Update in Anaesthesia

HIV in children and anaesthesia

Based in part upon: Wilson S. HIV and Anaesthesia. *Update in Anaesthesia* 2010; **25,1**: 25-29.

S Wilson* and S Patel
*Correspondence Email: wdrsam@googlemail.com

Summary

It is estimated that 3.3 million children under 15 years of age are living with HIV, the vast majority of them in sub-Saharan Africa. A significant number of these children will require surgery. It is essential to understand the implications for anaesthesia in order to formulate an appropriate anaesthetic management plan.

In order to safely anaesthetise an HIV-infected child, we require a reasonable understanding of HIV infection: its pathophysiology, potential multisystem complications and the pharmacology of ART. An accurate assessment of the child with HIV may affect your choice of anaesthesic agents, how to manage pain including whether to use regional anaesthesia, approaches to infection control, and general issues surrounding peri-operative care.

Wilson S
Consultant in Anaesthesia, Hampshire Hospitals Foundation Trust

S Patel
Consultant in Paediatric Infectious Diseases and Immunology Southampton Children's Hospital

It is estimated that 3.3 million children under 15 years of age are living with HIV, the vast majority of which are in sub-Saharan Africa. Due to improved HIV prevention a 35% reduction in numbers from 2009 means that in 2012 approximately 260,000 children under 15 were diagnosed with HIV and 647,000 children were receiving antiretroviral therapy (ART).

A significant number of these children will require surgery for elective or emergency procedures, either directly related or unrelated to HIV. For this reason, it is essential for us to fully understand the implications for anaesthesia. In order to safely anaesthetise an HIV-infected child, we require a reasonable understanding of HIV infection: its pathophysiology, multisystem complications and the pharmacology of ART. An accurate assessment of the child with HIV can potentially impact upon your choice of anaesthesic agents, whether to use regional anaesthesia, how to manage pain, approaches to infection control and general issues surrounding peri-operative care.

PATHOGENESIS, AETIOLOGY AND CLASSIFICATION

HIV is a single-stranded RNA virus with HIV-1 and HIV-2 types and multiple subtypes recognised. These subtypes express differences in geographical prevalence as well as disease progression and transmission rates. Like other retroviruses, HIV contains the enzyme *reverse transcriptase* that enables viral RNA to be transcribed to DNA, which then becomes incorporated into the host cell genome and is able to replicate freely. Inhibition of this viral replication process is the target of ART. HIV preferentially infects T helper lymphocytes (CD4+ T cells) and leads to their progressive quantitative and qualitative destruction. This makes the host increasingly immunocompromised, and thus more susceptible to opportunistic infections and malignancies.

More than 80% of HIV infections in children are due to vertical transmission (ie.trans-placental exposure to maternal HIV during the perinatal period). Perinatal transmission can occur during any one of three phases: in utero, during the peripartum period, or during breastfeeding. The risk of perinatal acquisition without intervention (such as maternal ART, caesarean delivery, avoidance of breast milk) is 25-40%. Other routes of transmission, as for adults, are sexual or via contaminated blood through the administration of blood products, organ donations or by sharing contaminated needles during intravenous drug use.

The Centers for Disease Control and Prevention (CDC) classification system (Table 1) clearly shows the increasing severity of symptoms as HIV infection progresses.

MULTISYSTEM INVOLVEMENT

In order to perform a thorough preoperative assessment of the child with HIV, it is important that you appreciate which organ systems may be affected, either as a direct consequence of HIV infection (opportunistic infection / malignancy), or indirectly such as from side effects of ART, chemotherapy or anti-infective agents. Awareness of these effects allows us to appropriately adapt our anaesthetic.

Haematological system

The haematological system can be greatly affected during HIV infection; anaemia, neutropaenia and thrombocytopaenia are common. Persistent generalised lymphadenopathy may be a feature and may also be the target of surgery for the affected child in the early stages of disease for diagnostic purposes. Haematological malignancies are often seen as are coagulation abnormalities, with obvious implications for surgical and anaesthetic interventions.

