Human immunodeficiency virus and anaesthesia

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Introduction

In the daily practice of anaesthesia, patients who are infected with the human immunodeficiency virus (HIV) will present. These patients can be at various stages of the disease process, and may or may not be on antiretroviral therapy (ART). This article will concentrate mainly on the clinical and practical aspects of dealing with a patient with HIV for anaesthetists.

Clinical manifestations

Patients who are infected with HIV may present at any stage of the disease process, and each stage is characterised by the presence of certain clinical stigmata. The World Health Organization (WHO) has developed a clinical staging system ranging from Stage 1 (essentially asymptomatic) to Stage 4 [acquired immune deficiency syndrome (AIDS)-defining].

By taking a history, examining the patient, and carrying out special investigations, the stage of the disease process in the patient can be determined.

The following symptoms and signs should be sought during the taking of the history and the examination:

Clinical Stage 1

- Asymptomatic
- Persistent generalised lymphadenopathy
- Performance status 1: asymptomatic with normal activity.

Clinical Stage 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections, such as otitis media, otorrhoea, sinusitis, or tonsillitis
- Performance status 2: symptomatic, but nearly fully active.

Clinical Stage 3

- Unexplained moderate malnutrition, that does not adequately respond to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent, or constant for longer than one month)
- Persistent oral candidiasis (after the first six to eight weeks of life)
- Oral hairy leukoplakia
- Acute necrotising ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease, including bronchiectasis
- Unexplained anaemia (< 8 g/dl), neutropenia (< 0.5 x 10^9 per litre) and/or chronic thrombocytopenia (< 50 x 10^9 per litre)
- Performance status 3: in bed < 50% of daytime of past month.

Clinical Stage 4

- Unexplained severe wasting, stunting, or severe malnutrition that does not respond to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections, such as empyema, pyomyositis, bone or joint infection, or meningitis, but excluding pneumonia
- Chronic herpes simplex infection (oro-labial or cutaneous of more than one month's duration, or visceral at any site)
- Extra pulmonary tuberculosis
- Kaposi's sarcoma
- Oesophageal candidiasis, or candidiasis of the trachea, bronchi or lungs
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or cytomegalovirus infection that affects another organ
- Extra pulmonary cryptococcosis, including meningitis
- Disseminated endemic mycosis (extra pulmonary histoplasmosis and coccidiomycosis)

Table I: Examples of antiretroviral drugs

NRTIs[a]	NtRTIs	NNRTIs	Protease inhibitors	Fusion inhibitors	CCRAs	Integrase inhibitors
Zidovudine Didanosine Lamivudine Stavudine Abacavir Emtracitabine	Tenofovir	Efavirenez Nevirapine	Indinavir Ritonavir Saquinavir Lopinavir/ritonavir	Enfurvirtide	Maraviroc	Raltegravir

NRTIs = nucleoside reverse transcriptase inhibitors, NtRTIs = nucleotide reverse transcriptase inhibitors, NNRTIs = non-nucleoside reverse transcriptase inhibitors, CCRAs = chemokine co-receptor antagonists

- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated non-tuberculous mycobacterial infection
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy, or HIV-associated cardiomyopathy
- HIV-associated rectovaginal fistula
- Performance status 4: in bed > 50% of daytime of the past month

Special investigations

The choice of special investigations should be guided by the history and examination.

Blood tests

Blood tests should include:

- A full blood count: anaemia, thrombocytopaenia, increased or decreased white cell count
- Urea and electrolyte: a low total CO_2 may indicate the presence of a lactic acidosis, in which case, carrying out an arterial blood gas should be considered
- Clotting profile: hypercoagulability
- Liver function tests: hypoalbuminaemia, and raised liver enzymes, especially with nevirapine
- Arterial blood gas analysis: hyperlactataemia and lactic acidosis
- Viral load and CD4+ count: mortality is inversely related to CD4+ count

Chest X-ray

- Cardiac shadow abnormalities (pericardial effusion), and dilated cardiomyopathy
- Evidence of infection, such as bacterial pneumonia, *Pneumocystis jiroveci* pneumonia (PCP), tuberculosis
- Kaposi's sarcoma of airway or mediastinum
- Mediastinal compression or lymphadenopathy.

Electrocardiogram

- Conduction defects
- Prolonged QT time

Antiretroviral drugs

Patients who are HIV positive may be on ART. These drugs can have significant side-effects, and can also interact with anaesthetic agents.

Treatment of patients (who are HIV positive) with antiretroviral drugs, is based on guidelines provided by the National Department of Health.

