Antiretroviral therapy and anaesthesia

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SAJAA 2008; 14(2): 31-38

ABSTRACT

HIV has reached pandemic proportions in Southern Africa. Great emphasis is placed on the prevention and containment of HIV transmission by suppressing virus replication using highly active anti-retroviral therapy (HAART). HAART has proven to be highly effective if taken correctly, and has lead to increased life expectancy. Increasing numbers of HIV-positive patients on antiretroviral (ARV) therapy or HIV-exposed individuals taking prophylaxis present for surgery and critical care management. The anaesthesiologist should be familiar with the anaesthetic implications of HIV as well as the possible drug interactions while on ARV treatment. This article focuses specifically on the anaesthetic implications of the patient on HAART.

HAART is HIV treatment with a combination of three or more ARV drugs from five broad classes. The specific HAART regimen in use in South Africa is considered in detail in this article.
The pharmacokinetics of the ARV drugs is complex, and subject to interactions at many different sites. Serious drug interactions are possible, including drugs commonly used in anaesthesia. Drug interactions and recommendations are discussed in detail.

ARVs are known to cause multiple systemic side effects, including lactic acidosis, Immune Reconstitution Inflammatory Syndrome (IRIS), premature atherosclerosis and increased cardiovascular risk, hyperlipidaemia, insulin resistance, skeletal disorders, hepatotoxicity, lipodystrophy, mitochondrial abnormalities, allergic reactions and pancreatitis.

Non-compliance is common, and leads to the rapid development of resistance. The anaesthesiologist may inadvertently exacerbate this in the perioperative period. Recommendations regarding the interruption of treatment and fasting are made. Alternative routes for HAART administration are also explored. The management of the critically ill patient on a HAART regimen is discussed.

Introduction

Two decades have passed since the first cases of HIV were reported[1] and today the HIV syndrome has reached pandemic proportions. The epidemic continues to spread at a rate of almost 10 000 new cases daily, especially in Africa and South East Asia.[2]

The availability of effective anti-retroviral (ARV) therapy, while unable to cure the disease, has lead to an increased life expectancy and has convincingly been demonstrated to decrease mortality.[3] Since these patients are still more likely to require diagnostic or therapeutic interventions, increasing numbers of HIV-positive patients on ARV therapy present for surgery and critical care management. The anaesthesiologist should be familiar with the pathogenesis of HIV/AIDS, possible drug interactions while on ARV treatment, anaesthetic implications in the HIV-positive patient and infection control policies currently recommended. This article will focus specifically on the anaesthetic implications of the patient on highly active anti-retroviral therapy (HAART).

Pharmacology of HAART

A HAART regimen suppresses viral replication and the progression to AIDS without eradicating the virus.[4] The objective with HAART is to sustain plasma viral load levels to < 50 copies/ml on ultra sensitive viral load assays.[5] The treatment plan must therefore include ARV drugs with different resistance profiles to minimise the chances of a viral strain that will be resistant to all the prescribed drugs.[4] Furthermore, strict patient adherence to the ARV cocktail is extremely important in preventing viral resistance to the chosen HAART regimen.[6]

Antiretroviral drug class classification[7]

Five broad classes of ARVs are being used, often in combination.[6]
1. Protease inhibitors (PIs)
2. Nucleoside reverse transcriptase inhibitors (NRTIs)
3. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
4. Cell membrane fusion inhibitors
5. Integrase inhibitors

HAART is HIV treatment with a combination of three or more ARV drugs. Either one or two NRTIs, one NNRTI and/or one PI is used in combination as a cocktail.[6,8] A fourth agent may be added for a patient who exhibits developing resistance due to previous ARV exposure.

HAART regimen currently used in South Africa[9]

This review will focus only on the drugs in use in South Africa. The protocol for first- and second-line treatment is summarised in Table I.