Cardiovascular system

The cardiovascular system may be affected in a number of ways in an HIV-infected child. The pericardium, myocardium or endocardium may be involved or there may be vascular lesions or neoplasms. Important and common cardiovascular complications that have major implications for patient management are:

- Pulmonary hypertension
- Pericardial effusions

Table 1. *CDC classification of paediatric HIV infection*

Category	Associated symptoms
N - Asymptomatic	No symptoms 1 category A symptom only.
A - Mild symptoms	2 or more of the following symptoms: Lymphadenopathy Hepatomegaly Splenomegaly Dermatitis Parotitis Recurrent or persistent upper respiratory infection, sinusitis, or otitis media.
B - Moderate symptoms	Anaemia, neutropenia, or thrombocytopenia Bacterial meningitis, pneumonia, or sepsis Candidiasis, oropharyngeal (thrush), Cardiomyopathy Cytomegalovirus infection, with onset before 1 month Diarrhoea, recurrent or chronic Hepatitis Herpes simplex virus (HSV) stomatitis, recurrent HSV bronchitis, pneumonitis, or oesophagitis Herpes zoster (shingles) Leiomyosarcoma Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex Nephropathy Nocardiosis Persistent fever Toxoplasmosis Varicella, disseminated (complicated chickenpox).
C - Severe symptoms:	Serious bacterial infections, multiple or recurrent Candidiasis, oesophageal or pulmonary Coccidioidomycosis, disseminated Cryptococcosis, extrapulmonary Cryptosporidiosis or isosporiasis Cytomegalovirus disease Encephalopathy Herpes simplex virus infection Histoplasmosis, disseminated Kaposi's sarcoma Lymphoma Mycobacterium tuberculosis, disseminated or extrapulmonary Mycobacterium, other species disseminated Mycobacterium avium complex or Mycobacterium kansasii Pneumocystis carinii pneumonia Progressive multifocal leukoencephalopathy Salmonella (nontyphoid) septicemia, recurrent Toxoplasmosis of the brain.

- Endocarditis and valvular lesions
- Vasculitis
- Cardiomyopathies.

Respiratory system

Both the upper and lower airway can be involved in HIV infection in children, and respiratory symptoms are a common presenting complaint. These include:

- Upper respiratory tract infections (chronic otitis media)
- Bacterial pneumonia
- Atypical infections (commonly tuberculosis, non-tuberculous mycobacteria, and fungal infections)
- Lymphocytic interstitial pneumonia (LIP)
- Bronchitis
- Sinusitis
- Airway obstruction.

Gastrointestinal system

Commonly encountered complications of the gastrointestinal tract associated with HIV infection and its treatment can have major effects on the metabolism of our anaesthetic agents and any other drugs used. These effects include:

- Poor nutritional status with resultant delayed healing times
- Difficulty or pain on swallowing
- Increased gastric emptying times.

Acute or chronic diarrhoea is common, with associated dehydration and electrolyte dysfunction and in addition, there can be hepato-biliary and pancreatic impairment.

Renal system

Acute and chronic renal disease can be associated with HIV. Potential causes of renal impairment include:

- Drug induced nephrotoxicity
- Hypertension
- Diabetes
- HIV-associated nephropathy.

It is important to avoid nephrotoxic drugs where possible in these children and to dose adjust renally excreted drugs and adequately hydrate the child in order to prevent further renal damage.

Neurological system

HIV can affect the neurological system directly (HIV encephalopathy) or indirectly via opportunistic infections, neoplasms or immune deficiency. These can involve all structures including the meninges, brain, spinal cord, peripheral nerve or muscle. Neurocognitive impairment, developmental delay, encephalopathy, autonomic neuropathy and seizures are all recognised complications of HIV which have important implications in our clinical management.

Full neurological examination pre-operatively with appropriate documentation is essential especially if you plan to use regional anaesthesia.

Endocrine and metabolic system

ART has common endocrine side effects including lipodystrophy, insulin resistance (metabolic syndrome), hypothalamic-pituitary-adrenal axis dysfunction, hypo- or hyperthyroidism and lactic acidosis.

ANTIRETROVIRAL THERAPY

The use of a combination ART or highly active antiretroviral therapy (HAART) has been a major advance in the treatment of HIV infection. These drugs are classified into the following five classes according to the mechanisms of inhibition of viral replication (Table 2):

- Reverse transcriptase enzyme inhibitors
- Protease enzyme inhibitors
- Integrase inhibitors
- Entry inhibitors
- Fusion inhibitors.

