

HIV and Anaesthesia

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Summary

Human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) are major global health concerns. The most recent WHO/UNAIDS report (2008) has estimated that there are 33 million people worldwide living with this infection, with 2.7 million new infections acquired in 2007. Given that approximately 25% of HIV-infected patients will require surgery during the time of their illness, it is important for anaesthetists to understand the implications of anaesthesia in the HIV-infected patient. This requires a basic understanding of HIV infection itself, the clinical symptoms and organ involvement in HIV infection, the pharmacology of anti-retroviral agents (ARVs), as well as implications for regional anaesthesia, the child with HIV and issues surrounding infection control. With this basic understanding we will be better equipped to formulate a plan for anaesthetising the HIV infected patient.

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PATHOGENESIS DIAGNOSIS AND CLASSIFICATION

HIV is a single-stranded RNA virus of the lentivirus subfamily of the retrovirus family. Two subtypes have been identified, HIV-1 and HIV-2. 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 antiretroviral agents (ARVs). HIV preferentially infects T helper lymphocytes (CD4 T cells) and leads to their progressive quantitative and qualitative destruction, making the host more susceptible to opportunistic infections and malignancies.

Several modes of infection exist including sexual intercourse (60-70%), mother to child transmission (during pregnancy, labour and breast-feeding) (20-30%), contaminated blood, blood products and organ donations (3-5%) and contaminated needles (2-3%). This leads to the identification of several high-risk groups including: promiscuous hetero- and homosexuals, patients with other sexually transmitted diseases, intravenous drug users, haemophiliacs, and patients from endemic areas.

HIV infection is classified according to its associated clinical symptoms (see Table 1 below), as well as the severity of immunological depression reflected by age-related CD4+ T cell counts. The diagnosis of advanced HIV infection is made when the patient is in stage 3 or 4 and/or has advanced immunodeficiency. Severe clinical conditions and/or severe immunodeficiency are known as AIDS.

MULTISYSTEM INVOLVEMENT

To enable a thorough preoperative assessment it is important to be aware which organ systems can be involved in the HIV infected patient, both as a direct consequence of HIV infection due to opportunistic infection or neoplasm, as well as related to other causes such as side effects of the ARV medications.

Cardiovascular system

The cardiovascular system may be involved in a number of ways in HIV infection. There may be pericardial,

Table 1. Clinical staging of HIV infection

Stage	Associated symptoms
1 Asymptomatic	No symptoms Persistent generalised lymphadenopathy
2 Mild symptoms	Moderate weight loss (<10% body weight) Recurrent upper respiratory tract infection Viral or fungal skin infection Oral or skin lesion
3 Advanced symptoms	Severe weight loss (>10% body weight) Chronic diarrhoea Persistent fever Oral lesions or candidiasis Pulmonary tuberculosis Severe bacterial infections Anaemia, neutropenia, thrombocytopenia
4 Severe symptoms: AIDS	Wasting syndrome (weight loss >10% body weight with wasting or body mass index <18.5) Chronic diarrhoea Persistent fever Encephalopathy, nephropathy, cardiomyopathy Recurrent bacterial infections Opportunistic infections Malignancy

myocardial, endocardial or vascular lesions, as well as neoplasm. These may be directly related to HIV infection or to the side effects of ARVs, chemotherapy or anti-infective agents. Important and common cardiovascular complications include the following:

- Dilated cardiomyopathy
- Pericardial effusions
- Endocarditis and valvular lesions
- Acute coronary syndrome
- Vasculitis
- Pulmonary hypertension.

Respiratory system

Both the upper and lower airway can be involved in HIV infection. These complications can be due to primary HIV infection, associated malignancies, opportunistic infections or side effects of medication. The following respiratory complications are seen:

- Airway obstruction (by Kaposi sarcoma or infections)
- Bronchitis
- Sinusitis
- Pneumonia
- Pneumonitis
- Atypical infections (commonly tuberculosis, other mycobacteria and fungal infections).

Gastrointestinal system

Commonly encountered complications of the gastrointestinal tract associated with HIV infection and its treatment include:

- Difficulty or pain on swallowing
- Increased gastric emptying times
- Bleeding tendency on airway instrumentation/nasogastric tube insertion
- Diarrhoea with associated electrolyte dysfunction & dehydration
- Hepatobiliary impairment
- Pancreatitis.

Renal system

Acute and chronic renal disease can be associated with HIV and the causes of renal impairment can be multifactorial:

- Drug-induced nephrotoxicity, hypertension & diabetes
- HIV-associated nephropathy.

