Anaesthetic considerations of the HIV-infected patients

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Purpose of review

Human immunodeficiency virus (HIV) infection is one of the major global health problems. Because the advances in treatment of HIV infection increase the patient's survival, anaesthesiologists may care for these patients during their practice. This article highlights HIV infection and anaesthetic implications.

Recent findings

HIV infection is a spectrum of disease varying from asymptomatic to multiple organ involvement. Safe anaesthetic management in HIV-infected patients includes understanding basic knowledge of HIV infection, organ involvement, pharmacology and adverse reactions of antiretroviral agents. There are no specific anaesthetic agents and techniques for HIV-infected patients. Issues on central neural blockade and immunological aspects on HIV infection were discussed. Infection control to prevent transmission of infections to and from HIV-infected patients must be strictly conducted.

Summary

Anaesthesia in HIV-infected patients should be individualized and depend on the status of the patient.

Keywords

anesthesia, HIV, human immunodeficiency virus, surgery

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Introduction

The acquired immunodeficiency syndrome (AIDS) was first described in adults and children in 1981 and 1982, respectively [1,2]. The disease is caused by human immunodeficiency virus (HIV) which was isolated in 1983 [3]. In 2007, there were 33 million people who were living with HIV and 2.7 million were newly infected [4]. It has been estimated that 20–25% of HIV-infected patients require surgery during their illness [5]. This article will focus on anaesthetic management in HIV-infected adults. A brief review of basic HIV infection is essential for understanding of the disease. Anaesthesia in HIV-infected children and parturients were recently published [6••,7••].

Viral replication and pathogenesis

HIV is a single-stranded RNA virus, a member of the retrovirus family (Retroviridae), lentivirus subfamily [8•,9,10] (Fig. 1). Two subtypes – HIV-1 and HIV-2 – were discovered. The mechanism of HIV-infected cell starts from cell entry via binding of envelop protein GP160 to the specific CD4 receptor of T4 lymphocytes which is responsible for helper function in the immune system (helper T cells). The cell entry also requires a coreceptor, chemokine receptor (CCR5).

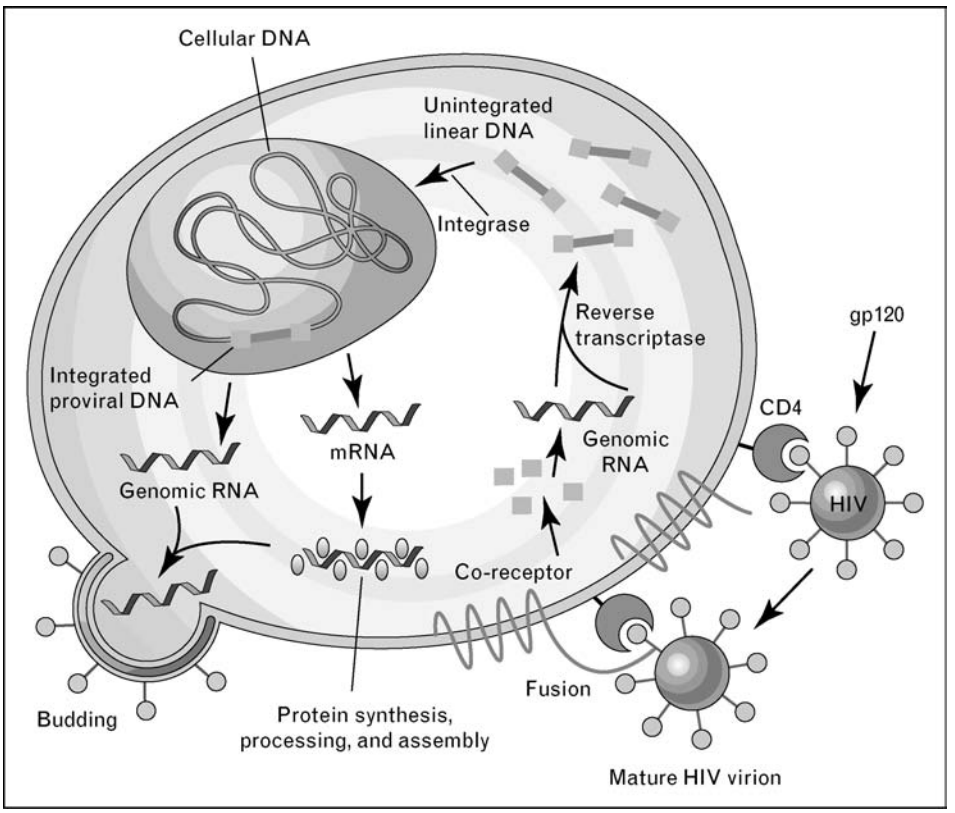
Following binding, the virion fuses with the host cell membrane and penetrates into the target cell. Once internalized, the viral RNA is transcribed to DNA by the enzyme reverse transcriptase. The proviral DNA is integrated into the host DNA through the action of enzyme integrase. Once cell activation occurs, the proviral DNA transcribes viral RNA and messenger RNA. The HIV mRNA is translated into proteins that undergo modification through glycosylation, myristylation, phosphorylation and cleavage. The protease enzyme catalyses the cleavage of the viral polyprotein precursors to generate function viral proteins. The viral particle is then formed and budding of the progeny virus from the host cell surface (Fig. 1). Inhibition of viral replication process is the target of antiretroviral agents (ARVs).