Adherence to antiretroviral therapy is of paramount importance; adherence levels below 95% are associated with increases in viral load and drug resistance. This naturally has implications for interruption of ART due to perioperative fasting. Fasting times should be kept to an absolute minimum.

Many adverse side effects are associated with ART and you should look for these during preoperative assessment. They can be divided broadly into four groups:

- **Allergic reactions**: skin rashes and hypersensitivity responses
- **Bone marrow suppression**: anaemia, neutropaenia and thrombocytopaenia.
- **Metabolic abnormalities:** fat maldistribution and change in body habitus, dyslipidaemia, hyperglycaemia and insulin resistance, bone disorders e.g. osteopaenia, osteoporosis and osteonecrosis
- **Mitochondrial dysfunction**: lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy.

Anaesthetic drugs may interact with ART. Anaesthetic agents may induce pharmacodynamic changes to affect their efficacy and toxicity via cytochome p450 induction/inhibition, and the pharmacokinetic effects of ART can affect the absorption, distribution, metabolism and elimination of anaesthetic and analgesic drugs.

Pharmacodynamic interactions can be managed by avoiding anaesthetic agents such as halothane or methoxyflurane that cause

hepatic or renal dysfunction. Propofol and NRTIs may both potentially promote mitochondrial toxicity and lactic acidosis,so it may be wise to avoid propofol infusions in patients receiving ART due to the already potentially compromised mitochondrial function.

Pharmacokinetic interactions are more complex and are primarily due to liver enzyme induction or inhibition, particularly of the CYP450 3A4 enzyme. Protease inhibitors (PIs) and NNRTIs are the most commonly implicated groups of drugs. Enzyme induction or inhibition can affect the action of several classes of anaesthetic drugs:

- **Opioids.** The effects of fentanyl may be enhanced by ritonavir due to both liver enzyme inhibition and induction. Enzyme inhibition reduces fentanyl clearance and enzyme induction increases metabolism to active metabolites such as normepiridine.
- **Benzodiazepines** Saquinavir may inhibit midazolam metabolism.
- Local anaesthetics such as lignocaine may have increased plasma levels due to enzyme inhibition with direct implications for toxic doses.
- Neuromuscular blocker effects may be prolonged, even after a single dose.
- Calcium channel blockers may have enhanced hypotensive effects due to enzyme inhibition.

These interactions are complicated and multiple and databases exist that describe these interactions in detail (such as www.hiv-druginteractions.org).Evidence for interactions specifically with anaesthetic drugs is relatively sparse.

Table 2. *ART*

Drug class	Available drugs
1. Reverse transcriptase inhibitors	
Nucleoside/nucleotide analogues (NRTIs)	Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Zidovudine (AZT, ZDV)
Non-nucleotide reverse transcriptase Inhibitors (NNRTIs)	Delavirdine (DLV) Efavirenz (EFV) Etravirine (ETR) Nevirapine (NVP)
2. Protease inhibitors (PIs)	Atazanavir (ATV) Darunavir (DRV) Fosamprenavir (FPV) Indinavir (IDV) Lopinavir (LPV) Nelfinavir (NFV) Ritonavir (RTV) Lopinavir/ritonavir (LPV/r) Saquinavir (SQV) Tipranavir (TPV) Amprenavir (APV)
3. Integrase inhibitors	Raltegavir (RAL) Dolutegravir
4. Entry inhibitors	
CCR 5 antagonists	Maraviroc (MVC)
5. Fusion inhibitors	Enfuviritide (ENF, T-20)

Due to the risk of developing resistance if doses are missed, it is recommended that ART be continued throughout the perioperative period if at all possible. Naturally this needs to be compatible with the proposed surgery and with the patient's gastrointestinal function. Some drugs are available in liquid form enabling administration via nasogastric feeding tube or gastrostomy. Parenteral preparations are limited to zidovudine and enfuvirtide only.

REGIONAL ANAESTHESIA

The presence of HIV infection is not an absolute contraindication to regional anaesthesia and there is no evidence that HIV progression is increased by central neuraxial blockade. Regional anaesthesia may be relatively contraindicated with several pathologies associated with HIV infections such as myelopathy, vertebral or spinal neoplasms, CNS infections and coagulopathies, as well as in the severely immunocompromised patient. You must conduct a full preoperative neurological assessment and document any pre-existing neurological deficit if you plan a regional anaesthetic technique.

