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Update on antiretrovirals

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Introduction

According to the WHO and UNAIDS, 36.7 million people were living with HIV worldwide at the end of 2016. About 1.8 million people were newly infected that year and 1 million died of HIV-related causes.[1]

South Africa has the largest HIV epidemic in the world, with an estimated 12% of the total population infected with the disease.[2] Statistics show that South Africa had approximately 270 000 new HIV infections and just over 110 000 AIDS-related deaths in 2016. Over 7 million people were living with HIV in 2017, and of these, about 56% were accessing antiretroviral therapy.[1]

With such a high infection rate in South Africa and with the advancements in the management of the disease,[3] a thorough understanding of this multi-systemic disease process as well as the antiretroviral treatment is paramount for anaesthesia.

Antiretroviral treatment has led to the increase in life expectancy of those infected[4] and anaesthetists see many patients presenting for surgeries at all stages of the disease.[5]

With more than 30 ARV drugs now available as either single or combination tablets, the drug interactions, side-effects and anaesthetic implications need to be understood in detail.[6]

Continuum of care[7]

It is important to understand the clinical stages and progression of the disease as patients can present for theatre at any time along the spectrum of the disease.

HIV life cycle

HIV is a single-stranded RNA virus of the lentivirus subfamily of the retrovirus family.[8]

Two subtypes HIV-1 and HIV-2 have been identified.[8] HIV-1 is the most common type globally and can be further subdivided into M, N and O subtypes.[9]

Knowledge of the HIV life cycle is important in understanding the action of ARVs.

The enzyme reverse transcriptase allows viral RNA to be transcribed to DNA, which is then incorporated into the host's DNA. This can then be replicated freely.

ARVs work at these different stages in the HIV life cycle to prevent the virus' replication[10]:

1. Binding/Attachment

HIV attaches to the receptors on the surface of the CD4 cell. GP 120 and GP 41 surface proteins bind to the CD4 receptor and the CCR5 and CXCR4 co-receptors on the cell membrane of the host.[9]

ARVs effective at this stage:

- CCR5 antagonists
- Post-attachment inhibitors/T-20

2. Fusion

The glycoproteins undergo conformational change so that the HIV envelope and the CD4 cell membranes can fuse, allowing HIV to enter the host cell.[11]

ARVs effective at this stage:

- Fusion inhibitors

Figure 1. WHO continuum of HIV care

WHO clinical staging of HIV disease[7]

Adults and adolescents	Children
Clinical stage 1	
Asymptomatic Persistent generalised lymphadenopathy	Asymptomatic Persistent generalised lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (< 10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
Unexplained severe weight loss (> 10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one month Unexplained persistent fever (intermittent or constant for longer than one month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotising ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (< 8 g/dl), neutropaenia (< 0.5 × 109/L) and/or chronic thrombocytopaenia (< 50 × 109/L)	Unexplained moderate malnutrition not adequately responding 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 first six weeks of life) Oral hairy leukoplakia Lymph node tuberculosis; pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotising ulcerative gingivitis or periodontitis Unexplained anaemia (< 8 g/dL), neutropaenia (< 0.5 × 109/L) or chronic thrombocytopaenia (< 50 × 109/L) Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4	
HIV wasting syndrome Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month in duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or cardiomyopathy Recurrent septicaemia (including nontyphoidal Salmonella) Invasive cervical carcinoma Atypical disseminated leishmaniasis	Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs with onset at age older than one month) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Cerebral or B-cell non-Hodgkin lymphoma HIV-associated nephropathy or cardiomyopathy

3. Reverse transcription

In the CD4 cell the enzyme reverse transcriptase is used to convert single-stranded HIV RNA into double-stranded DNA. This conversion allows the HIV to enter the nucleus of the cell.[11]

ARVs effective at this stage:

- NRTIs
- NNRTIs

4. Integration

In the cell the HIV uses the enzyme integrase to integrate its viral DNA into the host's DNA in the CD4 cell.[12]

ARVs effective at this stage:

- Integrase inhibitors

5. Replication

Protein chain production and transcription of the HIV messenger RNA begins in the host's CD4 cell. This allows for the creation of new HIV proteins.[13]

6. Assembly

New HIV proteins move to the cell surface and aggregate around the cell membrane where viral maturation starts to occur.[13]

7. Budding

HIV produces the enzyme protease to cleave the long protein chain precursors into mature smaller infectious HIV proteins as they push out of the CD4 cell.[13]

ARVs effective at this stage:

- Protease inhibitors

When to start antiretroviral treatment (ART)

According to the World Health Organization, ART should be initiated in all adults and adolescents (10–19 years) living with HIV, regardless of WHO clinical stage and at any CD4 cell count.[7]

Certain recommendations have been made to prioritise patients based on CD4 count, staging and pregnancy.