These potential complications necessitate the avoidance of nephrotoxic drugs, dose adjustment of renally excreted drugs and the need for adequate hydration to prevent further deterioration of renal function.

Neurological system

HIV can involve the neurological system by direct infection, inflammation, demyelination or a degenerative process. It can also

be secondary to opportunistic infections, neoplasms or immune deficiency. This can involve all structures including the meninges, brain, spinal cord, peripheral nerve or muscle. Also recognised are:

- Neurocognitive impairment (with implications for consent)
- Encephalopathy
- Autonomic neuropathy
- Seizures.

Full neurological examination pre-operatively with appropriate documentation is essential especially if regional anaesthesia is being considered.

Haematological system

The following are commonly seen during HIV infection:

- Anaemia
- Neutropenia
- Thrombocytopenia
- Persistent generalised lymphadenopathy
- Haematological malignancies
- Coagulation abnormalities.

Endocrine & metabolic system

Common side effects of ARVs include:

- Lipodystrophy (truncal obesity, buffalo hump, peripheral wasting)
- Metabolic syndrome (raised plasma triglycerides, cholesterol, glucose)
- Disorders of the hypothalamic–pituitary–adrenal axis including Cushing's syndrome and Addison's disease
- Hyponatraemia due to syndrome of inappropriate antidiuretic hormone or adrenal failure
- Hypo- or hyperthyroidism
- Lactic acidosis

ANTIRETROVIRAL THERAPY

The use of a combination ARVs or highly active antiretroviral therapy (HAART) has been a major advance in the treatment of HIV infection. These drugs are classified into four classes according to the mechanisms of inhibition of viral replication: reverse transcriptase enzyme inhibitors, protease enzyme inhibitors, integrase inhibitors and entry inhibitors (see table below).

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

Adverse effects

Many adverse side effects are associated with ARVs and should be

Table 2. Summary of antiretroviral drugs

Drug class	Available drugs	
1. Reverse transcriptase inhibitors		
Nucleoside/nucleotide analogues (NRTIs)	Abacavir (ABC)	
	Didanosine (ddl)	
	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	
		Raltegravir (RAL)
4. Entry inhibitors		
Fusion inhibitors	Enfuvirtide (ENF, T-20)	
	CCR 5 antagonists	Maraviroc (MVC)

looked for during preoperative assessment. They can be divided broadly into four groups:

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

Drug interactions

Anaesthetic drugs may interact with ARVs. Anaesthetic agents may induce pharmacodynamic changes to affect the efficacy and toxicity of ARVs, and pharmacokinetic effects of ARVs can affect the absorption, distribution, metabolism and elimination of anaesthetic 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 and it may be wise to avoid propofol infusions in patients receiving ARVs.

Pharmacokinetic interactions are more complicated and are primarily due to liver enzyme induction or inhibition, particularly the CYP450 3A4 enzyme. Protease inhibitors (PIs) and NNRTIs are the most commonly implicated group of ARVs in drug interactions. 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 normeperidine.
- *Benzodiazepines*. Saquinavir may inhibit midazolam metabolism.
- *Calcium channel blockers* may have enhanced hypotensive effects due to enzyme inhibition.
- *Local anaesthetics* such as lignocaine may have increased plasma levels due to enzyme inhibition.
- *Neuromuscular blocker* effects may be prolonged, even a single dose of vecuronium for instance.

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

Perioperative management of ARVs

Due to increasing problems of drug resistance in the treatment of HIV, it is recommended that ARV therapy be continued throughout the perioperative period if at all possible. Naturally this needs to be compatible with surgery and the patient's gastrointestinal function. Some ARVs are available in liquid form enabling administration via

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. However, the presence of HIV complications may pose relative contraindications to regional anaesthesia:

- Myelopathy
- Vertebral or spinal neoplasms
- CNS infections
- Coagulopathy.

It is essential to conduct a full preoperative neurological assessment and to document any neurological deficit.

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.