As HIV infection progresses, there are qualitative and quantitative deficiencies of helper T cells that lead to opportunistic diseases, particularly the infections and neoplasms. Autoimmune phenomena have also been proposed to cytopathicity associated with HIV infection such as autoantibodies to platelet, lymphocyte or nerve. However, the exact pathogenetic mechanisms of HIV disease are multifactorial and multiphasic and are different at different stages of the disease.

Diagnosis and classification of HIV infection

According to the World Health Organization (WHO) and the Centers for Disease Control and Prevention

Figure 1 The replication cycle of HIV



Reproduced with permission from [8•].

(CDC), the diagnosis of HIV infection depends upon the demonstration of antibodies to HIV and/or the detection of HIV or one of its components [11–14]. In children born to HIV-infected mothers, who are younger than 18 months, diagnosis of HIV infection relies on virologic assays because of transplacental passage of maternal HIV antibodies during pregnancy.

HIV infection is classified according to clinical symptoms associated with HIV infection (Table 1) and the severity of immunological depression reflected by age-related CD4+ T lymphocyte or percentage of CD4+ counts (Table 2). Advanced HIV infection is diagnosed when the patient is in stage 3 or stage 4 condition and/or advanced immunodeficiency (Table 1). Severe clinical conditions and/or severe immunodeficiency are known as AIDS.

Organ system involvement

Organ involvement in HIV infection may be a direct consequence of HIV infection because of an opportunistic infection or neoplasm, or related to other causes such as side effects of the medications [8•].

Respiratory involvement

Both upper and lower airway can be involved during HIV infection. Airway obstruction from Kaposi's sarcoma or opportunistic infections was described [15–20]. Bronchitis, sinusitis and pneumonia can be found at all stages of the disease. The organisms are encapsulated bacteria such as *Haemophilus influenzae, Streptococcus pneumoniae. Mycobacterium tuberculosis* infection can develop in the early course and may be early clinical sign of the disease. Atypical mycobacterial and fungal infections are associated with low CD4+ T cell counts. *Pneumocystis jiroveci* (*Pneumocystis carinii*) pneumonia (PCP) has dramatically declined because of prophylactic drug regimens. Idiopathic interstitial pneumonia, lymphoid interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NIP) may occur in HIV infection.

Cardiovascular involvement

A variety of cardiovascular diseases are affected: pericardial, myocardial, endocardial, vascular lesions or neoplasms [21,22]. These conditions can be related to HIV infection or the side effects of ARV as part of lipodystrophy syndrome (see below). Dilated cardiomyopathy, known as HIV-associated cardiomyopathy, occurs

Table 1 Clinical staging of HIV infection

Stage	Associated symptoms
1 (Asymptomatic)	No symptoms Persistent generalized 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, neutropaenia, thrombocytopaenia
4 (Severe symptoms)	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

Modified from [11].