South African DOH guidelines for initiating ART (Updated 2015)[14]

Adults and adolescents ≥ 15 years[14]:

Eligible to start ART

- If CD4 count ≤ 500 cells/µl, irrespective of clinical stage.

or

- Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count

or

- Irrespective of CD4 count or clinical stage if:
  - Active TB disease (including drug-resistant and extra pulmonary TB)
  - Pregnant and breastfeeding women who are HIV-positive
  - Known hepatitis B viral (HBV) co-infection
  - Prioritise those with CD4 ≤ 350 cells/µl or advanced HIV disease

Fast-tracking (initiating ART within seven days of being eligible) if:

- Patients with CD4 count ≤ 200 cells/µl
- HIV stage 4, even if CD4 is not yet available

Adolescents 10–15 years and < 40 kg[14]

Eligible to start ART

- WHO stage 3 or 4
- CD4 count ≤ 500 cells/µl

Fast-tracking (initiating ART within seven days of being eligible) if:

- CD4 count of ≤ 200 cells/µl
- WHO stage 4 disease
- MDR/XDR-TB

Children < 10 years[14]

Eligible to start ART

- Children under five to start on ART regardless of CD4 count or clinical stage
- Children between 5–10 years to start if symptomatic (stage 3–4) irrespective of CD4 OR CD4 < 500 cells/µl irrespective of WHO stage

Fast-tracking (initiating ART within seven days of being eligible) if:

- Children < 1 year
- CD4 count ≤ 200 cells/µl
- WHO stage 4 disease
- MDR/XDR-TB

Pregnant/breastfeeding women[14]

Eligible to start ART

- Immediate initiation of lifelong ART for all HIV-positive women who are pregnant, breastfeeding or within one year post partum, regardless of CD4 cell count (as long as no active TB)
- Use of EFV as part of the first-line regimen, regardless of the gestation of the pregnancy
- Use of maternal lifelong ART throughout pregnancy and breastfeeding to reduce MTCT

Antiretroviral drugs

There are currently six main classes of antiretroviral drugs[12]:

1. Reverse transcriptase inhibitors:

   This group includes:

   1.1 Nucleoside reverse transcriptase inhibitors (NRTIs)

   1.2 Nucleotide reverse transcriptase inhibitors (NtRTIs)

   1.3 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

2. Protease inhibitors

3. Fusion inhibitors

4. CCR5 Co-receptor antagonists

5. Integrase inhibitors

6. Maturation inhibitors

Table I. Examples of each class of ARVs[5,15]

NRTIs	NtRTIs	NNRTIs	Protease inhibitors	Fusion inhibitors	CCRAs	Integrase inhibitors	Maturation inhibitors
Zidovudine (AZT)	Tenofovir (TDF)	Nevirapine (NVP)	Indinavir (IDV)	Enfuvirtide (T-20)	Maraviroc	Raltegravir	Beviramat
Didanosine (DDI)		Efavirenz (EFV)	Ritonivir (RTV)		Vicriviroc	Elvitegravir	
Lamivudine (3TC)		Delavirdine (DLV)	Saquinavir (SQV)				
Stavudine (D4T)		Etravirine	Nelfinavir (NFV)				
Emtricitabine (FTC)			Lopinavir (LPV)				
Abacavir (ABC)			Tiprinavir				
Elvucitabine			Darunavir				
Apricitabine			Atazanavir				

Combination drugs are also available. Some examples include[16]:

- Combivir = zidovudine (AZT) + lamivudine (3TC)
- Trizivir = zidovudine (AZT) + lamivudine (3TC) + abacavir (ABC)
- Truvada = emtricitabine (FTC) + tenofovir (TDF)
- Epzicom/Kivexa = abacavir (ABC) + lamivudine (3TC)

ARV regimen (simplified)[14]

- 1st line treatment:

