Blood borne viruses in infancy: diagnosis and management

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OUTLINE

- Background
- HIV
- Hepatitis B
- Hepatitis C

Detection and Prevention: *RANZCOG Statement (Nov 2012)*

- It is imperative that the woman is provided with appropriate counselling as to the limitations of screening for viral infections in pregnancy and the implications of both positive and negative findings.

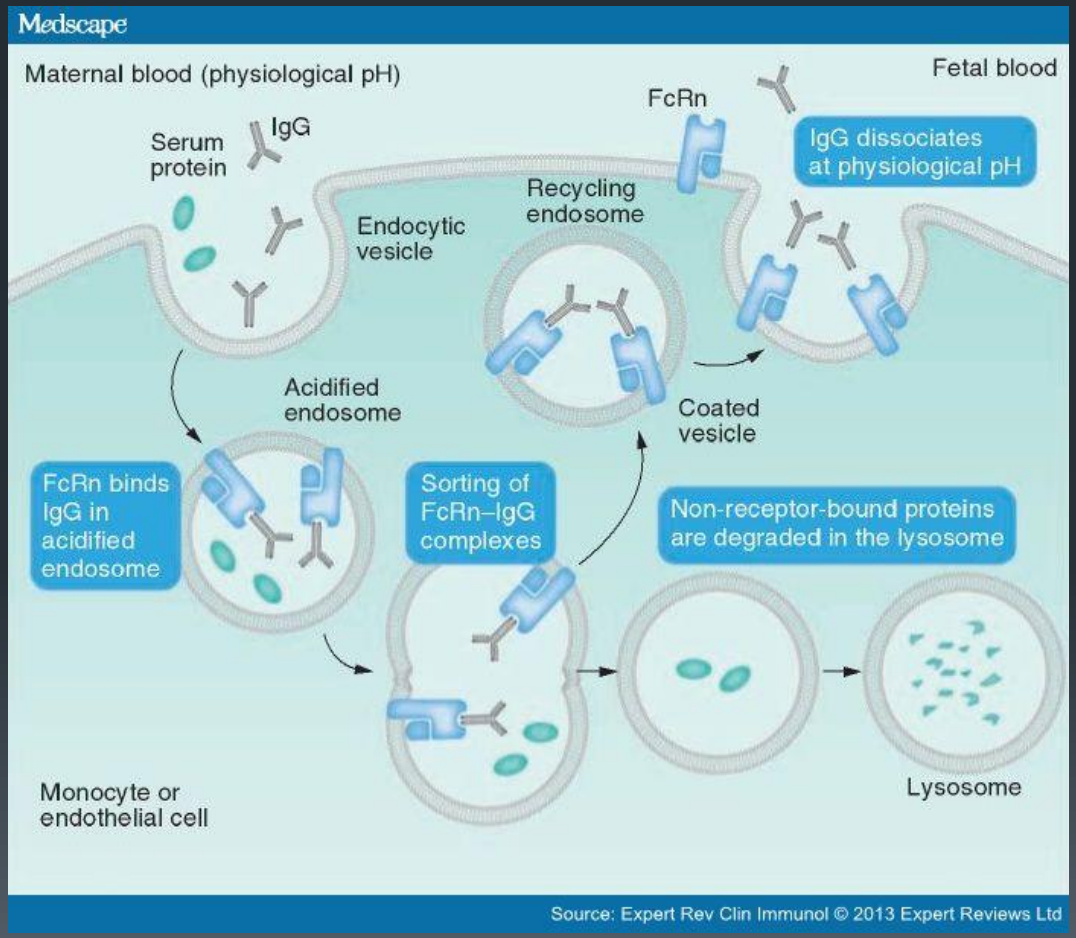
- **HIV**
  - All pregnant women should be recommended to have HIV screening at the first antenatal visit.

- **Hepatitis B serology**
  - All pregnant women should be recommended to have Hepatitis B screening in pregnancy.