Antiretroviral drugs (Table I) are classified as follows:

- Reverse transcriptase inhibitors which include nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Entry inhibitors, including fusion inhibitors and chemokine co-receptor antagonists (CCRAs)
- Integrase inhibitors.

Who is eligible to receive antiretroviral treatment?

The Standardized National Eligibility Criteria for starting ART regimens in adults and adolescents are as follows:

- CD4 count < 200 cells/mm^3 irrespective of clinical stage; or
- CD4 count < 350 cells/mm^3 in patients with tuberculosis/HIV, or in pregnant women; or
- WHO Stage 4, irrespective of CD4 count; or
- Multi-drug-resistant (MDR)/extreme drug-resistant (XDR) tuberculosis, irrespective of CD4 count.

What are the antiretroviral treatment regimen in South Africa?

Table II lists the first-line antiretroviral treatment regimen in South Africa.

Table III lists the salvage therapy treatment regimen in South Africa.

Antiretroviral treatment drug side-effects

Reverse transcriptase inhibitors: NRTIs and NtRTIs

- NRTIs are associated with many adverse effects, most of which are benign and self-limiting.
- Mainly renal elimination.
- Mitochondrial toxicity may result in pancreatitis, hepatosteatosis, peripheral neuropathy, and lactic acidosis.
- Abnormal fat deposition can result in central obesity and facial fat wasting, as well as deranged lipid distribution, leading to metabolic derangement.
- Zidovudine is associated with a high incidence of

Table II: First-line treatment

Patient group	Treatment	Comments
All new patients needing treatment	Tenofovir + lamivudine/emtracitabine + efavirenez/nevirapine	Efavirenez is preferred for tuberculosis co-infection. Navirapine is preferred in pregnant women, or women of child-bearing age who are not on reliable contraception.
Currently on stavudine-based regimen, with no side-effects	Stavudine + lamivudine + efavirenez/nevirapine	The patient should remain on stavudine if it is well tolerated. Early switch with any toxicity. Substitute tenofovir if the patient is at high risk of toxicity, e.g. with a high body mass index, older, female, or on tuburculosis treatment.
Contraindication to tenofovir: renal disease	Zidovudine + lamivudine + efavirenez/nevirapine	

Table III: Second-line treatment for patients who fail first-line treatment virologically

Patient group	Treatment	Comments
Failing on a stavudine- or zidovudine-based first-line regimen	Tenofovir + lamivudine/emtracitabine + lopinavir/ritonavir	Virological failure must be followed by intensive adherence management as resuppression is often possible. If repeat viral load remains >1 000 in 3 months despite adherence intervention, switch.
Failing on a tenofovir-based first-line regimen	Zidovudine + lamivudine + lopinavir/ritonavir	Virological failure must be followed by intensive adherence management as resuppression is often possible. If repeat viral load remains > 1 000 in 3 months despite adherence intervention, switch.

Table III: Salvage therapy

Patient group	Treatment	Comments
Failing any second-line regimen	Specialist referral	Virological failure on protease inhibitors is almost always due to non-adherence. Intensively exploring and addressing issues relating to causes of non-adherence will most often lead to resuppression. If viral load remains high, refer where possible, but maintain on failing regimen.

fatigue, headaches, and gastrointestinal side-effects. including severe nausea, vomiting and diarrhoea.

NNRTIs

- Rashes, including Steven-Johnson syndrome, and toxic epidermal necrolysis.
- Nevirapine is used in the prevention of mother-to-child transmission. It is also a potent inducer of cytochrome p450 enzymes. As a result, it induces its own metabolism, and may lead to a reduction in the effect of midazolam, rifampicin and oral contraceptives.
- Markedly increase opioid metabolism requires an increased dose of synthetic opioids.
- Premature atherosclerosis, metabolic syndrome with glucose intolerance, decreased high-density lipoprotein levels and hypercholesterolaemia also occur.
- NNRTIs have a very long half-life, resulting in a "hangover effect" on discontinuation, i.e. increased risk of resistance to ARV.

