Congenital HIV and Childhood AIDS

HIV infection in young children most commonly arises as a result of mother-to-child transmission (MTCT). It is thought that only 1.5-2% of MTCT occurs transplacentally during pregnancy. The vast majority occurs due to maternofetal transmission of blood during parturition or postnatal breast-feeding. A negative maternal HIV test at booking does not preclude neonatal infection - maternal infection and seroconversion can occur at any time during pregnancy and lactation. This is well documented in countries with a high prevalence of HIV and has been seen in the UK.

Other routes of infection, such as precocious intravenous drug use or sexual abuse/activity, should be borne in mind as rarer scenarios, which become increasingly common as children approach adolescence.

Children suffer not only from the direct effects of AIDS itself but from the fact that their primary caregivers are very likely also to be affected or to have died from the disease. In 2014, approximately 17.8 million children had been orphaned by HIV.

Epidemiology

The World Health Organization (WHO) estimates that in 2014 there were approximately 3.2 million cases of childhood HIV infection worldwide.

- 91% of the world's HIV-positive children live in sub-Saharan Africa.
- In the UK, the unlinked anonymous surveillance programme of 2011 revealed that 2.2 in 1,000 women giving birth in England and Scotland were HIV-positive.
- In 2013, 1 in 6 HIV-positive women had not been diagnosed at the time of delivery.
- The prevalence of UK-born women living with HIV had increased from approximately 17,000 in 2006 to 26,000 in 2013.
- Without intervention, between 15-45% of babies born to HIV-infected mothers in the most severely affected countries are also infected. With appropriate interventions transmission rates can be reduced to less than 1%.
- Worldwide, there was a 58% reduction in the number of new HIV infections in children between 2002 and 2013. Nevertheless, more than 240,000 children were infected with HIV during 2013 - 700 new infections every day. The majority of these were infected via MTCT, during pregnancy, labour, delivery or breast-feeding.
- By the end of March 2014, 1,873 HIV-infected children had been reported to the Collaborative HIV Paediatric Study (CHIPS - a multi-centre cohort study of HIV-infected children in the UK and Ireland). 44% were born in the UK or Ireland, 55% were born abroad and 2% were of unknown origin.

Risk factors

The following factors increase the risk of MTCT:

- Higher levels of maternal viraemia.
- HIV core antigens.
- Lower maternal CD4 count.
- Primary HIV infection occurring during pregnancy.
- Chorioamnionitis.
- Co-existing other sexually transmitted infection (STI).
- Invasive intrapartum procedures - eg, fetal scalp electrodes, forceps, ventouse.
- Rupture of membranes (especially if delivery is more than four hours after the membranes ruptured).
- Vaginal delivery.
- Advanced maternal age.
The firstborn of twins (born to an HIV-infected mother).
Preterm birth.
Female babies more likely to be infected early (transplacental/perinatal routes).
Co-existent malaria may increase HIV transmission rates although this is not firmly established.

Presentation
It is to be hoped that most cases of UK-based HIV infection in pregnant mothers will be identified before delivery, so that HIV infection of the child is unlikely/anticipated. However, appropriate vigilance and suspicion of HIV infection in unwell children are important.

Impairment of cellular immune defences (the type found in HIV infection) should be suspected in children who present with:

- Recurrent bacterial infections, particularly invasive infections like meningitis, septicaemia and pneumonia.
- Recurrent/frequent common childhood infections such as otitis media, chest infection, urinary tract infections, sinusitis.
- Unusual infections such as *Mycobacterium avium* complex (MAC), *Pneumocystis jirovecii* pneumonia.
- Persistent oral candidiasis that fails to respond to standard therapy.
- Recurrent or severe viral infections - eg, *herpes simplex*, *herpes varicella-zoster* infection as shingles, cytomegalovirus (CMV) retinitis.
- Growth failure, failure to thrive or generalised wasting with no obvious nutritional, metabolic, endocrine or other cause.
- Developmental delay, particularly language impairment, may suggest HIV encephalopathy.
- Developmental regression caused by HIV encephalopathy or opportunistic central nervous system (CNS) infection - eg, *Toxoplasma gondii*.
- Older children may show subtle diminution in intellectual skills such as concentration and memory, or schooling problems, due to HIV encephalopathy.
- Unusual rashes: erythematous, papular rash due to HIV dermatitis, shingles rash, candidal dermatitis with marked erythema, purpura/bruising in rare cases of HIV-induced thrombocytopenia.
- Parotid enlargement, large tonsils, oral aphthous ulcers, oral/pharyngeal plaques due to thrush or leukoplakia, CMV retinitis.
- Signs of congestive cardiac failure due to cardiomyopathy. Peripheral oedema can also be caused by hypoalbuminaemia due to HIV nephropathy or malnutrition due to gastrointestinal dysfunction.
- Hepatomegaly and splenomegaly are relatively common findings in HIV-infected children.