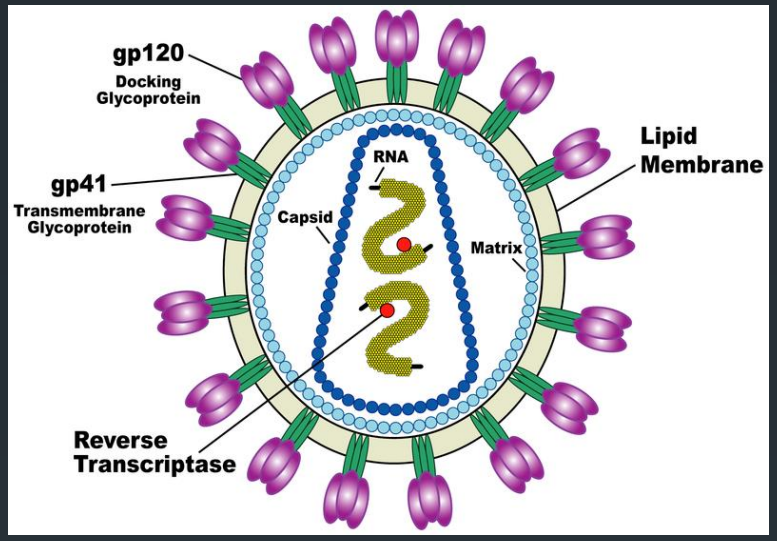
- **Hepatitis C serology**
  - All pregnant women should be recommended to have Hepatitis C screening in pregnancy. However it is acknowledged that this is a contentious area of practice.

http://www.ranzcog.edu.au/component/docman/

Diagnostic issues in infants



HIV


gp120
Docking
Glycoprotein
gp41
Transmembrane
Glycoprotein
RNA
Capsid
Matrix
Lipid
Membrane
Reverse
Transcriptase

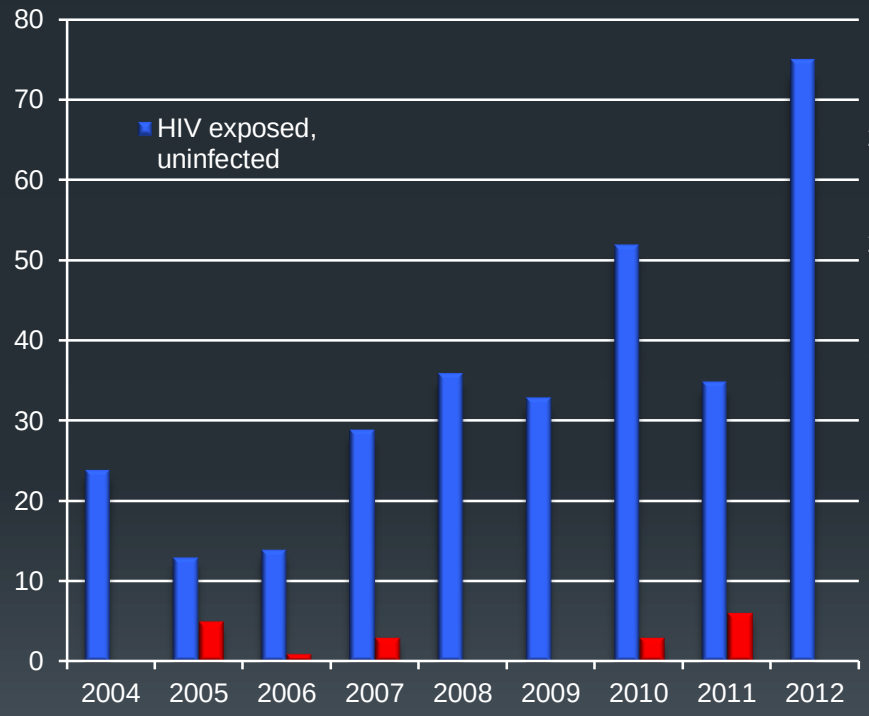
Mother-to-child Transmission (MTCT) of HIV