BLOOD TRANSFUSION

There is evidence that allogeneic blood transfusion in the HIV infected patient can lead to transfusion-related immunomodulation (TRIM) and can result in an increase in HIV viral load. Blood should therefore only be transfused where unavoidable to maintain patient safety.

PAIN

Pain is common in advanced HIV disease and can be very difficult to treat. The aetiology of this pain can be multifactorial, including:

- Opportunistic infections such as herpes simplex
- HIV-related arthralgia
- Peripheral neuropathy
- Drug-related pain.

Pre-existing pain and its treatment can affectthe treatment of postoperative pain and will necessitate a multimodal approach.

INFECTION CONTROL

Infection control is an important issue both for the protection of the immunocompromised child from opportunistic infections, as well as for the professionals caring for the child during any procedures. Use a strict aseptic technique for all procedures.

The cumulative risk of contracting HIV over an anaesthetic career can be as high as 4.5%. This can occur due to a needlestick injury (transmission risk of 0.3%); the risk is increased if there is a higher volume of blood injected, such as with hollow needles or deep punctures. Risk of transmission via the mucocutaneous route (splashing of a mucosal surface or broken skin by body fluid) is extremely low (0.03%).

There are universal precautions that should be taken to reduce the risk of HIV transmission to healthcare workers:

- Dispose of sharps safely (into a rigid locking container prior to incineration)
- Do not re-sheath needles
- Wear gloves
- Cover any cuts or broken skin with an impermeable dressing
- Strongly consider eyeshields and facemasks
- Use disposable equipment where possible; clean reusable equipment properly.

Post-exposure prophylaxis for healthcare workers should be available and should commence as soon as possible after potential high risk exposure (ideally within the first 1-2hrs).

If tuberculosis is suspected or likely in a patient known to have HIV, all healthcare workers should wear a tight fitting facemask to reduce the risk of transmission (ideally a high quality particulate mask if available e.g. N95 or HEPA).

APPROACH TO FORMULATING AN ANAESTHETIC MANAGEMENT PLAN FOR THE HIV-INFECTED CHILD

A multisystem and multidisciplinary approach is recommended.

Thorough preoperative assessment for status of HIV infection:

- History, including risk factors (for child & parents)
- Physical examination
- Laboratory tests
- Assess organ involvement
- Drug history and side effects.

Investigations ideally include:

- Full blood count
- Clotting function to exclude coagulation abnormalities (consider use of TEG/platelet mapping if available)
- Biochemical tests including glucose, electrolytes, renal & liver function to exclude possible metabolic, liver or renal disturbances
- Viral load and CD4 count
- Chest radiography to screen for opportunistic infections and tuberculosis
- Cardiac evaluation with electrocardiography and echocardiography (if possible) to screen for cardiomyopathy.

Preparation of operating theatre and personnel:

- Infection control preparation including universal precautions with gloves, aprons, visors available

- Sharp object collection devices with appropriate sharps handling (no re-sheathing of needles)
- Staff fully aware of protocols in the event of occupational exposure
  - Rinse and wash affected area with soap & water
  - Recipient lab tests: HIV, acute hepatitis panel
  - Determine infectious status of source
- Availability of post exposure prophylaxis to be started as soon as possible following accidental high risk exposure (ideally within 1 hour of exposure)
  - HIV PEP protocol with 3 or more antiretroviral drugs if known HIV positive donor or high-risk patient or with 2 or more if low risk. ART is given for 4 weeks or until source is found to be negative for HIV
  - Follow up with counselling and HIV testing for at least 6 months post exposure (tests done at baseline, 6 weeks, 12 weeks and 6 months)
  - Hepatitis B immune globulin +/or hepatitis B vaccine
  - Achieve early identification of chronic hepatitis C disease.

Perioperative considerations for the child with HIV:

- Minimise interruptions in ART as far as possible to diminish the risk of developing drug resistance
- Consider drug interactions between ART and drugs affected by hepatic enzyme inhibition and/or induction
- Exercise strict aseptic technique as HIV infected children are immunocompromised and are susceptible to opportunistic infections
- Additional emotional and psychological support may be necessary as primary caregivers may have been affected by HIV/AIDS
- The anaesthetic plan should of course be tailored to the individual child and the type of surgery to be undertaken.

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