (e.g. mother 1:8, infant 1:16) does not exclude congenital syphilis**
- False negative RPR can occur with late congenital syphilis, i.e., infection diagnosed after age 2 years

TPPA/EIA

- Positive TPPA/EIA in infancy represents passive transfer of maternal antibody and does not represent congenital syphilis
- Infant titres in the first year of life are not significant
- Titres should gradually decrease over 12-18 months
- Infants should serorevert, i.e. become TPPA negative by 18 months

- All syphilis exposed should have a final TPPA test at 12-18 months to demonstrate loss of maternal antibody
- Persistence of TPPA antibody beyond age 18 months supports a diagnosis of treated congenital syphilis in which case TPPA usually remains reactive for life

Treponemal IgM

- Treponemal IgM is not recommended as a routine diagnostic test for infants unless clinically indicated as described in the algorithm
- If performed in the newborn period, results must be interpreted in conjunction with the maternal history, infant clinical signs and results of other infant syphilis blood tests
- A positive treponemal IgM test may be supportive of a diagnosis of congenital syphilis, however a negative IgM test does not exclude infection as the IgM response may be delayed or suppressed

CSF

- CSF abnormalities suggestive of congenital neurosyphilis include; elevated white blood cell count $> 5 \text{ WBC/mm}^3$, protein concentrations $> 0.4\text{g/l}$ and a reactive RPR
- A negative CSF RPR does **not** exclude congenital neurosyphilis

For any queries regarding infant management or serology/CSF interpretation contact Dr Wendy Ferguson via The Rotunda Hospital switchboard 01-873 0700 bleep # 417

If unavailable contact a member of The Rainbow Team at Our Lady's Children's Hospital Crumlin via the hospital switchboard 01 409 6100

Appendix 1: Scenarios in the Management of HIV in Pregnancy

On ARVs Pre-conception			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
Stably virologically suppressed throughout pregnancy Continue PCP prophylaxis if CD4 <200	N/A	≤40	In general continue ARVs	If HIV VL ≤40 @36/40 NOT for IV ZDV Continue oral ARVs in labour	If HIV VL ≤40 @36/40 await SOL	Continue	If HIV VL ≤40 @36/40 and ROM <12hrs, ZDV x 4/52
							If ROM >12 hrs triple ARV x 4/52
Virological failure in pregnancy Continue PCP prophylaxis if CD4 <200	N/A	>40	Optimise ARVs with guidance of GRT and previous ARV history	If HIV VL ≤40 @36/40 NOT for IV ZDV Continue oral ARVs in labour	If HIV VL ≤40 @36/40 await SOL	Case by case	If HIV VL ≤40 @36/40 and ROM <12hrs, ZDV x 4/52
					If HIV VL >40 but ≤400 ELCS may be indicated*		If HIV VL >40 @36/40 or ROM >12 hrs Triple ARV x 4/52
				If HIV VL >40 @36/40 IV ZDV as per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	If HIV VL >400 at 36/40 ELCS @39/40		

Not on ARVs or New HIV Diagnosis in Pregnancy Presenting at <20/40 & CD4 ≤350			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
Because of ↓ baseline CD4, mother requires ARVs for own health	≤ 350	N/A	Send baseline GRT prior to commencing ARV Commence ARVs ASAP (it may be reasonable to wait until after 1 st trimester). No later than 20/40 NB - Commence PCP prophylaxis ASAP if CD4 <200 If baseline HIV VL >100, 000 c/ml or potential for early delivery consider RAL based regimen	If HIV VL ≤40 @36/40 NOT for IV ZDV Continue oral ARVs in labour	If HIV VL ≤40 @36/40 await SOL	Continue	If HIV VL ≤40 @36/40 and ROM <12hrs, ZDV x 4/52
					If HIV VL >40 but ≤400 ELCS may be indicated*		If HIV VL >40 @36/40 or ROM >12 hrs Triple ARV x 4/52
				If HIV VL >40 @36/40 IV ZDV as per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	If HIV VL >400 at 36/40 ELCS @39/40		

Not on ARVs or New HIV Diagnosis in Pregnancy Presenting at <20/40 & CD4 >350			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
Antenatal ARV primarily for PMTCT	>350	N/A	Send baseline GRT prior to commencing ARVs	If HIV VL ≤40 @36/40 NOT for IV ZDV Continue oral ARVs in labour	If HIV VL ≤40 @36/40 await SOL	Case by case decision re continuing or discontinuing ARVs post partum. If ARVs are discontinued see for GRT at ~6 weeks	If HIV VL ≤40 @36/40 and ROM <12hrs, ZDV x 4/52
			Commence ARVs as soon as possible in the second trimester. No later than 20/40.		If HIV VL >40 but ≤400 ELCS may be indicated ^d		If HIV VL >40 @36/40 or ROM >12 hrs Triple ARV x 4/52
			If baseline HIV VL >100, 000 copies or potential for early delivery consider RAL based regimen	If HIV VL >40 @36/40 IV ZDV as per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	If HIV VL >400 at 36/40 ELCS @39/40		

^d The decision to recommend ELCS in women with HIV VL >40 but ≤400 will be guided by factors including maternal adherence, virological response and duration of ARVs

Not on ARVs or New HIV Diagnosis in Pregnancy Presenting at >20/40 & CD4 ≤ 350			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
Because of ↓ baseline CD4, mother requires ARVs for own health	≤ 350	N/A	Send GRT but commence ARVs ASAP Consider RAL based regimen if presents in third trimester or baseline HIV VL >100,000c/ml If CD4 <250 consider NVP based regimen	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 ≤40 @ 36/40 & mother on ARVs x ≥4/52 await SOL	Continue	If HIV VL ≤40 @36/40 +ROM <12hrs + mother on ARVs x ≥4/52: ZDV X 4/52
					If HIV VL >40 but ≤400 ELCS* may be indicated		
				If HIV VL >40 @36/40 or mother on ARVs x <4/52 IV ZDV as per protocol and consider addition of Double dose TDF, RAL or SD-NVP	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 weeks

Not on ARVs or New HIV Diagnosis in Pregnancy Presenting at >20/40 & CD4 >350			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
Antenatal ARV primarily for PMTCT	>350	N/A	Send GRT but commence ARVs asap Consider RAL based regimen if presents in third trimester or baseline HIV VL >100,000	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 ≤40 @ 36/40 and mother on ARVs x ≥4/52 await SOL	Case by case decision re continuing or discontinuing ARVs post partum. If ARVs are discontinued see for GRT at ~6 weeks	If HIV VL ≤40 @36/40 +ROM <12hrs + mother on ARVs x ≥4/52: ZDV X 4/52
				If HIV VL >40 @36/40 or mother on ARVs x <4/52 IV ZDV as per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	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