as late complication of HIV infection. The causes can be primary infection from HIV or secondary infection, toxic effects of ARVs, in particular nucleotide reverse transcriptase inhibitors associated mitochondrial toxicity, nutritional deficiencies or autoimmunity. Pericardial effusion may be related to opportunistic infections, neoplasm or unclear disorder. Infective or thrombotic endocarditis has been found in HIV-infected patients. Patients who receive protease inhibitors may have a higher risk of developing acute coronary syndromes. This should be emphasized in patients with preexisting cardiovascular risk factors. A variety of vasculitis, including polyarteritis nodosa, Henoch–Schonlein purpura, drug-induced vasculitis, Kawasaki-like syndrome and Takayasu's arteritis, has also been described. Pulmonary hypertension associated with HIV infection is found with increasing frequency during recent years [23]. Other medications such as chemotherapy for treatment of Kaposi's sarcoma, lymphoma, antiinfective agents for treatment of fungal, CMV, Pneumocystis infections also have cardiovascular side effects.

Haematologic involvement

Haematologic manifestations including anaemia, neutropaenia or thrombocytopaenia are common during the course of HIV infection. Anaemia is the most common haematologic abnormality and in the absence of specific treatable cause is associated with a poor prognosis. Neutropaenia is usually mild but can be severe and can put patients at risk of developing spontaneous bacterial infections. Thrombocytopaenia may be an early consequence of HIV infection. The cause of this haematopoietic depression can be the direct result of HIV infection, secondary infections, neoplasms, side effects from medications such as zidovudine, trimetroprim/sulfamethoxazole, gancyclovir, dapsone, interferon-α. Persistent generalized lymphadenopathy is an early clinical manifestation in some asymptomatic patients. Haematologic malignancies are found in advanced HIV infection. Coagulation abnormalities have also been reported. Hence, checking the coagulation status and platelet count is essential before anaesthesia and surgery.

Neurologic involvement

Neurologic involvement may be the pathogenic processes of HIV infection such as direct infection, inflammation, demyelination or degenerative process [24]. Opportunistic infections or neoplasms of the nervous system, secondary to immune deficiency, are also found. Every structure can be involved such as meninges, brain, spinal cord, peripheral nerve or muscle. HIV-associated neurocognitive impairment (HNCI) is a spectrum of disorders ranging from asymptomatic to most severe, considered as AIDS dementia complex or HIV encephalopathy. Autonomic neuropathy has also been described in HIV-infected individuals and this has anaesthetic implications [25]. New onset of seizures can also occur and can progress to status epilepticus. A thorough evaluation of the nervous system should be conducted before performing neural blockade and this will be discussed later.

Renal involvement

Renal involvement in HIV-infected patients can present as acute or chronic renal disease [26]. Acute renal failure is frequently caused by drug-induced nephrotoxicity. End-stage renal disease can be caused by multiple mechanisms and is referred to as HIV-associated nephropathy. Hypertension and diabetes secondary to ARVs are also contributed to renal damage in HIV-infected patients. Drugs used in anaesthesia need to be adjusted in patients with renal insufficiency, and nephrotoxic drugs avoided.

Table 2 Immunological staging of HIV infection

	Age-related CD4+ value (absolute number per mm^3 or %CD4+)			
Immunodeficiency	<11 months	12–35 months	36–59 months	>5 years
Not significant	>35%	>30%	>25%	>500
Mild	30–35%	25–30%	20–25%	350–499
Advanced	25–29%	20–24%	15–19%	200–349
Severe	<25%	<20%	<15%	<200 or <15%

Modified from [11].

Adequate hydration during anaesthesia is suggested to prevent deterioration of renal function.

Gastrointestinal involvement

Oral and oesophageal lesions are frequent in patients with HIV infection and can cause dysphagia (difficulty in swallowing) or odynophagia (pain with swallowing). The causes can be due to candidal infection, leukoplakia or other infiltrative tumours. Instrumentation of the airway or insertion of nasogastric tube should be carefully performed because these lesions can easily bleed. Diarrhoea is also common during the course of HIV infection. The causes can be bacteria such as salmonella, shigella, campylobacter, mycobacterium, or fungus such as histoplasma, coccidioides, penicillum, or protozoa such as cryptosporidia, microsporidia, and isospora, or virus such as cytomegalovirus, or no causative organism identified which is known as HIV enteropathy or AIDS enteropathy. Fluid and electrolyte status needs to be checked before anaesthesia in patients with diarrhoea.