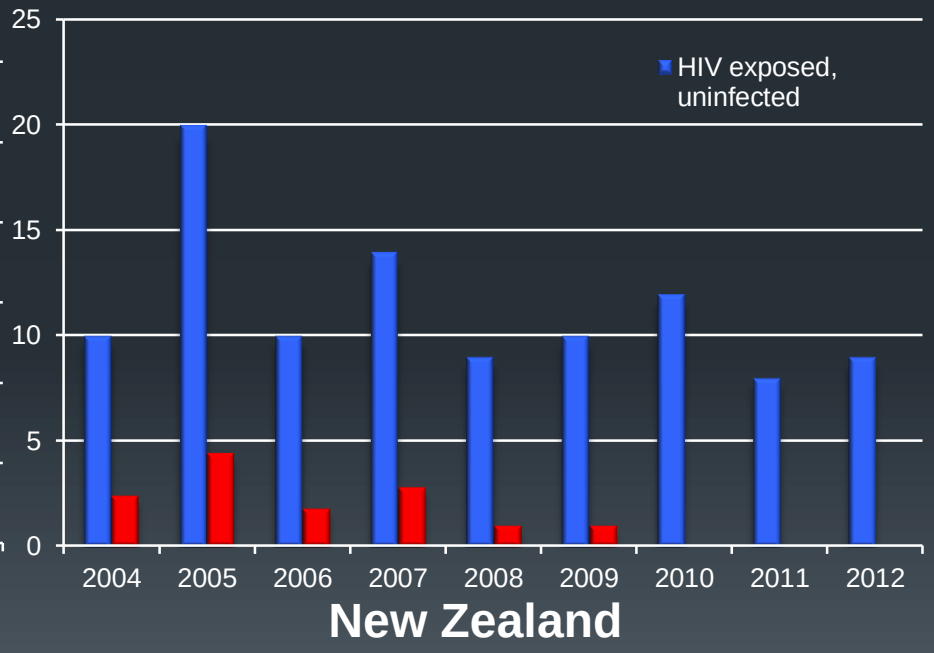
- This is the mechanism of infection for the vast majority of children with HIV

- Without intervention the rate is between 25-40%
  - With intervention, the risk of transmission is <1%

- Rate of transmission is influenced by the current clinical status of the mother
  - (importance of cART during pregnancy)

HIV-exposed uninfected children (HEUC) – Growing cohort of children





Management = Prevention

- Maternal ART
  - During pregnancy
  - Prenatal boost if high risk/late diagnosis
- Infant PEP
  - 4 weeks AZT if standard risk
  - 3 drugs if increased risk
- Avoidance of breastfeeding
- Follow-up and testing

Standard adult HIV Testing

- Screening with 4th generation ELISA
- Confirmation with supplementary tests and Western Blot
  - Subsequent testing for HIV RNA viral load and resistance genotyping
- Not appropriate for testing infants for MTCT (all positive Ab)

Infant HIV Testing

- Proviral DNA PCR

or

- HIV RNA PCR (viral load)

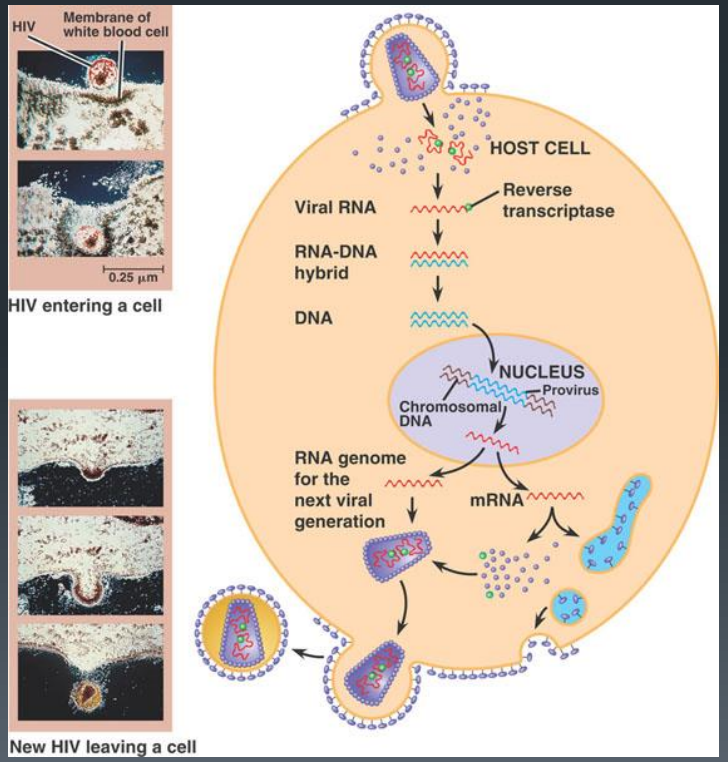
- *At birth*, 2 weeks and 6 weeks after cessation of PEP*