Premature Labour Stably Virologically Suppressed on ARVs			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
<37/40	N/A	≤40	Steroids and tocolysis as obstetrically indicated Continue ARVs	IV ZDV per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	As obstetrically indicated. MDT discussion recommended	Continue	If ROM <12 hours ZDV monotherapy where possible
							If ROM >12 hours Triple ARVs x 4/52 where possible

Premature Labour, Failing ARVs			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
<37/40	N/A	>40	GRT Steroids and tocolysis as obstetrically indicated Consider RAL or NVP (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay	IV ZDV per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	As obstetrically indicated. MDT discussion recommended	Case by case decision re continuing or discontinuing ARVs post partum. If ARVs are discontinued see for GRT at ~6 weeks. If NVP used and stopped, stagger ARV discontinuation	Triple ARVs x 4/52 where possible

Premature Labour Not on ARVs			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
<37/40	N/A	>40	GRT Steroids and tocolysis as obstetrically indicated Consider RAL or NVP (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay	IV ZDV as per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	As obstetrically indicated. MDT discussion recommended	Case by case decision re continuing or discontinuing ARVs post partum. If ARVs are discontinued see for GRT at ~6 weeks. If NVP used and stopped, stagger ARV discontinuation	Triple ARVs x 4/52 where possible

Pre-labour Ruptured Membranes at Term			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
On effective ARVs	N/A	≤40	Continue ARVs	IV ZDV as per protocol	Expedite delivery, aim for shortest duration of ROM	Continue	If ROM <12 hours ZDV x 4/52
							If ROM >12 hours triple ARVs x 4/52
Failing ARVs		>40	Optimise ARVs with clinical and resistance data Consider RAL based regimen to facilitate rapid virological decay	IV ZDV as per protocol and consider addition of oral TDF (double dose), RAL or SD NVP		Continue optimised ARVs	Triple ARVs x 4/52
Not on ARVs		>40	Consider RAL based regimen to facilitate rapid virological decay			Case by case decision re continuing or discontinuing ARVs post partum. If ARVs are discontinued see for GRT post cessation	

Pre-labour Ruptured Membranes Pre-term			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
On effective ARVs	N/A	≤40	Steroids as obstetrically indicated Continue ARVs Urgent VL Consider sdNVP to mother to pre load infant	IV ZDV as per protocol and consider addition of oral TDF (double dose), RAL or SD NVP	As obstetrically indicated	Continue	If ROM <12 hours ZDV x 4/52
							If ROM >12 hours triple ARVs x 4/52 where possible
Failing ARVs		>40	Steroids as obstetrically indicated. Optimise ARVs with clinical & resistance data. Consider RAL or NVP (if CD4 <250 & no NNRTI resistance) based regimen to facilitate rapid virological decay		As obstetrically indicated. MDT discussion recommended	Continue optimised ARVs	Triple ARVs x 4/52 where possible
Not on ARVs		>40	Steroids as obstetrically indicated. Consider RAL or NVP (if CD4 <250 and no NNRTI resistance) based regimen to facilitate rapid virological decay		As obstetrically indicated. MDT discussion recommended	Case by case decision re continuing or discontinuing ARVs post partum. If ARVs are discontinued see for GRT post cessation	

Diagnosed in Labour			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant*
	N/A	N/A		<p>Membranes ruptured: IV ZDV loading over 1 hour</p> <p>Membranes intact: IV ZDV loading dose over 1 hour and 2 hours infusion (if in early labour and time permits)</p> <p>Consider addition of oral TDF (double dose), RAL or SD NVP</p>	<p>Expedite delivery</p> <p>If premature labour and steroids and/or tocolysis indicated MDT discussion recommended</p>	<p>Urgent confirmation of HIV status</p> <p>Assessment at adult HIV service post partum</p>	<p>Urgent initiation of triple ARVs and urgent confirmation of maternal HIV</p> <p>Ensure not breastfeeding</p>

Diagnosed \leq 72 Hours Postpartum			RECOMMENDATIONS				
Clinical	CD4	HIV VL	Antepartum	Intrapartum or prior to CS	Mode of delivery	Postpartum mother	Postpartum infant
	N/A	N/A				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	Mode of delivery	Postpartum mother	Postpartum infant*
	N/A	N/A		Offer IV ZDV +/- sdNVP, RAL or double dose TDF	Offer ELCS	Offer adult HIV service assessment	Triple ARVs Ensure not breastfeeding Seek permission through courts if parents not agreeable

Appendix 2: Management of Infants Born to HIV Positive Women

	Pregnant Mother	Day 1	2wk	4wk	6wk	3-4 mth (ensure ≥ 3mos old)	6mth	2 years
HIV antibody	✓				✓			✓
PCR	✓	✓	✓		✓	✓	✓	
T cell subsets*			*		*	*		
FBC		✓	✓		✓	✓		
LFT's		✓					Note For 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 National Virus Reference Laboratory and request ultrasensitive PCR assay. 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	
CMV IgG, IgM	✓#	Urine						
Toxoplasma Ab	✓#							
Hep BsAg	✓#							
Hep C Ab	✓#							
Haemaglobinopathy screen/G6PD (if indicated)					✓			
Management considerations		Hep B vaccine		Discontinue ARVs	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 HBV at birth and childhood immunisations as per National Guidelines. Infants born to HBsAg + co-infected mothers should receive HBIG and Hepatitis B Vaccine as soon as possible following delivery.
- BCG vaccine should be deferred until 6 week PCR is confirmed negative.
- *T cell subsets should be taken in the event of a positive PCR result
- # If status unknown at time of delivery.
- If the mother is Hep C or Hep BsAg positive, please refer respective section, appendix 6

Appendix 3: Antiretroviral Drug Information

Zidovudine (ZDV, Retrovir)

Administration of intravenous zidovudine (Retrovir®) to pregnant women intrapartum

Presentation: Zidovudine 200mg/20ml

Use: Indicated in selected situations 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 is clamped.

Planned caesarean section:

Loading dose: 2mg/kg IV infusion over one hour starting 3 hours before the C/Section

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
ZDV	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. Discard if any visible turbidity appears either before or after dilution or during infusion. From a microbiological point of view, should be used immediately; however prepared infusions may be stored at 2-8°C and infused at room temp within 24 hours.