ARV naïve adult (weight > 60 kg):

A. First-line therapy:
- stavudine 30 mg 12-hourly with
- lamivudine 150 mg 12-hourly and
- efavirenz 600 mg at night or
- nevirapine 200 mg daily for two weeks, then 200 mg 12-hourly

B. Second-line therapy (patients who fail virologically):
- didanosine 400 mg daily
- zidovudine 300 mg 12-hourly

- lopinavir/ritonavir 400/100 mg 12-hourly

ARV non-naïve patient:

A tailored regimen of three different drugs to which the patient has never been exposed.

The pregnant patient:
- stavudine 30 mg 12-hourly
- lamivudine 150 mg 12-hourly
- nevirapine 200 mg daily for two weeks, then 200 mg 12-hourly
- initiate treatment only after first trimester, unless CD4 count is < 50 cells/mm^3 – start immediate treatment
- efavirenz is contraindicated due to teratogenicity

Effectiveness of HAART

A reduction in measured viral load with an increase in CD4 count is a good predictor of the clinical treatment response.[5] When the patient is adherent to the treatment protocol, viral load rebound and drug resistance is minimal and treatment usually successful.[5] Discontinuation of HAART, even in the patient who has been on treatment for more than two years, results in a rapid rise in the viral load, back to the pre-treatment values.[5,10] Close adherence to the drug regimen is extremely important to achieve complete viral suppression and to prevent drug resistance.[11,12]

Which patients may be on HAART?

1. HIV-negative individuals requiring prophylaxis after exposure.
2. HIV-positive patients fulfilling the criteria of the local guidelines. In South Africa, the criteria for starting HAART is:[9]

1) World Health Organization (WHO) stage 4 disease
2) WHO stage 1, 2, 3 disease with CD4 count < 200 cells/mm^3

Current international treatment guidelines recommend that no treatment should be given to an asymptomatic person with a plasma HIV RNA concentration of < 100 000/ml unless the CD4 count is less than 200.[9] The viral load is not considered when initiating HAART in South Africa or other developing countries.

Pharmacokinetic overview of the ARV drugs in clinical use

Pharmacokinetics is simply what the body does to drugs. Pharmacokinetics for orally administered drugs includes absorption, distribution, metabolism and elimination.[13] Interactions of metabolism especially affect the following:[14]
- Drug absorption due to changes in gastric pH
- Cytochrome P450 system
- Modulation of P-glycoprotein
- Induction of glucoronidation
- Renal elimination

Most ARVs are well absorbed when administered orally,[15] undergo passive diffusion through the gastro-intestinal system and are then metabolised by cytochrome P450 (CYP)3A and CYP2B6 isoenzymes.[13] Absorption of drugs can be altered by changes in the gastric pH, which has specific implications for the critically ill individual where antacids may decrease drug absorption.[14,15] Lipophilic drugs such as the PIs and NNRTIs are oxidatively metabolised by the P450 system to more polar forms for biliary or renal excretion.[13] These drugs can further be classified according to their effects as cytochrome P450 enzyme inducers or inhibitors.[14] This means that the plasma concentration of drugs taken concurrently with these ARV drugs can either be increased or decreased,[14] and some drugs may alter their own metabolism over time. However, some drugs like ritonavir and efavirenz may have properties of both induction and inhibition depending on the combination used.[14] Thus, drugs that induce cytochrome enzymes increase the hepatic metabolism of other drugs and lead to lower plasma concentration.[14,15]

NRTIs are water soluble (except for zidovudine) and are eliminated renally.[13] However, the NRTIs are prodrugs and require intracellular phosphorylation to be activated.[13] Drugs that affect phosphorylation can affect the activity of the NRTIs.[13]

P-glycoprotein is a potential site for ARV-associated drug interactions, thus potentially decreasing the effectiveness of drugs that are P-glycoprotein substrates.[16,17] All the NNRTIs and a few NRTIs increase P-glycoprotein activity.[17] The induction of P-glycoprotein by especially anti-TB drugs like rifampicin results in a reduction of both PI and NNRTI plasma levels, which may decrease the efficiency of the HAART regimen.[18] The available

Table I: HAART regimen currently used in South Africa[9]