* Or while in hospital, first days of life

HIV Proviral DNA PCR

- Qualitative PCR
- Target is HIV-1 *gag* gene
- Limit of detection 10 copies/mL
- The “standard”

- Limitations
  - Blood volume and transport
  - Access to testing
  - Non-subtype B virus or cART



HIV RNA PCR

- Use: mainly as viral load PCR
- Levels relatively low at birth but high by 1-2 months of age
- Appears as sensitive and specific as DNA PCRs
- More widely available and may require less blood

- Limitations
  - Potential interference from antiretroviral therapy
  - Possible false positives with low copy numbers

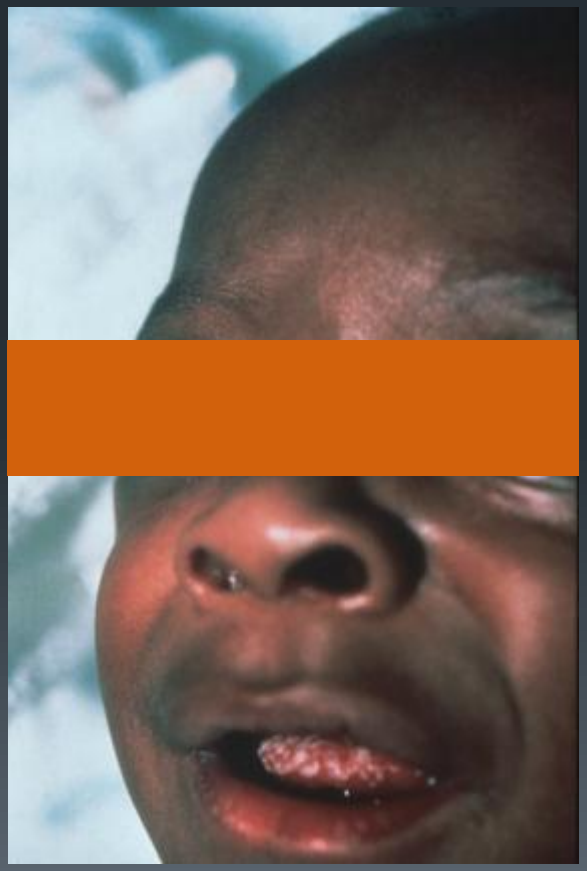
Time	TEST	CLINICAL CARE
Week 1 (while in hospital)	HIV proviral DNA PCR (2 ml, EDTA tube)	• Clinical review • **AZT** syrup (**4 mg/kg per dose, BD**) for **4 weeks** (start within 6 -12 hours of birth) • Neonatal hepatitis B vaccine
Week 6	HIV proviral DNA PCR	• Clinical review • Ensure AZT syrup was stopped at **WEEK 4** • Infant vaccines as per Australian Immunisation Schedule
3 months	HIV proviral DNA PCR	• Clinical review • Infant vaccines as per Australian Immunisation Schedule
6 months	No tests	• Clinical review • Infant vaccines as per Australian Immunisation Schedule
12 months	No tests	• Clinical review • Infant vaccines as per Australian Immunisation Schedule
18 months	HIV antibody	• Clinical review • Infant vaccine as per Australian Immunisation Schedule

What is different about HIV in children compared to adults?

- Children with HIV have higher mortality and morbidity in the first 2 years than adults if untreated
- Approximately 50% untreated infants develop moderate immune suppression by 12 months
- Untreated infants have poorer growth and neurodevelopmental outcomes

Infants presenting with HIV

- Hepatosplenomegaly / lymphadenopathy
- Failure to thrive
- Persistent oral thrush
- GI symptoms
- Recurrent infections
- Respiratory disease
- Encephalopathy



CHER Trial
Children with HIV Early antiretroviral study

- Starting ART by 12 weeks of age reduces early mortality by 75%

- Substudy: infants treated early had significantly better gross motor and neurodevelopmental profiles