Notes:

- **Contraindications:** known hypersensitivity to zidovudine, or any of the excipients. Manufacturer advises to avoid in patients with abnormally low neutrophil counts ($<0.75 \times 10^9/\text{litre}$) or low Hb ($<7.5 \text{ g/deciliter}$)
- **Renal/Hepatic impairment:** Patients with advanced renal failure should receive ZDV at the lower end of the dosage range. For dose management in patients with hepatic impairment contact the Pharmacy Department or see Summary of Product Characteristics (SPC) available on www.medicines.ie
- **Side effects:** include anaemia (usually not observed before 6 weeks of ZDV therapy but occasionally occurring earlier), neutropenia (usually not observed before 4 weeks of ZDV 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 ZDV.
- **Potential drug interactions:**
 - Increased risk of toxicity with potentially nephrotoxic and myelosuppressive drugs (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon). If concomitant therapy with any of these drugs is necessary then renal function and haematological parameters should be closely monitored.
 - Increased risk of haematological toxicity when given with NSAIDs.
 - Rifampicin appears to increase the clearance of ZDV.
 - Sodium valproate, fluconazole, methadone, probenecid decrease ZDV clearance.
 - ZDV may decrease or increase phenytoin levels.
 - For full details see SOP at www.medicines.ie or consult the Pharmacy Dept.

Administration of intravenous zidovudine (Retrovir®) to HIV exposed infants unable to take oral medication

Presentation: Zidovudine (ZDV) 200mg/20ml

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

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

- Term neonates ≥ 34 weeks 1.5mg/kg 6hrly IV infusion over 30 minutes
- Preterm neonates ≤ 34 weeks 1.5mg/kg/12hrly IV infusion over 30 minutes

Dosage adjustment is required in patients who develop neutropenia or anaemia – contact the Pharmacy or see SPC available on www.medicines.ie

Administration Details:

Drug Name	Route of Administration	Infusion Fluids	Final Concentration	Notes
ZDV	IV infusion over 30 minutes	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:

- **Contraindications:** infants with hyperbilirubinaemia requiring treatment other than phototherapy, or with increase transaminase levels over 5 times upper limit of normal.
- **Renal/Hepatic impairment:** Patients with advanced renal failure should receive ZDV at the lower end of dosage range. For dose management contact Pharmacy or see SPC on www.medicines.ie
- **Side effects:** 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 ZDV.
- **Potential drug interactions**
 - Increased risk of toxicity with potentially nephrotoxic and myelosuppressive drugs (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon). If concomitant therapy with any of these drugs is necessary, renal function and haematological parameters should be closely monitored and if required dosage reduced.
 - Increased risk of haematological toxicity when given with NSAIDs. Rifampicin appears to increase clearance of ZDV.
 - Sodium valproate, fluconazole, methadone, probenecid decrease ZDV clearance
 - ZDV may increase or decrease phenytoin levels.
 - For full details on interactions see SPC at www.medicines.ie or consult Pharmacy

References

1. Retrovir SPC last updated 27/5/2014 accessed via www.medicines.ie
2. Injectable Drugs Guide accessed via www.medicinescomplete.com 1/12/2014
3. Stockley's Drug Interactions accessed via www.medicinescomplete.com 1/12/2014
4. British HIV Association and Children's HIV Association Guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Medicine (2014), 15 (Suppl.4), 1-77

Administration of oral zidovudine to HIV exposed infants

Zidovudine (ZDV) 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 other antiretrovirals.

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

Dosing of Zidovudine for HIV exposed infants:

- **Full term neonate:** 4mg/kg 12hrly PO for 4 weeks.
- **Preterm neonate:**
 - (> 30 – 34 weeks gestation)
 - Week 1 - 2 2mg/kg/dose 12 hourly PO
 - Week 2 - 4 2mg/kg/dose 8 hourly PO
 - (≤ 30 weeks gestation) Week 1 - 4 2mg/kg/dose 12 hourly PO
- **Sick infants unable to take oral medications:**
 - Term 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.

- ZDV 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, ZDV 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 10⁹/l confirmed on 2 occasions) while taking ZDV, the following is recommended:

- Stop ZDV 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, ZDV 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 ZDV 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:

- ZDV 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. Retrovir SPC last updated 25/5/2014 accessed via www.medicines.ie
2. Neofax 2011 edition
3. British HIV Association and Children's HIV Association Guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Medicine (2014), 15 (Suppl.4), 1-77

Lamivudine (3TC, Epivir®)

Administration of Lamivudine to HIV exposed infants

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 other antiretrovirals.

Availability: Lamivudine oral solution 10mg/ml

Dosing:

Full term neonate: 2mg/kg/dose 12hrly PO for four weeks^(1,2,3).
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.

Renal impairment: dose adjustment required – contact Pharmacy or consult SPC available at www.medicines.ie

Liver impairment: no dose adjustment required

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 is recommended:

- Stop Lamivudine therapy for 3-5days.
- Repeat the FBC after the 3-5day-stoppage period.
- 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.

References:

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 2012. (2014 interim review). HIV Medicine (2014), 15 (Suppl.4) 1-77
4. Epivir Summary of PSC last updated 31/10/2014 accessed via www.medicines.ie

Nevirapine (NVP, Viramune®)

Administration of Nevirapine to HIV exposed infants

NVP 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 other antiretrovirals.

Availability: Nevirapine Liquid 10mg/ml

Dosing of NVP for HIV exposed infants:

Dose to be prescribed: 2mg/kg/dose PO⁽¹⁾ **2 doses only** (with or without food) as outlined below.

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

Side effects

NVP is generally well tolerated, but some may develop rash, allergic reactions, vomiting, diarrhoea, and stomach cramps, headache, sleepiness and muscle pain. There are generally no side effects attributable to NVP using just one or two doses.

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

Appendix 4: PCP chemoprophylaxis

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 $900\text{mg}/\text{m}^2/\text{dose}$.

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: $2\text{mg}/\text{kg}/\text{day}$ (Maximum dose $100\text{mg}/\text{day}$) – if the patient develops neutropenia then follow recommendations for dosage adjustment for Co-trimoxazole.