	FIRST-LINE				SECOND-LINE		
Anti-retroviral drug	**Stavudine 30 mg**	**Lamivudine 150 mg bd**	**Efavirenz 600 mg nocte**	**Nevirapine 200 mg/d for 2 weeks, then 200 mg bd**	**Didanosine 400 mg daily**	**Zidovudine 300 mg 12-hourly**	**Lopinavir/ritonavir 400/100 mg 12-hourly**
DRUG CLASS	NRTI	NRTI	NNRTI	NNTRI	NRTI	NRTI	PI
ARV naïve adult	√	√	√ *	Or √ *	√	√	√
ARV naïve adult with sustained viral count >50 copies/ml despite therapy					√	√	√
ARV non-naïve patient Any three drugs to which the patient has not had exposure	√	√	√	√	√	√	√
Pregnant patient	√	√	C/I	√			
Post-exposure prophylaxis	√	√	√				

* Either efavirenz OR nevirapine

data on the other ARV drugs' effect on P-glycoprotein are conflicting.

Group-specific pharmacokinetic and drug interactions (Table II)

PIs
Pharmacokinetics[15]
- PIs target viral protease, the key enzyme for structural viral protein synthesis.
- All PIs are inhibitors of CYP3A.
- Extensively metabolised by cytochrome P450 system.
- Inhibitors of P-glycoprotein transporter.
- Potent inducers of P450 isoenzymes (ritonavir).
- Multitude of drug interactions.

Interactions
- **Benzodiazepines**: PIs in combination with midazolam and diazepam may lead to major respiratory depression and prolonged sedation. Dose reduction is advised.[11]

- **Opiates:** Of particular interest is the interaction between PIs and opiate dependence,[8] especially methadone. Approximately 30% of HIV-positive people in the USA are IV drug users and methadone is the most widely used opiate dependence therapy.[8] ARVs that induce cytochrome P450 lead to a decrease in plasma concentration of opiates (methadone) and can precipitate acute drug withdrawal due to a decrease in the plasma opiate concentration.[8]

An impairment of 70% in fentanyl and alfentanyl metabolism has been observed, resulting in higher serum levels and a major risk for respiratory depression.[15,19,20]

Pethidine is best avoided due to the accumulation of metabolites with an associated risk for seizures.

- **Thiopentone** and **dexamethasone**[11] can reduce PI plasma concentration.

- **Etomidate, atracurium, remifentanyl and desflurane** are not dependent on P450 metabolism and are therefore the preferred agents to use to minimise drug interactions.[7]

- **Antiarrhythmics**: In combination with PIs, amiodarone, disopyramide and quinidine pose a risk of major cardiovascular toxicity and should be used with extreme caution.[11]

- **Statins:** Simvastatin and lovastatin are absolutely contraindicated due to the risk of rhabdomyolysis and myopathies.[3] Pravastatin is safe in combination with PIs due to a non-cytochromic enzyme metabolism.[3]

NNRTIs
Pharmacokinetics
- Resistance to NNRTIs can develop rapidly.[13]
- Can lead to both cytochrome P450 enzyme induction and inhibition,[14] depending on the specific drug being used.

Interactions
- **Opioids**: Of particular concern is the effect on plasma methadone and opiate concentration.[8,14,21] Both nevirapine and efavirenz reduce plasma methadone concentration by 50%.[14] This leads to an increased risk for methadone withdrawal.

Due to sub-therapeutic levels of fentanyl, and alfentanyl observed in combination with NNRTIs, opiate doses administered should be increased.[19]

NRTIs
Pharmacokinetics
- Prodrugs.[11]
- Require intracellular phosphorilation to active moiety.[14]
- Dual NRTIs is the conventional backbone of triple therapy.
- Do not interact with drugs through the P450 cytochrome system.[14]
- Can be given with PIs and NNRTIs without any dose adjustment.[14]
- Primarily renal elimination.[14]

Interactions
- **Antibiotics**: The combination with metronidazole poses a risk for peripheral neuropathy after long-term use.[20]

Hydroxyurea
Ribonucleotide reductase inhibitor that improves the phosphorilation of NRTIs.[14]

Fusion inhibitors[2]
- New class of ARV drugs.
- Binds to protein on HIV viral membrane and prevents conformational change required for the HIV cells and healthy cells to fuse.
- Enfuvirtide: Expensive.
  Available as abdominal subcutaneous injection.