Adults and adolescents ≥ 40 kg, all TB and HBV co-infections

TDF + 3TC (or FTC) + EFV

If psychiatric comorbidities or intolerance to EFV, change to NVP

Can also substitute LPV/r for EFV

If patient has renal disease, TDF can be changed to AZT

Adolescents < 15 years or < 40 kg

ABC + 3TC + EFV

d4T should be discontinued in first-line regimens due to its metabolic toxicities[7]

Children < 15 years (doses based and adjusted on weight)

< 10 kg < 3 years: ABC + 3TC + LPV/r

> 10 kg 3–10 years: ABC + 3TC + EFV

If regimen fails or if intolerant, expert consultation required.[14]

Pregnant and breastfeeding women

TDF + 3TC(or FTC) + EFV

If renal dysfunction, AZT can replace TDF

- 2nd line treatment (failing on TDF-based regimen) [14]:

Adults and adolescents > 40 kg

AZT + 3TC + LPV/r

AZT + TDF + 3TC + LPV/r (if HBV co-infected)

TDF + 3TC (or FTC) + LPV/r (if failing on d4T or AZT 1st line regimen)

Timing of ART initiation

- ART should be started as soon as the patient is ready, and within at least two weeks of CD4 count being done
- If diagnosed with TB, start with TB treatment first, followed by ART as soon as possible and within eight weeks
- If CD4 < 50 cells/µl initiate ART within two weeks of starting TB treatment, when the patient's symptoms are improving and TB treatment is tolerated
- If CD4 > 50 cells/µl initiate ART within 2–8 weeks of starting TB treatment
- In cryptococcal or TB meningitis: Defer ART initiation for 4–6 weeks

Antiretroviral side-effects and drug interactions

ARVs commonly have unpleasant side-effects ranging from mild to severe.

Depending on the severity of the reaction the ART regimen may need to be changed but it should preferably never be stopped.

Most ARVs are well absorbed orally, then they diffuse through the gastrointestinal tract and are metabolised by cytochrome P450, CYP3A and CYP2B6 isoenzymes.[4]

Anaesthetists need to be aware of the main side-effects, the pharmacokinetics and pharmacodynamics of each drug class, and the interactions that the drugs have with anaesthetic agents.

1.1. NRTIs[15]

Side-effects

- Mitochondrial toxicity can result in pancreatitis, hepatosteatosis, liver damage, lactic acidosis, lipodystrophy and peripheral neuropathy
- Gastrointestinal complaints
- Headache

Drug interactions

- Minimal interactions with drugs through CYP450 system. NRTIs are eliminated by the renal tubules[9]
- Can interact with antibiotics. Combination with metronidazole can cause peripheral neuropathy after prolonged use[4]

1.2. NtRTIs

Minimal interactions – they do not affect the CYP450 system

Tenofovir is nephrotoxic and creatine clearance should be monitored regularly[14]

Can also cause gastrointestinal complaints and lactic acidosis

1.3. NNRTIs[5,15]

Side-effects

- Rashes, allergic reactions, Steven Johnson Syndrome
- Dizziness and impaired concentration
- Metabolic syndrome and hypercholesterolaemia
- Peripheral neuropathy
- Psychosis

Drug interactions[15]

- Nevirapine is a potent inducer of CYP450 while delavirdine is an inhibitor of CYP3A4
- NVP and efavirenz increase metabolism of opioids, e.g. fentanyl and alfentanil therefore increased dosages are required
- EFV and delavirdine can potentiate the effects of midazolam
- NNRTIs may increase the effects of warfarin. INR monitoring is important[9]
- NNRTIs may cause a reduction in the effects of oral contraception[9]
- Anticonvulsants, e.g. phenytoin, phenobarb and carbamazepine can decrease the NNRTI concentrations
- Nevirapine concentration is reduced by rifampicin[9]

2. Protease inhibitors

Inhibitors of CYP450, especially CYP3A[9] and other hepatic enzymes

Lopinavir/ritonavir (Kaletra) combination improves potency as the one prevents the metabolism of the other.[12]

Side-effects[5]

- Metabolic abnormalities, dyslipidaemia, insulin resistance
- Lipodystrophy
- Gastrointestinal disturbances
- Osteoporosis due to impaired VIT D absorption
- Liver dysfunction

Drug interactions[15]