Pentamidine: PCP Prophylaxis: <5years: $4\text{mg}/\text{kg}$ IV every 4weeks
>5years: 300mg aerosolised every 4weeks

Pentamidine 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 is recommended:

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 5: Immunisation of HIV positive infants & children

VACCINATION	HIV exposed, uninfected infants	HIV infected CD4≥15 %	HIV ^e infected CD4<15%	TIMING	COMMENTS
HBV	Yes	Yes	Yes*	At birth then 2, 4, 6 months as part of the national immunisation schedule	
BCG	> 6 weeks of age	No	No	2-3 months of age in HIV exposed but uninfected infants.	Defer until HIV PCR at birth & 6 weeks are negative.
DTaP/IPV/Hib/Hep B (Infanrix-Hexa®)	Yes	Yes	Yes*	2, 4, 6 months	NB: Hib booster required at 13 months
DTaP/IPV	Yes	Yes	Yes*	4 – 5 years	
Tdap	Yes	Yes	Yes*	11 – 14 years.	
Meningococcal B	No	Yes	Yes	2 -<6mos: 3 doses, min interval 1 mos and booster at ≥12mos 6 - <12 mos: 2 doses, min interval 1 mos and booster at ≥12mos, at least 2 mos after primary series. 12 -<24 mos: 2 doses, min interval 2 mos and booster 12 – 23 mos after primary series >2yrs: 2 doses, 2 mos apart.	Meningococcal B vaccine is not yet part of the National Immunisation programme but is licenced for use for those who wish to prevent meningococcal B .
Meningococcal C	Yes	Yes	Yes*	For infants ≤ 12 months age: 4 and 12-13 months and 12 – 13 yrs For children >12 months age & ≤ 12 yrs: single dose only and booster at 12 – 13 yrs For children > 12 yrs 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.
Meningococcal ACWY	No	Yes	Yes	Single dose given at ≥ 15 mos of age and at least 2 mos after Meningococcal C vaccine	
Prevenar 13 (PCV13) 13 valent protein conjugate vaccine	Yes	Yes	Yes*	<12 months (min. 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 (PPV 23)	No	Yes	No*	Single dose given at >24 months of age at least 2 months after dose 3 PCV13 A single booster dose can be considered 5 years after the first dose.	The use of PPV in this population is controversial and is being replaced by use of conjugated vaccines. The need for repeated booster doses is not proven
MMR	Yes	Yes	No	12-15 months and 4-5 years	
Influenza vaccine	Not routine.	Yes	Yes*	For infants more than 6 months Yearly as appropriate	Those < 9 years not previously vaccinated a second dose should be given ≥4 wks.
Varicella vaccine	Not routine. Can use if wish to reduce risk of Varicella	Yes	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≥15% Children with no contraindications such as steroid therapy
Hepatitis A	Not routine can use if wish to reduce risk of Hep A	Yes	Yes*	Mono component vaccine - At ≥12 mos of age 2 doses with 6 month interval. Combined with HBV - Baseline, 1 month and 6 months	
HPV Vaccine (>9yrs)	Yes	Yes	Yes*	3 doses: Baseline, 2 and 6 months	Can be given to boys and girls

^e Children with severe immune deficiency (CD4<15%) can receive inactivated vaccines but are unlikely to generate a strong protective response to vaccination, if immune recovery is anticipated

Appendix 6: Follow-up of Infants exposed to maternal Hepatitis B or C

Follow-up of Infants exposed to maternal Hepatitis B						
Mother	Birth	2 months	4 months	6 months	8 months	
HBsAg+	Give HBIG (Hepatect CP®) And vaccinate HBV	HBV (given as part of 6:1)	HBV (given as part of 6:1)	HBV (given as part of 6:1)	Serology: HBsAg * Anti-HBs	Anti-HBs ≥ 100IU/ml = satisfactory HBsAb ≥10 and <100, give booster dose HBsAb <10: Check HBsAg. If HBsAg is neg reimmunise
HBcAB + HBsAg -	HBV	HBV (given as part of 6:1)	HBV (given as part of 6:1)	HBV (given as part of 6:1)	Serology: HBsAg* Anti-HBs	Anti-HBs ≥ 100IU/ml = satisfactory Anti-HBs ≥10 and <100, give booster dose Anti-HBs <10: Check HBsAg. If HBsAg is neg reimmunise

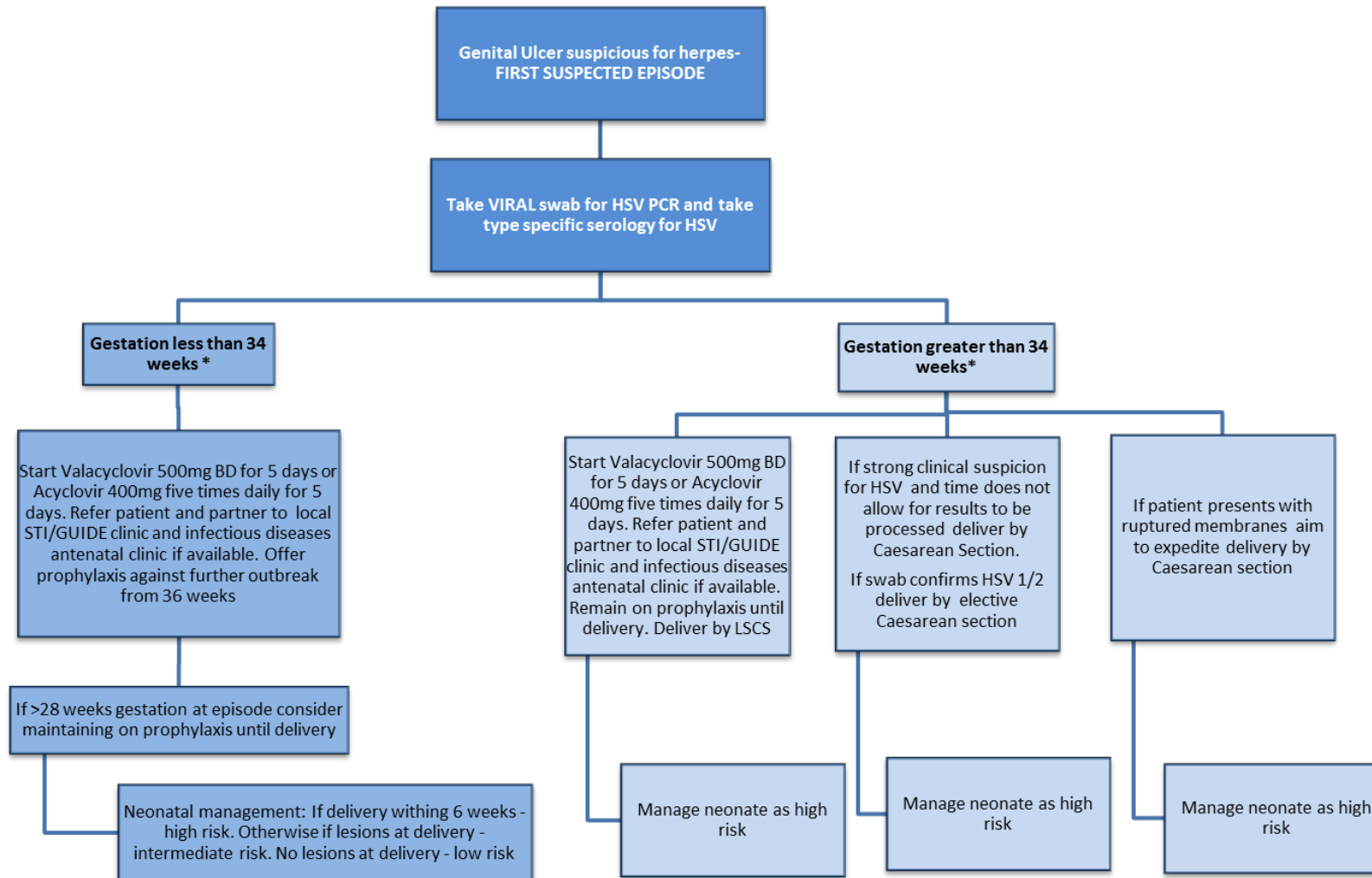
** Refer to Rainbow Clinic if HBsAg positive*