Integrase inhibitors
A new category of drugs, but not yet available.

Systemic and metabolic complications of ARV drugs

ARVs are known to cause multiple systemic side effects that commonly lead to poor compliance. These side effects are summarised in Table III and discussed below according to their significance as being either potentially acutely life threatening, associated with chronic exposure, or detrimental to the patient's quality of life.

A. Potentially life-threatening and serious adverse events:[3,25]

1. Lactic acidosis[3,24]
- Although lactic acidosis is uncommon, it has major morbidity and associated mortality.
- Lactic acidosis results from mitochondrial toxicity.

2. Immune Reconstitution Inflammatory Syndrome (IRIS)[26,27]
- The immune reconstitution inflammatory syndrome is an acute exacerbation of inflammatory disorders in the patient started on HAART.
- This uncommon pro-inflammatory state may manifest as a paradoxical worsening of infectious symptoms.

B. Adverse events associated with potential long-term complications:[3]

1. Risk of cardiovascular disease[28]
- Patients with HIV develop premature atherosclerosis[3] due to pro-inflammatory effects on the endothelium.[25]
- PIs further impair endothelial function[3] with accelerated onset of atherosclerosis and coronary artery disease.[29]
- These complications will become especially apparent as the HIV population ages.[3]
- The SMART study demonstrated that effective ARV treatment reduces short-term cardiovascular risks.
- The Aids Clinical Trials Group Study 5152S demonstrated improved endothelial function during effective ARV treatment.
- PIs increase cardiovascular risk modestly and long-term outcome studies are needed.

2. Hyperlipidaemia[25,30]
- Progression of HIV disease leads to increased VLDL and triglycerides, and lowered HLD.
- After as little as two weeks of PI exposure, the lipid profile changes, with around 60% of patients demonstrating dyslipidaemia.

3. Insulin resistance
- Insulin resistance and impaired glucose tolerance have

Table II: Summary of drug interactions between HAART regimens and some drugs commonly used in anaesthesia

	FIRST-LINE				SECOND-LINE		
Drug:	**Stavudine**	**Lamivudine**	**Efavirenz**	**Nevirapine**	**Didanosine**	**Zidovudine**	**Lopinavir/ritonavir**
GROUP:	**NRTI**	**NRTI**	**NNRTI**	**NNTRI**	**NRTI**	**NRTI**	**PI**
P450 ENZYME EFFECT	~	~	↑↓ [14]	↑ [14]	~	~	↓↓ [14]
DRUG EFFECTS:	**CARDIOVASCULAR DRUGS:**						
Amiodarone	Ø	Ø	Ø	Ø	Ø	Ø	Avoid[11]
Calcium channel blockers	Ø	Ø	Ø	Ø	Ø	Ø	↓ dose[15]
Digoxin	Ø	Ø	Ø	Ø	Ø	Ø	↓ dose[15]
Quinidine	Ø	Ø	Ø	Ø	Ø	Ø	UWC[11] ↓ dose [11]
HMG CoA Reductase inhibitors: • Simvastatin	Ø	Ø	Ø	Ø	Ø	Ø	Avoid[11,22]
• Atorvastatin	Ø	Ø	Ø	Ø	Ø	Ø	UWC[11]
• Lovastatin	Ø	Ø	Ø	Ø	Ø	Ø	UWC[22]
• Pravastatin	Ø	Ø	Ø	Ø	Ø	Ø	Safe[15]
RECOMMENDATION:	Avoid simvastatin or lovastatin, choose pravastatin as a safe option.						
	NEURO-MUSCULAR BLOCKING AGENTS						
Atracurium	Ø	Ø	Ø	Ø	Ø	Ø	Preferred agent
	VOLATILE AGENTS						
Desflurane	Ø	Ø	Ø	Ø	Ø	Ø	Preferred agent[7]
	ANALGESICS						
Codeine	Ø	Ø	Unlikely effect	Unlikely effect	Ø	Ø	↑ dose[9]
Methadone	Ø	Ø	↑ dose[8,14]	↑ dose[8,14]	Ø	Ø	↑↑ dose by 36%[8,19]
Fentanyl	Ø	Ø	↑ dose[19]	↑ dose[19]	Ø	Ø	↓↓ dose [7,15,19]
Remifentanyl	Ø	Ø	Ø	Ø	Ø	Ø	no change
Alfentanyl	Ø	Ø	↑ dose[19]	↑ dose[19]	Ø	Ø	↓↓ dose [7,19]
Pethidine	Ø	Ø	↑ dose[19]	↑ dose[19]	Ø	Ø	Avoid[15]
Morphine	Ø	Ø	Ø	Ø	Ø	Ø	↑ dose [15,19,20]
Buprenorphine	Ø	Ø	Ø	Ø	Ø	Ø	No adjust-ment[15]
RECOMMENDATION:			Increase dose of synthetic opioids	Increase dose of synthetic opioids			Avoid pethidine Drug of choice: Remifentanyl