Differential diagnosis

- Causes of **growth impairment or failure to thrive**.
- Causes of developmental delay or regression.
- Other causes of childhood anaemia ± immunosuppression.
- **Bruton's agammaglobulinaemia** or transient **hypogammaglobulinaemia** of infancy.
- Common variable immunodeficiency.
- Causes of lymphadenopathy.
- **Intestinal malabsorption**.
- Neglect or malnutrition of child.
- **Infectious mononucleosis**.
- Severe combined immunodeficiency.
- Thymic aplasia.
- **Primary tuberculosis** (TB).
- Metabolic childhood disease - eg, organic acidurias.
- **Primary dermatological disease**.
- **Cystic fibrosis**.

Investigations

Expectant mothers should be offered routine screening for HIV infection during pregnancy. Those with positive results should be referred to a centre with expertise in managing the mother’s HIV diagnosis and the pregnancy, in order to reduce the likelihood of MTCT.
Testing a child for HIV has large implications for the family, as most cases involve vertical transmission. Information given should be culturally appropriate and interpreters used as needed. See also separate article Consent to Treatment in Children (Mental Capacity and Mental Health Legislation).

**Diagnostic tests**

Early diagnosis of HIV infection is crucial and ideally should occur rapidly postnatally where mothers are known to be HIV-positive, as this allows for prophylaxis against and early detection of and treatment of, opportunistic infection in neonates.

Standard ELISA tests are unreliable for the first 18 months because of the transmission of maternal antibodies which persist for some time in the baby.

Polymerase chain reaction (PCR) of viral DNA can be used for early detection in infants of HIV mothers and is usually performed at 0-2 days, 6 weeks and 3 months.

Second-line, confirmatory tests include:

- HIV RNA PCR.
- Baseline HIV resistance (+/- maternal HIV resistance).
- CD4 count.

**Additional tests**

Additional tests are performed at diagnosis to assess concurrent infection and risk of different opportunistic infection and can include:

- Serology for hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus, CMV, herpes simplex virus, mumps, measles, rubella, VDRL and toxoplasmosis.
- Malaria film.
- Mantoux test/TB cultures.
- Baseline CXR.
- Brain ultrasound/MRI (where there are neurological signs).
- HLAB5701 genotype (strongly associated with hypersensitivity to the antiretroviral agent abacavir).

**Monitoring**

- CD4 counts.
- Viral load.
- Screening - audiology, dental, neurodevelopmental, ophthalmology, TB.
- Additional tests in line with drug therapy protocols and clinical status.

**Staging**

A number of clinical staging systems are available, the most common used being the Centers for Disease Control and Prevention (CDC) paediatric HIV classification and the WHO classification systems :[14, 15]

- **Category N** - asymptomatic.
- **Category A** - mildly symptomatic. 2 or more of:
  - Lymphadenopathy.
  - Hepatomegaly.
  - Splenomegaly.
  - Dermatitis.
  - Parotitis.
  - Recurrent/persistent upper respiratory tract infection (URTI), sinusitis or otitis media.
• **Category B** - moderately symptomatic with illnesses that result from HIV infection. These include:
  - Bacterial meningitis, pneumonia or sepsis (single episode).
  - Oropharyngeal thrush lasting longer than two months.
  - Recurrent or chronic diarrhoea.
  - Lymphoid interstitial pneumonia.
  - Nephropathy.
  - Fever lasting at least one month.
  - Disseminated varicella.

• **Category C** - severely symptomatic with an AIDS-defining illness.

Within these categories, a measure of immunological suppression (based on CD4 count related to age) is designated by a number (1 = no suppression, 2 = moderate suppression and 3 = severe suppression). For example, A2 refers to a mildly symptomatic child with moderate suppression of CD4 count.