Follow-up of Infants exposed to maternal Hepatitis C				
Maternal HCV Status	Test	6 Weeks in Maternity Hosp	6 Months Local Paeds Clinic	18 Months Local Paeds Clinic
Follow-up of infants where mother is both HCV Ab and PCR positive	HCV Ab	✓	✓	✓*
	HCV PCR*	✓	✓	
Follow-up of infants where mother is only HCV Ab (i.e. PCR negative)	HCV Ab			✓
	HCV PCR*			✓

** Refer to Rainbow Clinic if HCV- PCR positive or if HCV Ab positive at >18months of age*

Appendix 7: Algorithms for women with suspected HSV in pregnancy

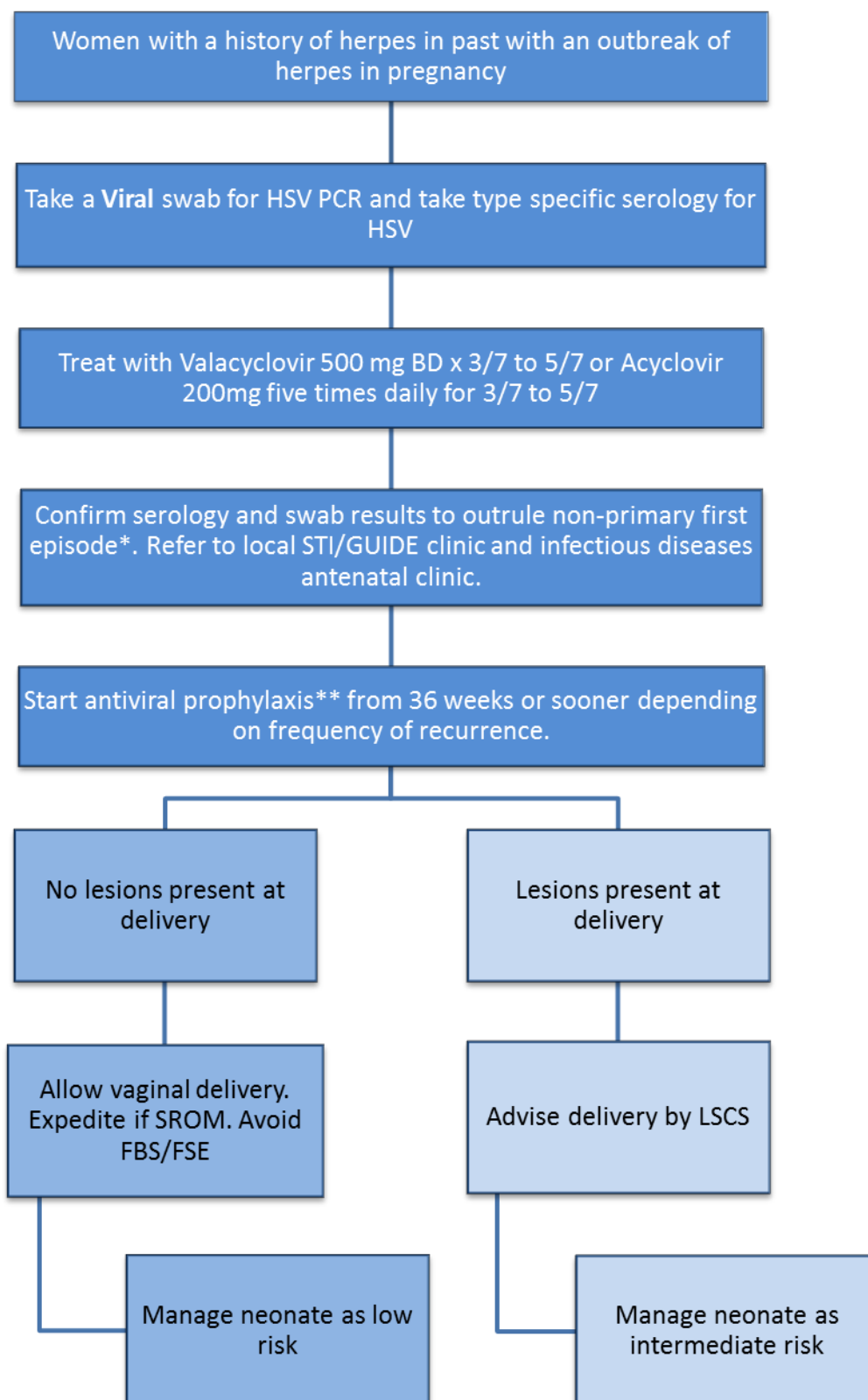
Women Presenting with Suspected First Episode of Genital HSV in Pregnancy



*34 weeks where delivery expected at 40 weeks. Adjust if delivery expected sooner. Significant viral shedding and exposure in the genital tract to a neonate is expected within 6 weeks of a primary episode**