	FIRST-LINE				SECOND-LINE		
Drug:	**Stavudine**	**Lamivudine**	**Efavirenz**	**Nevirapine**	**Didanosine**	**Zidovudine**	**Lopinavir/ritonavir**
GROUP:	**NRTI**	**NRTI**	**NNRTI**	**NNTRI**	**NRTI**	**NRTI**	**PI**
SEDATIVE/HYPNOTICS							
Oxazepam	Ø	Ø	No predicted effect[19]	No predicted effect[19]	Ø	Ø	Ø
Midazolam	Ø	Ø	↑ dose[19]	↑ dose[19]	Ø	Ø	↓ dose[7,15]
Diazepam	Ø	Ø	↑ dose[19]	↑ dose[19]	Ø	Ø	↓ dose[15,19]
Lorasepam	Ø	Ø	no predicted effect[19]	no predicted effect[19]	Ø	Ø	Ø
Haloperidol	Ø	Ø	Ø	Ø	Ø	Ø	↓ dose[15]
RECOMMENDATION:	Effect of midazolam and diazepam unpredictable. Choose lorasepam or titrate dose carefully. Risk of respiratory depression and increased sedation.						
INDUCTION AGENTS							
Thiopentone	Ø	Ø	↑ dose	Ø	Ø	Ø	Limited data[20]
Propofol	Ø	Ø	No predicted effect	No predicted effect	Ø	Ø	↑ dose[19]
Etomidate	Ø	Ø	Ø	Ø	Ø	Ø	?Preferred agent[7]
RECOMMENDATION:	Titrate thiopentone and propofol to effect or choose etomidate.						
LOCAL ANAESTHETICS							
Lignocaine	Ø	Ø	Ø	Ø	Ø	Ø	↓ dose[15]
RECOMMENDATION:	Considered safe, limit use and do not exceed maximum recommended dose in patients on PIs.						
ANTIBIOTICS							
Clarithromycin	Ø	Ø	Ø	Ø	Ø	Ø	↓ dose
Co Trimoxazole	Ø	↑ lamivudine concentration with co trimoxazole	Ø	Ø	Ø	Ø	Ø
Erythromycin	Ø	Ø	Ø	Ø	Ø	Ø	↓ dose[20]
Metronidazole	Ø	Ø	Ø	Ø	Ø	Ø	Disulfiram like reaction
RECOMMENDATION:	Generally safe, except for macrolides and metronidazole in the presence of PIs.						
OTHER DRUGS							
Antacids	Ø	Ø	Ø	Ø	Avoid[20]	Ø	Ø
Dexametasone	Ø	Ø	Ø	Ø	Avoid[11] Risk for ↑ viral resistance	Ø	Ø
Prednisone	Ø	Ø	Ø	Ø	↓ dose	Ø	Ø
Warfarin	Ø	Ø	↑ dose[15] monitor INR	↑ dose[15] monitor INR	↓ dose[15]	Ø	Ø
Prometasine dose	Ø	Ø	Ø	Ø	↓ dose[15]	Ø	Ø