**Management**

In the developing world, management is largely dictated by the availability of healthcare resources and by the lack of recognition of HIV infection in pregnant women. Bottle-feeding may present significant risks in areas where there is poor access to clean, potable drinking water, and needs to be balanced against the reduction in risk of HIV transmission.

**Developed world management of HIV-infected pregnant women**

Antiretroviral therapy (ART) for expectant mothers and for newborns (particularly if breast-feeding).

- ART is given to prevent MTCT and to prevent maternal disease progression. The optimal regimen is determined on a case-by-case basis according to prevailing guidelines.
- Zidovudine (ZDV) is indicated for use in pregnancy for prevention of MTCT of HIV but single-agent ZDV therapy which does not suppress plasma viraemia to undetectable levels may allow the emergence of resistant virus.
- Potent combinations of three or more antiretroviral drugs have now become the standard of care. (Combined ART is sometimes given the acronym cART.) Women with advanced HIV should be treated with an ART regimen. The start of treatment should be deferred, if possible, until after the first trimester and should be continued after delivery.

For further details, see separate article Management of HIV in Pregnancy.

**Neonates born to HIV-infected mothers**

- ZDV monotherapy for the infant is appropriate when a mother on combination therapy delivers with a viral load of <50 HIV RNA copies/mL. Twice-daily ZDV monotherapy for four weeks is the treatment of choice.
- Where the mother’s viral load is >50 HIV RNA copies/mL, three-drug therapy should be given for four weeks. A common combination is ZDV, lamivudine and nevirapine. Treatment should be started as soon as possible and no later than 72 hours after birth.
- Babies born to untreated HIV-positive mothers should likewise receive three-drug therapy for four weeks.
- *P. jirovecii* pneumonia prophylaxis, with co-trimoxazole, should be started from four weeks of age in:
  - All HIV-infected infants.
  - Infants with an initial positive HIV DNA/RNA test result until HIV has been excluded.
  - Infants whose mother’s viral load at 36 weeks of gestation or at delivery is >1,000 HIV RNA copies/mL despite ART or unknown and continued until HIV infection has been excluded).

**Children with confirmed HIV seroconversion**

They should receive specialist paediatric infectious disease management. Children and young people should be involved as much as possible in decisions about their care, even when they are not able to make independent decisions.
Antiretroviral therapy (ART) \[^{18}\]

Treatment options have improved significantly in a period of 14 years and, as for adults, the mainstay of treatment is a potent combination of antiretroviral drugs:

- ART has significantly reduced the incidence of opportunistic infection in children and reduced mortality rates by 80-90\%. \[^{18}\]
- The drugs used will vary according to the guidelines. There are current controversies in the literature with regard to triple versus quadruple therapy and the relative effectiveness, cost and toxicity of the various agents. \[^{19}\]
- Currently, triple therapy is usual but those with a very high viral load or symptomatic disease may commence on quadruple therapy.

Important differences exist between treating children and adults for AIDS:

- Pharmacokinetic differences: dosage is usually based on body weight and surface area but, in certain instances, a paediatric dose may exceed an adult dose - for example, with protease inhibitors, as a child's hepatic metabolism is more rapid than an adult's.
- Dosage in children needs to be adjusted for growth. \[^{20}\]
- Children have a relatively immature immune system.
- CD4 counts need to be interpreted differently with different ranges according to age.
- Natural history of AIDS is different in children compared with that of adults.
- Potentially, children may be exposed to antiretrovirals for much longer periods of time. This is particularly important in view of the lack of long-term data regarding their safety.
- Adherence: when to start ART critically depends on the readiness and motivation of a child and family to embark on long-term complex medication regimes. This is usually dependent on adult caregivers and so it is important to consider supporting the family as a whole rather than the child alone. Children are frequently difficult to administer medications to and many of the drugs have previously not been available as paediatric formulations, adding to problems with compliance. Issues surrounding medication and compliance will be very different in an infant compared with an adolescent.

When should ART be started in children?

- This is highly controversial. Whilst there are UK consensus guidelines for the use of ART in adults and neonates, similar guidelines for older children have yet to be developed. In the absence of these, European guidelines are available, published by the Paediatric European Network for Treatment of AIDS (PENTA). \[^{20}\] It advocates a move away from treatment which simply prolongs survival to an approach which promotes an active and healthy life. The guidelines recommend that ART should be started:
  - In all HIV-infected children under 1 year of age.
  - In all children with significant disease (WHO stage 3 or 4 or CDC stage B or C).
  - In asymptomatic children over 1 year of age based on age-specific CD4 count thresholds (as detailed in the PENTA guidelines).
  - Before the CD4 count reaches the CD4 treatment threshold.
  - In those with hepatitis C virus or active TB co-infection.