**Acyclovir 400mg BD or Valacyclovir 500mg OD

Women Presenting with Recurrent HSV



*If true non primary first episode refer to suspected first episode algorithm

** Acyclovir 400mg BD or Valacyclovir 500mg OD

Appendix 8: Scenarios for Management of Infants Born to Women with HSV

Scenario 1: First Episode, Primary Infection at, or within, 6 Weeks of Delivery								
MATERNAL HISTORY					RECOMMENDATIONS			
Hx HSV lesions	Lesion PCR	Maternal Serology	Classification of maternal infection	Lesions at labour onset	Mode of delivery	Infant evaluation (HIGH RISK)	Infant treatment	Infant follow up
Suspected primary infection at or within, 6 weeks of delivery	HSV-1 or HSV-2 DNA detected	HSV-1 Ab negative & HSV-2 Ab negative	<p>Primary infection. 40 – 60% risk for infant transmission.</p> <p><i>If no history HSV & type specific serology and PCR results unavailable, assume first episode primary infection.</i></p> <p><i>Obtain maternal serology ASAP and PCR from visible lesions</i></p>	Present or absent	ELCS recommended Avoid other invasive procedures	<p>At 24-48 hours: obtain infant mucosal viral swabs for HSV-PCR^f (conjunctivae, nasal, oropharynx, rectal and skin swabs if vesicles present)</p> <p>EDTA blood sample for HSV PCR</p> <p>Consider evaluation, as above, immediately (rather than 24 – 48 hrs) following delivery for infants ROM > 4-6 hrs, gestation <37 wks, as they may have had pre-delivery exposure.</p>	<p><u>Manage as high risk:</u> IV ACV: 60mg/kg/day in 3 divided doses.</p> <p>If symptomatic & CSF HSV-PCR positive, treat for 21 days OR if CSF negative, treat for 14 days</p> <p>If surface/Blood PCR + but asymptomatic & CSF neg treat for 10 days</p> <p>For SVD or CS with > 4hrs ROM treat for 10 days</p> <p>If ELCS delivery and infant PCRs negative, discontinue ACV & OPD follow-up.</p>	<p>Weekly f/u at paediatric clinic to 6 wks.</p> <p>Repeat PCR tests if clinical suspicion of HSV disease</p> <p>Educate parents and care givers re symptoms of neonatal HSV disease and seek prompt medical attention if concerns</p>

^f If infant symptomatic or PCR+, check LFTs, Coags & CSF for HSV DNA-PCR.

Scenario 2: First Episode, Non - primary Infection at, or within, 6 Weeks of Delivery

MATERNAL HISTORY					RECOMMENDATIONS			
Hx HSV lesions	Lesion PCR	Maternal Serology	Classification of maternal infection	Lesions at labour onset	Mode of delivery	Infant evaluation (HIGH RISK)	Infant treatment	Infant follow up
Suspected 1 st episode at or within 6 weeks of delivery	HSV-1 or HSV-2 DNA detected	HSV type specific Ab discordant to HSV serotype from genital lesion, i.e.; Genital swab positive for HSV-2 with serology positive for HSV-1 and negative for HSV-2 Ab (more likely) Or Genital swab positive for HSV-1 with serology positive for HSV-2 and negative for HSV-1 Ab (less likely)	First episode non primary infection. Risk of transmission to neonate, 25%	Present or absent	ELCS recommended. Avoid other invasive procedures	At 24-48 hours: obtain infant mucosal viral swabs for HSV-PCR ⁹ (conjunctivae, nasal, oropharynx, rectal and skin swabs if vesicles present) EDTA blood sample for HSV PCR	<u>Manage as high risk pending results:</u> IV ACV: 60mg/kg/day in 3 divided doses. If symptomatic & CSF HSV-PCR positive, treat for 21 days <u>OR</u> if CSF negative, treat for 14 days If surface/Blood PCR + but asymptomatic & CSF neg treat for 10 days Infants delivered vaginally or by CS with > 4hrs ROM, treat for 10 days If ELCS delivery and infant PCRs negative, discontinue ACV & OPD follow-up	Weekly f/u at paediatric clinic to 6 wks. Repeat PCR tests if clinical suspicion of HSV disease Educate parents and care givers re symptoms of neonatal HSV disease and seek prompt medical attention if concerns

⁹ If infant symptomatic or PCR+, check LFTs, Coags & CSF for HSV DNA-PCR.

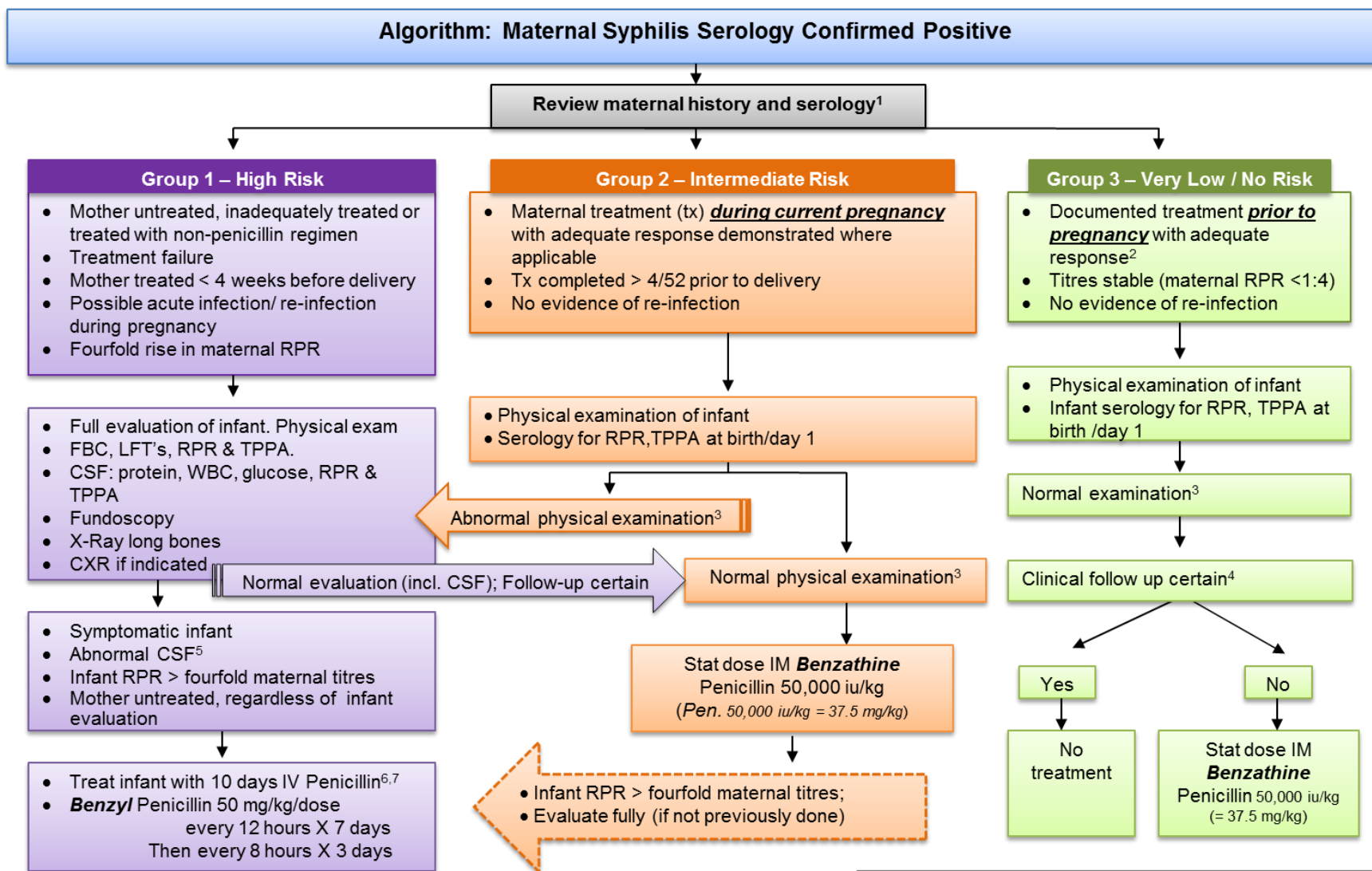
Scenario 3: Recurrent HSV with Visible Lesions at Delivery