THE CHILD WITH HIV

More than 80% of HIV-infections in children are due to transplacental exposure to maternal HIV during the perinatal period. 13% of HIV-infected children are exposed during blood transfusions and 5% from blood products for treatment of coagulation disorders. Paediatric AIDS is a disease of early childhood with 50% of cases displaying clinical manifestations by 1 year of age and 80% by 3 years of age. The disease affects many systems as described previously in adults, but the clinical manifestations do differ from adults in several ways:

- Pulmonary disease is the leading cause of morbidity & mortality.
- Lymphoid interstitial pneumonitis (chronic lung disease) is more common.
- Cardiac abnormalities are noted in both asymptomatic HIV infection as well as advanced AIDS.
- Most children infected with HIV will have neurological abnormalities including progressive encephalopathy with signs of developmental delay, progressive motor dysfunction, loss of milestones and behavioural changes.
- Opportunistic infections of the central nervous system are less common than in adults.
- Children with HIV often fail to thrive, primarily from chronic infectious diarrhoea and mucocutaneous candidiasis in 75%.
- Lymphadenopathy is a common presenting feature.
- The type of surgery in children infected with HIV is different from that of adults. Three common operations in adults with HIV are lymph node biopsy, splenectomy and partial colectomy. In children, therapeutic and diagnostic procedures predominate

(such as central venous catheter placement, gastrostomy tube placement, lung and liver biopsies). Common surgical procedures of childhood such as tonsillectomy or herniorrhaphy may also be required.

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 and drug-related pain. This can have impact also on the treatment of postoperative pain relief and will necessitate a multimodal approach.

CRITICAL CARE

HIV-infected patients may require intensive care treatment in one of many circumstances related to HIV disease and for medical and surgical conditions unrelated to HIV. Overall mortality rates for HIV-infected patients requiring intensive care have improved from approximately 70% in the early 1980s to 30-40% at present. New diagnosis of HIV in the ventilated, sedated patient who is unable to consent to testing presents an ethical problem. No evidence exists as yet to support whether or not the initiation of ART may improve outcome in the critically ill HIV patient.

INFECTION CONTROL

Healthcare workers should adopt universal infection control precautions for all patients to protect themselves against blood-borne infections as in areas of high HIV prevalence many patients will be asymptomatic and may be classified as ASA 1-2. The cumulative risk of contracting HIV over an anaesthetic career can be as high as 4.5% in areas of high prevalence. This may occur due to a needlestick injury, particularly if there is a high volume of blood injected, such as with hollow needles or deep punctures (transmission risk of 0.3%). Risk of transmission via the mucocutaneous route (splashing of a mucosal surface or broken skin by body fluid) is 0.03%. All healthcare workers should be immunised against hepatitis B.

Some precautions that should be taken to reduce the risk of HIV transmission to healthcare workers:

- Dispose of sharps safely
- Do not re-sheath needles
- Wear gloves
- Use disposable equipment where possible
- Clean reusable equipment promptly and properly.

If a healthcare worker suffers a needle stick injury or is exposed to potentially infected blood or body fluid, the following steps should be taken:

First aid

- Needle stick or contaminated wound – encourage bleeding from the skin wound and wash the area with copious soapy water or disinfectant.
- Contaminated intact skin – wash with soap and water.

- Contaminated eyes – gently rinse eyes while open with saline or water.
- Contaminated mouth – spit out any fluid, rinse the mouth with water and spit out again.

If the patient is known to be HIV positive, the healthcare worker should receive post-exposure prophylaxis as soon as possible after exposure (ideally within the first 1-2hrs).

If tuberculosis is suspected or likely in a patient, the healthcare worker 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). Anaesthetic breathing equipment should be decontaminated after use to protect future patients.

ANAESTHETIC MANAGEMENT PLAN

A multisystem and multidisciplinary approach is recommended. Thorough preoperative assessment for status of HIV infection includes:

- History, including risk factors
- Physical examination
- Laboratory tests
- Assess organ involvement
- Drug history and side effects.

Investigations should include:

- Full blood count
- Clotting function to exclude coagulation abnormalities (consideration of 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 theatre and personnel:

- Infection control preparation including universal precautions with gloves, aprons, visors etc.
- 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 & 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 exposure (ideally within 1 hour of exposure).

- Hepatitis B immune globulin and/or hepatitis B vaccine
- Achieve early identification of chronic hepatitis C disease
- HIV PEP protocol with 3 or more ARVs if known HIV positive donor or high-risk patient or with 2 or more ARVs if low risk. These ARVs are given for 4 weeks or until source person 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).

Perioperative considerations for the patient with HIV:

- Minimise interruptions in ARV therapy as possible to diminish drug resistance
- Consider drug interactions with ARV with use of drugs affected by hepatic enzyme inhibition and/or induction
- Strict aseptic technique to be exercised as HIV infected patients are immunocompromised and are susceptible to bacterial infections
- The anaesthetic plan should be tailored to the individual patient and the type of surgery as appropriate.

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