- Results support need for enhanced MTCT intervention/ early infant diagnosis

Violari *et al, N Engl J Med*. 2008;359:2233–2244

Management – Infant HIV

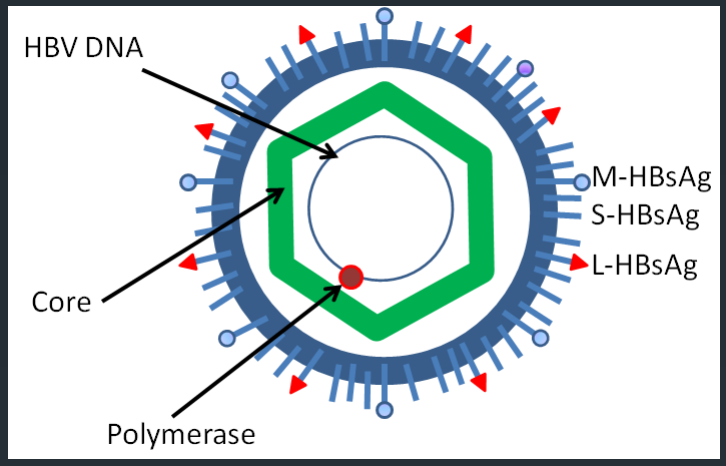
- ARVs
  - Triple therapy usual:
    - 2(3) NRTIs plus NVP or LPV/r
    - Consider maternal therapy (*NVP*) and obtain genotypic resistance assay
- Prophylaxis against *Pneumocystis jirovecii* should be given to all HIV-infected infants from age 1 month (cotrimoxazole)
  - *and to older children with low CD4 counts*
- Monthly clinical review (at least until 6m)
- Treatment of other infections

What is different about HIV in children compared to adults?

CD4 counts are age specific especially <5 years

Counts are measured in % (lymphocytes)

HIV disease category	CD4%	CD4 0-12 months old	CD4 1-5 years old	CD4 6-12 years old
Category 1 – no damage	25% or over	over 1,500	over 1,000	over 500
Category 2 – moderate	15-24%	750-1,500	500-1,000	200-500
Category 3 – severe	less than 15%	less than 750	less than 500	less than 200



Hepatitis B virus

Epidemiology

- Approximately two billion people have been infected with hepatitis B virus
- This virus is an important cause of cirrhosis and liver cancer worldwide
- Carriage rates vary geographically
- 160,000 people in Australia are living with chronic hepatitis B

Hepatitis B transmission in pregnancy

- Risk of transmission in pregnancy depends on maternal viral burden
- Maternal eAg positivity a known risk factor for transmission (>90% vs 40%)
- Emerging data on role of HBV DNA VL as an independent risk factor
  - Linear correlation between failure of immunoprophylaxis and HBV viral load

1. www.ashm.org.au
2. Zou et al, J Viral Hepat 2012

Maternal antiviral therapy

- PEG-IFN contraindicated
- Lamivudine, adefovir and entecavir are listed by the FDA as pregnancy category C drugs
- Telbivudine and tenofovir as category B drugs
- ASID perinatal guidelines recommend Rx for HIB VL >10^7 IU/mL from 30 weeks' gestation

1. www.ashm.org.au
2. Zou et al, J Viral Hepat 2012
3. ASID perinatal guidelines

Maternal antiviral therapy

- Lamivudine, telbivudine or tenofovir may be used in the 3rd trimester to reduce vertical transmission for those with ≥10% risk of transmission despite immunoprophylaxis

- Caution with cessation of therapy post-partum due to risk of flare

Interventions – infant

- HBV vaccination within 12 hours
  - Reduces risk of transmission by 70%
- HBV immunoglobulin within 72 hours*
  - In conjunction with HBV vaccine reduces risk of transmission by 90%
- Infant follow up at 12 months
  - (HBsAg and anti-HBs)

** Ideally give within 12h with HBV immunisation in different site*

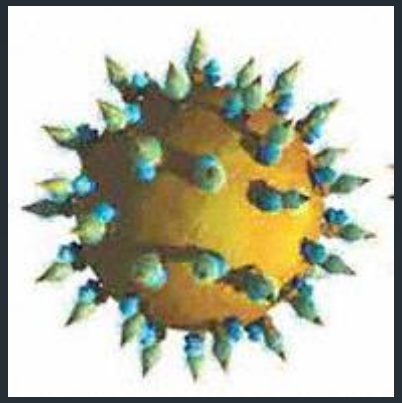
HBV+ infant: monitoring and treatment

- Clinical review including gastroenterology
  - (6-monthly)
- HBV serology and HBV DNA
- Annual alpha-fetoprotein + liver ultrasound
- Offer HAV vaccination and avoid hepatotoxins