MATERNAL HISTORY					RECOMMENDATIONS			
Hx HSV lesions	Lesion PCR	Maternal Serology	Classification of maternal infection	Lesions at labour onset	Mode of delivery	Infant evaluation (INTERMEDIATE RISK)	Infant treatment	Infant follow up
History of recurrent HSV prior to or during pregnancy Or History of first occurrence > 6 weeks prior to delivery	HSV-1 or HSV-2 DNA detected	HSV type specific Ab concordant with HSV type from genital lesion, i.e.; both swab and serology positive for HSV-1 Or Both swab and serology positive for HSV-2	Transmission risk < 2-3% <i>(If HSV PCR from genital lesion & type specific serology unavailable, determine if recurrent infection based on history. Obtain maternal serology ASAP and PCR from genital lesion to confirm recurrence vs first episode non primary infection)</i>	Present	ELCS, unless vaginal delivery imminent and in these situations avoid invasive procedures	At 24-48 hours: obtain infant mucosal viral swabs (conjunctivae, nasal, oropharynx, rectal and skin swabs if vesicles present) EDTA blood sample for HSV PCR	<u>Manage as intermediate risk</u> Commence treatment <u>only if infant PCR positive</u> Acyclovir dose: 60 mg/kg/day in 3 divided doses for 10 - 21 days depending on results of infant evaluation (see Scenario 1)	If delivered by ELCS, routine f/u with GP. If vaginal delivery or c-section with ROM >4 hours, f/u at paed's clinic at 6/52 Educate parents and care givers re symptoms of neonatal HSV disease and seek prompt medical attention if concerns

Scenario 4: Recurrent HSV without Visible Lesions at Delivery

MATERNAL HISTORY					RECOMMENDATIONS			
Hx HSV lesions	Lesion PCR	Maternal Serology	Classification of maternal infection	Lesions at labour onset	Mode of delivery	Infant evaluation (LOW RISK)	Infant treatment	Infant follow up
History of recurrent HSV prior to or during pregnancy Or History of first occurrence > 6 weeks prior to delivery	HSV-1 or HSV-2 DNA detected	HSV type specific antibody concordant with PCR from genital lesion, i.e.; both swab and serology positive for HSV-1 Or Both swab and serology positive for HSV-2	Recurrent infection. Risk of transmission to neonate 0-<1% in the absence of lesions at delivery <i>(If HSV PCR from genital lesion & type specific serology unavailable, assume recurrent infection based on history. Obtain maternal serology ASAP and PCR from genital lesion when present)</i>	Absent	Anticipate normal delivery Obstetric and delivery precautions not indicated	Not indicated	<u>Manage as low risk</u> Treatment not indicated	Routine f/u with GP Educate parents and care givers re symptoms of neonatal HSV disease and seek prompt medical attention if concerns

Appendix 9: Syphilis Algorithm



FOOTNOTES:

1. Maternal TPPA positive; RPR positive, neat or negative
 2. Maternal treatment prior to pregnancy assessed by adult GU/ID services and deemed adequate with satisfactory serological response.
 3. Any infant with signs of congenital syphilis should receive full evaluation and treatment regardless of maternal treatment history (see main text pg 7)
 4. If follow up uncertain in low risk infants, treat with stat dose IM Benzathine Penicillin
 5. CSF, WBC >5, protein >0.4g/l. Normal CSF does not exclude neurosyphilis. Interpret with clinical findings and serology
 6. If normal CSF result obtained during Tx with 10 days IV Penicillin, discontinue IV, give stat dose IM Benzathine Penicillin and discharge
 7. If > 1 day of therapy is missed, the entire course should be re-started
- NB: Always check other maternal serology - STI screen and HBV.

INFANT FOLLOW-UP:

- a) **Non-Treponemal test (RPR):** measures treatment response.
 - i. If 4x rise in infant RPR during f'up, re-evaluate and re-treat infant.
 - ii. Check RPR at 6 wks & 3 monthly, as necessary, until 2 consecutive RPRs are negative.
- b) **Treponemal test (TPPA):** includes/excludes congenital infection.
 - i. Check at 18 months; positive test diagnostic of congenital infection.
 - ii. If TPPA is negative (& RPR neg) at ≥12 mos can discharge from further f'up.
- c) If initial CSF abnormal repeat at 6 months.

Guide for Administration of benzATHINE penicillin

benzATHINE benzylpenicillin*

*Tall Man lettering has been used to differentiate benzATHINE benzylpenicillin and BENZYLpenicillin.

Benzathine benzylpenicillin is a prolonged release penicillin antibiotic used for the treatment of infections related to maternal syphilis serology reactive and confirmed positive.

MEDICATION SAFETY ISSUES

- A fatal neonatal medication error has been reported after confusion between BENZYLpenicillin and benzATHINE benzylpenicillin. A series of errors led to the IV administration of benzATHINE benzylpenicillin which should only be administered IM. Inadvertent I.V. administration has resulted in thrombosis, severe neurovascular damage, cardiac arrest, and death.
- DO NOT GIVE INTRAVENOUSLY**
- It is essential to use the correct needle size when reconstituting and administering this product to reduce the risk of the patient not receiving the full dose.

USES

Used for the treatment of congenital syphilis in infants during the first month of life.

PRESENTATION (EMP)

"Benzetacil" 2,400,000 (2.4 million units) or 1,200,000 (1.2 million units) powder for solution for intramuscular injection. 2.4 million units is equivalent to 1800mg of BenzATHINE benzylpenicillin.

DOSAGE

Neonatal: Asymptomatic congenital syphilis: I.M. 50,000 units/kg (i.e.37.5mg/kg) as a single dose.