Hepatobiliary involvement can be the co-infection of hepatitis virus or other infections such as mycobacterium or fungus. Many medications can cause liver injury and fatal hepatic failure in severe cases. Pancreatitis may be seen.

Endocrine and metabolic involvement

Lipodystrophy and metabolic syndrome are the common side effects of ARVs [27,28•]. There is fat redistribution and changes of the appearance such as truncal obesity, buffalo hump and peripheral wasting. The metabolic syndrome consists of elevation of plasma trigycerides, cholesterol and glucose.

Disturbances of hypothalamic–pituitary–adrenal axis is usually encountered, hypercortisolaemia in the early stage and adrenal insufficiency in the advanced stage of the disease. However, frank adrenal insufficiency is relatively rare. Hyponatraemia is found in advanced HIV disease due to the syndrome of inappropriate antidiuretic hormone (SIADH) or adrenal insufficiency. Hypothyroidism and hyperthyroidism may be found.

Nucleoside/nucleotide analogue (NRTI) treatment is associated with hyperlactataemia/lactic acidosis. The proposed mechanism is the inhibition of mitochondrial polymerase gamma enzyme and consequently mitochondrial DNA replication and failure of aerobic metabolism. Diagnosis is made by elevated blood lactate but the blood should be obtained without applying the venous tourniquet and stored on ice.

Associated infections

HIV infection can be found with other sexually transmitted and blood-borne infections such as viral hepatitis, as well as opportunistic infections such as tuberculosis. These infections should be treated when appropriate before anaesthesia.

Drug abuse

Intravenous drug abusers are at risk of HIV infection. Numerous medical problems can be countered and affect anaesthesia. The details are beyond the scope of this article.

Antiretrovitral therapy

Combination of ARVs or highly active antiretroviral therapy (HAART) is the great advancement in treatment of HIV infection. Drugs for treatment of HIV infection 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 (Table 3).

Adverse drug effects

Antiretroviral agents have several adverse effects and should be assessed as preanaesthetic evaluation [6••,28•,29•]. These side effects can be summarized below:

(1) Mitochondrial dysfunction: lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy
(2) Metabolic abnormalities: fat maldistribution and body habitus changes, dyslipidaemia, hyperglycaemia and

Table 3 Antiretroviral drugs for treatment of HIV infection

Drug class	Available drugs
Reverse transcriptase inhibitors	
Nucleoside/nucleotide analogues (NRTIs)	Abacavir (ABC)
	Didanosine (ddI)
	Emtricitabine (FTC)
	Lamivudine (3TC)
	Stavudine (d4T)
	Zidovudine (AZT, ZDV)
Nonnucleoside reverse transcriptase inhibitors (NNRTs)	Delavirdine (DLV)
	Efavirenz (EFV)
	Etravirine (ETR)
	Nevirapine (NVP)
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)
Integrase inhibitors	Raltegavir (RAL)
Entry inhibitors	
Fusion inhibitors	Enfuvirtide (ENF, T-20)
CCR 5 antagonists	Maraviroc (MVC)

insulin resistance; and bone disorders such as osteopenia, osteoporosis and osteonecrosis
(3) Bone marrow suppression: anaemia, neutropaenia and thrombocytopaenia
(4) Allergic reactions: skin rashes and hypersensitivity responses.

Drug interactions

Drug interactions should be taken into consideration since these groups of patients received many medications [29•,30•]. Changes in pharmacodynamics can affect the efficacy and toxicity and pharmacokinetics can affect absorption, distribution, metabolism and elimination. In anaesthesia context, pharmacodynamic interactions are easily managed by avoiding anaesthetic agents that may potentiate side effects such as renal and hepatic dysfunction, which is rare in modern anaesthetic practices. However, some issues remain unclear such as enhanced mitochondrial toxicity and lactic acidosis from propofol [31] and NRTIs.