PIs

- All are associated with metabolic abnormalities, including dyslipidaemia, insulin resistance with hyperglycaemia, and lipodystrophy ("protease paunch").
- Cause gastrointestinal tract disturbances and abnormal liver functions.
- Impair Vitamin D metabolism, leading to osteoporosis.
- The effects of midazolam and diazepam are potentiated, and require dose reduction. Lorazepam is probably safer.
- Significant reduction in metabolism of alfentanil and fentanyl is described. Reduction in clearance of fentanyl by nearly 70% has been described with ritonavir. Remifentanyl and morphine are safe alternatives. Pethidine is not recommended because of the risk of metabolite accumulation and seizures.
- Sodium thiopentone and dexamethasone may reduce PI concentration.
- Simvastatin and lovastatin are absolutely contraindicated, as there is a high risk of rhabdomyolysis and myopathies. Pravastatin is safe.
- PIs increase the cardiac toxicity of amiodarone, quinidine and disopyramide. May potentiate digoxin toxicity.
- Disulfiram-like reaction with metronidazole.

Fusion inhibitors

- Expensive
- Risk of hypersensitivity
- Neutropaenia.

CCRAs

- Elevations in liver function tests, coughing, diarrhoea and nausea.

Integrase inhibitors

- Elevations in amylase and liver function tests, pruritus and rashes, headaches.

Lactic acidosis

Lactic acidaemia can occur in patients taking NRTIs. The lactate is elevated in the presence of a normal pH, and is not of clinical importance, provided the patient is asymptomatic.

However, lactic acidosis is a rare, but potentially fatal complication of ART. It carries a mortality of up to 77%. The symptoms may be vague and non-specific, such as nausea, vomiting, abdominal pain, fatigue and weight loss. The patient may also present with hepatic steatosis and dysfunction. Treatment involves stopping the NRTI, and instituting supportive care. Patients booked for elective surgical procedures who have lactic acidosis should be postponed until the lactic acidosis has resolved.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) occurs when improving immune function unmasks a previously occult opportunistic infection which subsequently presents with an unusually aggressive inflammatory presentation. Patients with advanced HIV may become ill with IRIS. usually during the first three months of ART. Tuberculosis is the most common presenting IRIS reaction in South Africa. About a third of patients starting ART when on treatment for tuberculosis, will experience recurrence of their tuberculosis signs and symptoms, or new manifestations. Rashes, including zoster, herpes, molluscum and others, cryptococcal meningitis, and hepatitis due to hepatitis B or C, are other manifestations of IRIS.

IRIS is not indicative of drug failure or side-effects, and is not a reason to stop ART.

Perioperative fasting

Patients should continue treatment protocol despite *nil per os* orders, as there is clear evidence of increased mortality and adverse events during temporary interruption of the ART regimen. ARVs may also be administered via gastric or jejunal feeding tubes.

Premedication

Beware of potential drug interactions with midazolam and diazepam. Lorazepam and oxazepam are safer.

Universal precautions

Universal precautions are essential, including gloving and eye-splash protection. Avoid unnecessary invasive procedures, and dispose of sharps safely.

Potentially infectious materials include blood and blood-stained fluids or materials, vaginal or penile secretions, and tissue fluids, including ascites, liquor, cerebrospinal fluid, pleural and pericardial fluid, and breast milk.

Sweat, tears, saliva, sputum, urine and stools, are generally considered to be non-infectious, unless contaminated by the above.

The risk of HIV infection from needle-stick injury is 0.3%, and the risk of HIV transmission from exposure to mucous membranes is 0.1%, and to non-intact skin, < 0.1%.

The highest risk of infection is injury from hollow-bore needles containing visible blood, large-volume exposure, a deep injury, and if the patient has a high viral load.

Intraoperative management

General anaesthesia

General anaesthesia results in immunosuppression within 15 minutes of induction, and lasts for up to 11 days postoperatively. The possibility of unpredictable drug interactions must always be considered.

Etomidate is possibly the safest for induction (no metabolism by cytochrome P450). However, the risk of adrenal insufficiency should be considered. There are no clear contraindications to propofol or sodium thiopentone.

Desflurane is theoretically advantageous due to minimal metabolism.

Remifentanil is the opioid of choice. Morphine is generally safe. Doses must be tailored according to response, and may need to be increased in patients on NNRTIs, or reduced in patients using PIs. In general, pethidine should be avoided.

Scoline is probably safe. However, the risk of hyperkalaemia in patients with myopathy and neuropathy can exist.

Atracurium and cis-atracurium with organ-independent metabolism are theoretically safest.

Neuraxial and regional anaesthesia

This is the technique of choice in patients who are HIV positive, unless there is evidence of coagulopathy, sepsis, neuropathy or uraemia.

A platelet count is recommended to exclude thrombocytopaenia, and exclude or document pre-existing neuropathy.

An epidural blood patch is not contraindicated, although conservative treatment is usually preferable.

Postoperatively

It is essential to resume ART without interruption.

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