UWC = Use with caution
Ø = No recommendations or adverse reports in the literature

Table III: Common HAART-associated side effects

Systemic effects[2,11,20]	NRTIs	NNRTIs	PIs
Lipodystrophy			√
Insulin resistance			√
Abnormal lipid profile			√
Porphyria	Avoid: stavudine didanosine		Avoid: indinavir ritonavir
Allergic reactions	√	√	√
CNS abnormalities		√	√
GIT disturbances	√	√	√
Liver function abnormalities	√	√	
Mitochondrial toxicities	√		
Pancreatitis	√		
Peripheral neuropathy	√		

been observed since the introduction of PIs.[25]
- Insulin resistance further increases cardiovascular risk.

4. Skeletal disorders[25]
- PIs impair the conversion of vitamin D to active compounds.
- Osteopenia, osteonecrosis and osteoporosis have been demonstrated.
- Surgical procedures include core decompression and joint replacements. Careful positioning and manipulation of the patient is required intraoperatively.

5. Hepatotoxicity
- Nevirapine is associated with an increased risk of drug-associated hepatitis and abnormal liver function tests.[26]
- The risk for severe hepatic dysfunction is higher in the patient with a high CD4 count.[26]
- The risk of halothane hepatitis is not known.

C. Adverse effects compromising quality of life

1. Lipodystrophy[3]
- This is a syndrome of fat redistribution, including central fat accumulation and peripheral fat loss.[26]
- This disfiguration is especially troublesome to patients and may lead to the HIV patient presenting for plastic and reconstructive procedures.
- Clinical presentation might resemble Cushing's disease, but no abnormalities in the hypothalamic-pituitary-adrenal axis have been demonstrated[25] and there have been no reports of airway management difficulties.

Anaesthetic approach[7]

The approach to a patient with HIV is well documented elsewhere. The specific approach to the patient on HAART may be summarised as below.

Pre-operative assessment:

Pre-operative assessment should focus on:
- Stage of the disease (see WHO staging).
- Surgical procedure and type of anaesthetic.
- Coexisting opportunistic infections and malignancies.
- HAART and anti-opportunistic regimen and possible drug interactions.

Special investigations:
- ECG – look for prolonged QT time, conduction defects, ischaemic changes, pericarditis, and pericardial effusion.
- CXR – look for cardiac shadow abnormalities as above, infection, pneumocystis carini, Kaposi sarcoma of airway of mediastinum, mediastinal lymph nodes or compression, TB.
- FBC (pancytopenia, raised WCC, anaemia).
- Clotting profile (hypercoagulability).
- Liver function especially if on nevirapine (raised liver enzymes are common on ARV, albumin levels are often low).
- Renal function tests.
- CD4 count and viral load during the previous three months are important.
  - HAART effects may be exaggerated.
  - Regardless of the surgical procedure, there is a 13.3% mortality rate at six months post-operatively if the CD4 count is below 50.[7]

Patients with a history of cardiopulmonary disease should undergo a more thorough evaluation, which includes blood gas analysis (lactic acidosis), echocardiography, effort tolerance testing or even angiography.

Anaesthetic technique:
- Standard precautions should be in place for all cases, regardless of whether their HIV status is known. Remind all staff members to take caution.
  - Wear gloves and eye splash protection as prescribed by your institution and follow the local infection control policies.
  - Aseptic technique.
  - Stringent adherence to sharp object management drill.
  - Avoid unnecessary invasive procedures.