Altered pharmacokinetics is a more complicated interaction and is mostly mediated through inhibition or induction of hepatic liver enzyme, particularly CYP450 (CYP) 3A4 enzyme [32]. Protease inhibitors (PIs) and NNRTIs are the most implicated in drug interactions. For example, ritonavir has inhibitory effect on CYP and reduces fentanyl clearance [33] and also has inducing effect and increases normeperidine level [34]. Saquinair can inhibit midazolam metabolism and prolong midazolam effect [35,36]. This also applies to combinations of PIs or NNRTIs and benzodiazepines on excessive sedation. Inhibition of CYP 450 3A4 enzyme can enhance hypotensive effect of calcium channel blockers or increase level of lidocaine [30•,37,38]. Prolonged neuromuscular blockade in patients treated with ARVs are reported [39,40]. However, the interactions between drugs used in anaesthesia and HIV infection are complicated and the studies are scarce. The reader should refer to the database or the literature before administering anaesthesia.

Perioperative antiretroviral therapy

To diminish drug resistance, continuation of ARVs is highly recommended throughout the perioperative period so long as it compatible with surgery and patient's gastrointestinal function. However, parenteral drug formulations of ARV are limited to zidovudine (ZDV) and enfuvirtide (ENF). Some ARVs are available in liquid form that may be administered via feeding tube. Gastrostomy administration of ARV is also reported [41]. The complexities are some medications need to be taken with meals to facilitate absorption which may not be possible and also postoperative disturbances of gastrointestinal function. However, there is no study on ARV during the perioperative period.

Anaesthetic considerations

There is no major anaesthetic problem in an asymptomatic patient. Conversely, cautious anaesthetic management is needed in patients with advanced disease. A thorough preoperative assessment on the history, physical examination and laboratory tests for the status of HIV infection, organ involvement and drug side effects as stated above must be performed. Laboratory investigations include complete blood count and clotting functions to exclude coagulation abnormalities. Biochemical tests such as glucose, electrolytes, renal and liver function tests are necessary as HIV infection or the medications may cause metabolic, renal or liver function disturbances. Chest radiography is indicated in every patient to screen for tuberculosis or other pulmonary opportunistic infections. Cardiac evaluation such as electrocardiography and probably echocardiography are important to identify cardiomyopathy.

Anaesthetic technique

There is no particular anaesthetic technique in HIV infection. The type of anaesthesia used in patients with HIV infection will primarily be determined by the coexisting disease. There is issue on safety of performing central neural blockade in HIV-infected patients. Myelopathy, vertebral or spinal neoplasms, CNS infections are the main concern. There are studies on central neural blockade in obstetrics and epidural blood patch without any adverse events, provided that the patients do not have any neurologic symptoms [42–51]. However, the risks of developing neurologic complications following central neural blockade in HIV-infected patients are not known. It is suggested that central neural blockade is contraindicated in advanced disease or patients with neurologic symptoms in addition to other contraindications such as bleeding tendency.

Immunological effects of anaesthesia and blood transfusion

Anaesthesia, anaesthetic agents and stress responses following surgery have been reported to be associated with immunosuppression. This may effect the outcome or cancer recurrence [52–62,63•]. To date, the effect of anaesthesia and surgery *per se* on the outcome of HIV infection remains unclear.

There are data on immunomodulating effects of allogeneic blood transfusion or transfusion-related immunomodulation (TRIM) [64–66]. Blood transfusion results in an increase in HIV viral load in patients with advanced HIV infection [67,68]. Hence, blood should be judiciously transfused but must not preclude patient safety.

Transmission of infection

Anaesthesia personnel should use strict precautions on prevention of infections from and to HIV-infected

patients. HIV is found in body fluids of varying quantity [9]. Universal precautions and appropriate sharp object handling are particularly essential. Each institute should have a protocol in case of occupation exposure and counselling and postexposure prophylaxis should be started without delay [69,70•]. In addition, anaesthesia personnel should be cautious on transmission of HIV or other infections from HIV-infected patients to other patients by contaminated medications or equipment. Fortunately, there is no report on HIV transmission during anaesthesia. Finally, this group of patients is immunocompromised and susceptible to bacterial infections. Strict aseptic technique should be exercised throughout the anaesthesia and surgery.

Conclusion

Anaesthesia in HIV-infected patients is challenging. A careful preanaesthetic evaluation on organ system involvement is very essential. Side effects and interactions of the medications should be kept in mind. Anaesthesia should be tailored on a patient-to-patient basis. Infection control throughout anaesthesia must not be ignored.

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