- PIs potentiate the effects of benzodiazipines, especially midazolam and diazepam. Dose reduction is recommended. Lorazepam and temazepam are safer alternatives[9]
- Opioid metabolism and clearance are reduced, resulting in much higher plasma levels particularly with fentanyl and alfentanil. Remifentanil and morphine are safer options[5]
- Caution with pethidine. Ritonavir can cause increased levels of norpethidine resulting in seizures[9]
- Statins, e.g. lovastatin and simvastatin, are contraindicated due to the increased risk of rhabdomyolysis and myopathies[4]
- PIs can increase digoxin toxicity as well as amiodarone, quinine and disopyramide[5]
- PIs can cause a disulpharam-like reaction with metronidazole[5]
- Dexamethasone and thiopentone can decrease plasma concentrations of PIs[4]

3. Fusion inhibitors[9, 12]

Enfuvirtide is given as a subcutaneous injection. It does not have significant drug interactions but can cause local reactions, hypersensitivity and flu-like symptoms.

4. Chemokine co-receptor antagonists (CCRA)[15]

Side-effects

- Gastrointestinal complaints
- Liver dysfunction
- Flu-like symptoms

Drug interactions[15]

Maraviroc is a CYP3A substrate. Its concentration can be increased when given with a strong enzyme inhibitor, e.g. ritonivir. However, enzyme inducers, e.g. efavirenz and rimfampicin, can reduce its plasma levels.

Calcium channel blockers, fentanyl, alfentanil, midazolam, macrolides and azole antifungals can increase the absorption of maraviroc due to inhibition of the P glycoprotein transporter.[9]

5. Integrase inhibitors[5,15]

Can cause liver dysfunction, rashes, gastrointestinal complaints and increased creatinine kinase levels[9] but drug reactions and interactions are not common

6. Maturation inhibitors[15]

Can have gastrointestinal disturbances[9]

Drug reactions and interactions are not common

Of all the side-effects mentioned, lactic acidosis warrants further discussion. Although uncommon, it is associated with significant morbidity and mortality.[4]

Lactic acidosis

This is a result of mitochondrial toxicity

Patients at risk[9]:

- NRTIs started within the last nine months
- Increased BMI, or rapid weight gain
- Pregnancy
- Underlying liver disease
- African females

Patients may present with vague symptoms such as loss of weight, abdominal pain or fatigue.[5]

Treatment is to stop the offending drug or change to another class and supportive management depending on the lactate level and clinical severity.[12,14]

Riboflavin, thiamine, acetyl-L-carnitine and co-enzyme Q have been used to aid treatment but success has been limited.[9]

Severe acidosis may require ICU, ventilation and renal replacement therapy.[9]

Another significant issue associated with ART is IRIS.

IRIS (Immune reconstitution inflammatory syndrome)

This is an acute exacerbation of an inflammatory condition or an infection (e.g. tuberculosis) as a result of starting ARVs. This pro-inflammatory response is due to the recovering immune system, which allows a previously quiescent infection to have an exaggerated response.[14] IRIS usually occurs within three months of starting ARVs,[5] particularly in those patients with CD4 < 100 cells/µl.[14]

Patients who are on TB treatment when starting ARVs may experience a worsening of their symptoms.[14]

IRIS is not as a result of drug failure or a drug reaction and therefore ARTs should not be stopped or altered, unless absolutely necessary.[14]

Treatment involves continuation of ARTs, treating the underlying infection and potential use of steroids.[9]

Post-exposure prophylaxis (PEP)[10]

Any healthcare worker dealing with HIV-infected patients needs to be aware of the risks with respect to occupational exposure.[9] The rate of transmission from a needle stick injury is about 0.3% and about 0.1% with contaminated fluids on broken skin or mucous membranes.[9]

Post-exposure prophylaxis should be started as soon as possible after exposure and within 24 hours.[9]

South African and WHO Guidelines recommend the use of two NRTIs and either PI or NNRTI booster. This triple therapy is recommended for at least 28 days.[9]

PEP = TDF + 3TC (or FDC) with LPV/r or ATV/r

(EFV can be used as an alternative to the PI)

Conclusion

With antiretroviral therapy prolonging the lives of those infected with HIV, there will be an increase in numbers of patients coming to theatre for both HIV-related and unrelated surgeries during their illness.[9] Anaesthetic plans need to be tailored according to the patient's clinical condition and to the medication they are on. It is important for anaesthetists to stay up-to-date with respect to the disease profile and the antiretroviral therapy pharmacology, drug interactions and guidelines.

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