- Anaesthetic of choice:
  1. Regional anaesthesia – Does not directly interfere with ARV drugs or the immune system. HIV is not a contra-indication unless accompanied by clotting abnormalities, sepsis, neuropathies or uraemia. The advantage of a regional technique in the HIV-positive parturient has been confirmed.[7,31,32] This is the technique of choice with no increased risk of introducing the disease to the CNS.[33] There is no contraindication to an epidural blood patch if indicated in the HIV-positive patient, although conservative management may be preferred.[7,34,35]

  2. General anaesthesia – Multiple drug interactions are possible, and may be difficult to predict. Please refer to Table I. Immunosuppression from the use of general anaesthetics results within 15 minutes of induction and may persist for three to eleven days.[34] This is unlikely to be significant.

     Choice of general anaesthetic agents:
     - *Induction agents* – The clinical effect of these drugs is short and mostly predictable, since it is determined by redistribution rather than metabolism. There are no clear contra-indications to single boluses of the induction agents in routine use. Etomidate has been recommended as the drug of choice,[7] but should be used with caution in the HIV-positive patient with associated adrenal insufficiency, or with repeated use.
     - *Inhalation agents* – No specific references to HAART interactions were found, nor are they likely to be clinically significant due to the respiratory route of elimination and limited metabolism. Newer, less metabolised agents may theoretically be preferable, in the light of possible hepatic effects. More research is needed before recommendations can be made regarding the use of nitrous oxide or high inspiratory oxygen partial pressures. Hyperoxic gas mixtures have been found beneficial in immune compromised patients in other studies.[36]
     - *Opiates* – Complex and variable interactions are possible. Titrate the opioid dose according to Table II, or use remifentanyl. Lab data suggest a detrimental effect on immune function; however, the clinical significance of short-term use during general anaesthesia is unclear

and there is not enough data to justify complete avoidance.[7]

- *Suxametonium* – Complications such as hyperkalemia and malignant hyperpyrexia are potential risks in the HIV-positive patient with myopathy and neuropathy. No such complications have been reported to date and its use is not contraindicated.[7]
- *Atracurium and cis-atracurium* are attractive alternatives due to their specific route of elimination independent of P450, although no recommendations can be justified from the literature.

Antiretroviral therapy and the perioperative period

When patients are kept fasted and the HAART regimen is terminated abruptly, a rise in viral load and the development of resistant strains are a concern. Resistance to ARV drugs can develop very quickly. Once resistance to the ARV drug develops, it can persist indefinitely, resulting in treatment failure.[26]

Perioperative fasting

- Ideally all patients on HAART should continue with their treatment protocol.
- The nil per os (NPO) rules pertain to solids and liquid intake, not to prescribed medication.
- NNRTIs: These drugs have a long half life (three to five days) and abrupt termination results in sustained sub-therapeutic plasma levels with rapid resistance to NNRTIs due to viral replication.
- Suggestion: For anticipated ileus > 24 hours – discontinue the NNRTI regimen for one to two weeks prior to surgery and change to a dual NRTI regimen (Prof. PG Maartens, Clinical Pharmacology, UCT, 2007, personal communication).
- Obtain assistance from an infectious disease specialist.

Temporary perioperative interruption of the HAART regimen

- The SMART study clearly showed increased mortality and adverse events during prolonged interruption.[37-39]
- Structured treatment interruption (CD4 guided "drug holidays") has been investigated, but cannot be recommended as part of routine care – nor can it justify prolonged perioperative interruption of therapy.[37,40]
- Plasma levels for NNRTIs and PIs can readily be measured, but the levels of NRTIs are not useful for therapeutic drug monitoring, as they are prodrugs.[41]
- Consult an infection control specialist when anticipating an interruption of therapy.

Alternative routes for HAART administration

- The only available ARV for intravenous administration is Zidovudine (AZT).[41]
- Gastric and jejunal feeding tubes may be utilised.[41] All of the approved ARV drugs in use are available as capsules or tablets except for enfurvitide. Tablets and capsules can be crushed and delivered through the feeding tube.[24] In critical illness, however, the absorption of the ARVs remains a problem[24] due to ileus, decreased gastric motility, frequent suctioning, continuous feeding and stress ulcer prophylaxis.[24]
- Gastrostomy: A pilot study conducted by Jennifer King et al[42] suggests that most PIs and NNRTIs can be administered to HIV-infected children via a gastrostomy tube placed surgically. Plasma levels obtained were comparable to orally administered drugs. The results from this study should be applicable to adult patients as well.
- Enfurvitide can be administered via the subcutaneous route.