- Treatment not indicated in asymptomatic children in immune tolerant phase

Antiviral therapy for infants and children

- Options:
  - Lamivudine
    - May be used for infants (data from HIV therapy)
  - Entecavir/Tenofovir
    - May be used in children from 2 years
  - IFN therapies generally avoided



Hepatitis C Virus

Epidemiology and Vertical Transmission

- The global prevalence of hepatitis C virus (HCV) infection is 2%-3%, with 130-170 million HCV-positive people, most of them chronically infected
- Risk of vertical transmission approximately 5%
- High viral load (≥2.5 × 10^6 RNA copies/mL), HIV co-infection, and invasive procedures increase risk of transmission
- There is no evidence that breast-feeding is a risk factor for vertical transmission of HCV.

Floreani, *World J Gastroenterol* 2013

Management - prenatal

- Also screen for HBV/HIV and for Hepatitis A to prevent complications
- Antiviral therapy for HCV infection in pregnancy is generally contraindicated (ribavirin and interferon), less data available for newer antivirals
- Support and plan infant follow-up with HCV testing

http://aidsinfo.nih.gov/guidelines

Hepatitis C – exposed infant

- HCV RNA test at ≥3 months of age
- HCV Ab test at 18 months to document clearance of maternal antibody

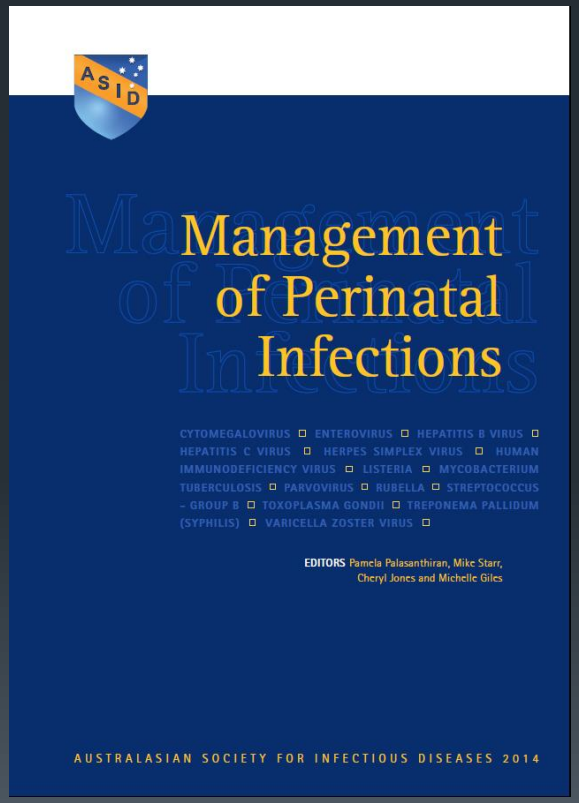
HCV+ Infant: Monitoring and therapy

- Clinical review including gastroenterology
  - Offer HAV/HBV vaccination and avoid hepatotoxins
- HCV RNA
  - Spontaneous clearance can occur (up to 30% of infected infants)
    - rare beyond age 3 years
  - Children who clear infection are negative for HCV RNA but remain antibody-positive
- Monitoring
  - Alpha-fetoprotein and liver ultrasound
  - Fibroscan (biopsy if concern about fibrosis)

HCV+ treatment in children

- Not generally required during infancy or childhood
- For children ≥3 years
  - PEG-IFN and ribavirin have been used
    - SVR better for genotypes 2 and 3
  - Most centres suggest deferring treatment for now (2015) until:
    - Direct acting antiviral agents (DAAs) now in Phase 2 trials
      - Sofosbuvir plus ribavirin for ages 3-17 years, with genotypes 2 or 3
      - Sofosbuvir/ledipasvir coformulation

ASID Perinatal Guidelines 2014



Further information and useful resources

- http://www.asid.net.au/resources/clinical-guidelines
- http://www.chiva.org.uk/
- http://aidsinfo.nih.gov/guidelines
- www.bhiva.org.uk
- www.ashm.org.au