- Other possible indications are:
  - Asymptomatic children over 5 years at CD4 counts of 350-500 cells/μl, to potentially optimize CD4 count in adulthood.
  - Children with a high viral load (>100,000 copies/mL).
  - Asymptomatic children aged 1-3 years irrespective of immune status and viral load.
  - Sexually active adolescents, to minimise the risk of onward transmission.
  - Significant HIV-related clinical symptoms.
  - Hepatitis B virus co-infection irrespective of immune status.

The National Study of HIV in Pregnancy and Childhood, organised by CHIPS, ensures that data are available to inform management guidelines and monitor outcomes in the UK. \[^{19}\]

Prophylaxis of opportunistic infection \[^{21}\]

Standardly, HIV-positive infants receive co-trimoxazole for the first year of life (regardless of CD4 count) against *P. jiroveci* pneumonia. Thereafter, its continued use depends on age-specific CD4 count.
Prophylaxis for other infections is also sometimes used, either to prevent primary infection or to avoid recurrence. See current guidelines.

**Immunisation**
- Routine schedule but avoid live immunisations (except measles, mumps and rubella (MMR), which is only contra-indicated in severe immunosuppression as defined by age-appropriate CD4 count).
- Children with AIDS may not develop protective immunity from immunisation so seek advice if there is contact with measles/chickenpox, etc.
- BCG is contra-indicated.
- A hepatitis B course should be given from birth for the same indications as for the non-HIV-infected population - all children should receive as adolescents unless previously immunised or there are other clinical indications.
- Vaccination should be delayed until six months of viral load <50 and CD4 >15%, if ART is required.
- The use of pneumococcal vaccine (normally given after the age of 2) in HIV-infected children is recommended by the 'Green Book' although there are some concerns about its safety (eg, there is some evidence of reduced CD4 counts post-vaccination). [22]
- Varicella virus (VZV) vaccine can be considered (as in the USA) in VZV-seronegative children over 1 year of age. Two doses should be given at least one month apart and in the absence of severe immunosuppression. Administration of MMR at the same time as VZV is not advisable as this would make monitoring for attributable adverse events difficult. There should be at least a one-month gap between MMR and VZV immunisation.

**Nutrition**
- Monitor weight and growth. Increase oral supplementation when nutritional deficits are identified.
- Enteral supplementation is sometimes warranted.

Future therapies may well be generated by current research, which is looking into efficient inhibition of the HIV infection life cycle. [23] The addition of micronutrients such as zinc and vitamin A may be important in resource-poor countries but in developed countries their benefits are less clear. [24]

**Complications**
- *P. jirovecii* and toxoplasmosis are the primary infections seen in infected children, with *P. jirovecii* pneumonia being the principle cause of death.
- Lymphocytic interstitial pneumonitis, a condition rarely seen in adults, may cause breathing to become increasingly difficult and require admission to hospital.
- Serious bacterial infections are more common in infected children than in adults.
- Severe and recurrent infection with *Candida* spp.
- HIV encephalopathy.
- Iatrogenic - related to side-effects and interactions from multiple medications.

**Prognosis**
- Perinatal infection promotes accelerated disease progression in children compared with adults, due to relative immaturity of the immune system.
- Children with untreated natural infection progress rapidly to disease and approximately 25% of children develop AIDS in the first year of life. In resource-poor settings, mortality is greater than 50% by 2 years of age. [25]
- Orphan status does not affect the outcome of ART providing extended family support is available. [26]

**Prevention** [27]
- Prevention of perinatal transmission necessitating appropriate medical and obstetric care through pregnancy and delivery worldwide. The widespread availability of antiretrovirals is an important aspect in the prevention of MTCT. Extended use of antiretrovirals in the postnatal period helps to prevent transmission associated with breast-feeding.
- Education of HIV-positive children and adolescents - as HIV-infected children survive into young adulthood, they need to be aware of how to manage their developing sexual identity in light of their HIV status.
Further reading & references


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