Continuing HAART in the ICU[41]

The HIV-positive patient admitted to the ICU presents a huge management challenge. Managing the critically ill patient on a HAART regimen is frequently based on physician experience only.[41] These patients are now less likely to be admitted with problems related to opportunistic infections but more likely to be admitted with conditions unrelated to the HIV infection or with conditions specifically related to the HAART regimen.[27]

Drug delivery, doses, interactions and HAART toxic side effects are a major concern.[24] A decision needs to be taken whether the ARVs should be stopped, continued or whether to switch to another regimen.[27] The exact risk of stopping HAART in the ICU patient is largely unknown, but carries the risk of viral load rebound and drug resistance. The SMART study, testing intermittent ARV treatment guided by CD4 count, clearly demonstrated increased rates of opportunistic disease and death.[39]

The intensivist needs to be familiar with ARV therapy and its possible toxicity.[27] Life-threatening toxicities are discussed above, and include lactic acidosis, hypersensitivity syndromes, drug-induced hepatitis, IRIS and cardiovascular events.[27] The associated drug interactions (see Table II) and metabolic complications, as stated previously, cause major management difficulties in the ICU. Much research is still needed.[24]

Poor absorption increases the possibility of resistance to ARV due to poor plasma concentrations. As previously stated, the only IV preparation available is zidovudine and literature on ARV absorption via the nasogastric and jejunal route in the critically ill patient is limited. Protocols in gastric acid suppression routinely followed in the ICU may also be problematic in many ARV regimens since H_2 antagonists and proton pump inhibitors are contraindicated if PIs are administered.[27]

Renal and hepatic impairment play a role in the HAART dose administration.[24] NRTIs must be adjusted during renal impairment.[24] Most of the fixed NRTI combinations cannot be used in renal impairment and must be individualised for a specific patient.[24] PIs and NNRTIs will require dose adjustments in the patient presenting with hepatic impairment.[24]

Despite the multiple difficulties in managing these patients, continuing HAART has merit in the ICU. No prospective studies so far have been published on the effects of ARVs in the ICU, but one retrospective study has focused on ARV benefits in the patient admitted to the ICU with severe pneumocystis carinii pneumonia (PCP).[27] Morris et al performed a retrospective study on 58 patients admitted to the ICU with PCP. Patients who were continued on ARVs or where HAART was initiated had a mortality rate of 25% compared to a 63% mortality rate in patients who did not receive ARVs.[43]

Conclusion

The AIDS epidemic is in its twentieth year and widespread ARV therapy is only in its infancy. The progress made against this once untreatable disease is unfortunately still limited. The introduction of HAART is in the pantheon of major medical achievements and has profound implications for the treating physician due to the multitude of treatment-associated complications and drug interactions. Especially the PIs and to a lesser extent the NNRTIs pose major difficulties due to the multiple drug interactions. Available data on the specific interactions between commonly used drugs in anaesthesia and HAART are very scanty and are often extrapolated from data gathered in chronically medicated psychiatric patients and addicts. Much research is still needed. Of extreme importance are the associated metabolic complications seen in the patient on a HAART regimen. HAART together with the underlying HIV infection result in major physiological ageing of the patient, particularly the cardiovascular system.

For the anaesthesiologist it is imperative to have a sound grasp on the disease profile, drug interactions and treatment complications. We can only hope that in the years ahead there

will be more effective treatment options, better patient awareness and prevention campaigns. An effective HIV management plan in South Africa may well mean that soon the majority of our patients presenting for surgery may have exposure to prophylactic or therapeutic HAART. SAJAA

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Product information (See page 39)