RECONSTITUTION

The reconstituted suspension must be used immediately

	Benzetacil 1,200,000	Benzetacil 2,400,000
Diluent Volume	3ml	6ml
Final concentration	400,000 units/ml	400,000 units/ml
Volume per kg to administer 50,000 units/kg	0.12ml	0.12ml

ADMINISTRATION

- The drug is only very slightly soluble in water and does not dissolve completely but forms a suspension
- The manufacturer has received many reports of the reconstituted drug thickening in the syringe and blocking the needle prior to injection or during injection
- The manufacturer states that the product is a suspension and if it's not quickly administered the particles may sediment and administration will not be possible
- The injection should be reconstituted immediately before use
- Introduce the solvent into the powder vial, turning the vial gently and extract the suspension with a needle
- To inject; use a different needle from the one used to draw up the suspension, i.e., one that does not contain Benzetacil suspension
- Administer the correct dose using the reconstituted solution immediately via the **intramuscular route**
- The needle may become blocked if injection is not made at a steady rate due to high concentration of suspended material in the product.
- A 20G needle is recommended for infants and adults.**
- Using a smaller diameter needle may lead to blockages and failed injection attempts
- Avoid injection into or near an artery or nerve.

SAMPLE CALCULATION

Case: 3.28 kg baby with congenital syphilis.

Dose: 50,000 units per kg = $50,000 \times 3.28\text{kg} = 164,000$ units

50,000 units in 0.12ml

= 0.12ml/kg by IM injection

Multiply the baby's weight in kg by 0.12ml

Total dose = $3.28\text{kg} \times 0.12\text{ml} = 0.39\text{ml} = 164,000$ units

STORAGE

Use immediately once reconstituted.

MONITORING

BenZATHINE benzylpenicillin is renally excreted. In young infants and patients with renal impairment, excretion is prolonged.

SIDE EFFECTS

Hypersensitivity reactions may occur.

Appendix 10: Developmental Assessment Check List

				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	<i>rolling before three months might indicate hypertonia</i>
FM	Retains rattle	Y	N	
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	<i>head lag, poor head control</i>
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	<i>absent babbling may indicate hearing deficit</i>
FM	Transfer objects hand to hand, raking grasp	Y	N	
LS	Babbles "baba" "gaga", lateral orientation	Y	N	
SA	Recognises strangers	Y	N	
Age: 18 months: Date		Doctor's name		
GM	Runs, throws objects from standing without falling	Y	N	<i>If not walking - refer hand dominance prior to 18 mos points to contra lateral weakness lack of social relatedness may indicate autism</i>
FM	Tower 3-4 cubes, scribbling, turns 2-3 pages at a time	Y	N	
LS	Points to 3 body parts, points to self, 7-10 words	Y	N	
SA	Plays with other children, feeds with spoon, imitates parents	Y	N	
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	

Appendix 11: Personnel Contact Details

Rainbow Team

Infectious Diseases Consultants

Prof. Karina Butler	01 409 6100
Dr Patrick Gavin	01 409 6100
Dr Ronan Leahy	01 409 6100
Dr Wendy Ferguson	01 873 0700

Clinical Nurse Specialists

Ms Michele Goode	01 409 6097 or 409 6100	Bleep 523
Ms Sinead McDonagh	01 409 6194 or 409 6100	Bleep 544
Ms Annette Rochford	01 409 6194 or 409 6100	Bleep 544

Registrar OLCHC

01 409 6100

Bleep 426

Registrar TCUH

01 878 4200

Bleep 871

Secretaries

Ms Jennifer Malone (OLCHC)	01 409 6338
Ms Deirdre Butler (Temple Street)	01 878 4449

Data Base Manager

Ms Amanda Walsh	01 409 6096
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Pharmacist

Ms Mary Worrell	01 409 6796/6536
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Adult HIV Services

St James's Hospital

Genitourinary Medicine & Infectious Diseases Consultants

Prof Fiona Mulcahy	01 416 2590	
Prof Colm Bergin	01 416 2407	
Dr Susan Clarke	01 428 4836	
Dr Fiona Lyons	01 410 3538	Mob: 086 2235462

Clinical Nurse Specialists

Ms Sinead Murphy	01 410 3539
Ms Georgina Nangle	01 410 3824

Or contact any of the above through switch on 01 410 3000, at weekends or after hours ask to speak to the HIV consultant on call

Mater Hospital

Infectious Diseases Consultants

Dr Jack Lambert	01 803 1122	Mob: 087 2613778
Dr Gerard Sheehan	01 803 1122	
Dr Patrick Mallon	01 803 1122	

Clinical Nurse Specialists

Mr Jeremy Farrell	01 803 1122
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Beaumont Hospital

Infectious Diseases Consultant

Prof Sam McConkey	01 809 3006	Bleep 801
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Secretary

Ms Jeanne Byrne	01 809 3006
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Clinical Nurse Specialist

Ms Deirdre Redmond	01 809 3006	Bleep 654
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Cork University Hospital

Infectious Diseases Consultant

Prof Mary Horgan	021 454 6400
Dr Arthur Jackson	021 454 6400

Paediatrician

Dr Brendan Murphy	021 492 0500
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Clinical Nurse Specialist

Ms Elizabeth Murphy	087 699 6272
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University College Hospital Galway

Infectious Diseases Consultant

Dr Catherine Fleming	091 525 200
Dr. Helen Tuite	091 580 580

Clinical Nurse Specialist

Ms Nicola Boyle	091 580 580	Bleep 469
Direct number	091 542 689	

Paediatrician

Dr Edina Moylett	091 544 084
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Limerick Regional Hospital

Infectious Diseases Consultant

Dr. Busi Mooka	061 482 382 or
contact mobile through switch	061 301 111

Nurse Manager

Josephine Clancy	061 482 767
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Obstetrics

Prof Amanda Cotter	061 301 111
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Maternity Hospital ID Services

Rotunda Hospital – Dove Clinic

Obstetrician

Dr Maeve Eogan 01 873 0700

Infectious Diseases Consultants

Dr Jack Lambert 01 803 1122
087 2613778

Clinical Midwife Specialist

Ms Mairead Lawless 01 873 0700 Bleep 883
087 4151478

Associate Specialist Paediatric Infectious Diseases

Dr Wendy Ferguson 01 873 0700

Coombe Women and Infants University Hospital

Obstetrician

Dr Michael O'Connell 01 408 5200

Clinical Midwife Specialist

Ms Orla Cunningham 01 408 5200 Bleep 215
01 408 5781

National Maternity Hospital

Obstetrician

Prof Fionnuala McAuliffe 01 661 0277

Midwife (Antenatal Clinic)

Ms Caroline Brophy 01 637 3530

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