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ARVS FOR THE ANAESTHETIST

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ARVS FOR THE ANAESTHETIST

INTRODUCTION

A PUBMED search for HIV, yields more than 288000 results, yet surprisingly many current day anaesthetists would not be able easily quote the latest ARV guidelines, pleading ignorance, blaming the government and even load shedding for the apparent lack of acknowledge that is freely available.

2014 marked a decade since the Anti-retroviral therapy roll out for South Africa was instituted, with ever changing guidelines and practices, due to better understanding of therapy and greater accessibility to newer drug therapy. The current guidelines have just been released in January 2015.

So where are we a decade later? For the general population at large, this means easier access to ARVs, with HAART being rolled at higher cd4 counts, better screening tools, and fewer opportunistic infections.

For the anaesthetist this has many implications, with the HIV positive population being a dynamic and ever changing one .In the pre and early ARV era, most patients presented to the anaesthetist, with stage 4 disease, for surgery for AIDS related pathology. These patients were ill, and presented confounders for critical care.

Today's HIV population are presenting as "healthy" individuals, for surgery for none HIV related pathologies. Access to ARV therapy has increased life expectancy significantly. The focus of the anaesthetist is shifting from disease related issues, to issues related to ARV – anaesthetic drug interactions, and issues related to side effect profiles.

PREVALENCE

HIV was first discovered in 1981. Today it has reached pandemic proportions. The Southern African sub-region, in particular, is experiencing the most severe epidemics. Statistics according to www.unicef.org[1], reveal that "Nine countries- Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe- have an adult prevalence of over 10%."

As per Statistics SA, "the total number of people living with HIV in South Africa increased from estimated 4.09million in 2002 to 5.51 million in 2014 .An estimated 10.6% of the total population is HIV positive, with approximately one fifth of South African women in their reproductive ages being HIV positive."[2]

Table 1: HIV prevalence estimates & the number of people living with HIV, 2002-2014[2]

YEAR	PREVALENCE				INCIDENCE ADULT 15 - 49	HIV POPULATION (MILLIONS)
	WOMEN 15 - 49	ADULT 15 - 49	YOUTH 15 - 24	TOTAL POPULATION		
2002	16,7	15,8	14,1	9,0	1,64	4,09
2003	16,9	15,9	13,2	9,1	1,64	4,20
2004	17,0	15,9	12,5	9,2	1,69	4,29
2005	17,1	15,9	11,9	9,3	1,73	4,38
2006	17,3	15,9	11,5	9,4	1,69	4,48
2007	17,5	16,0	11,1	9,5	1,59	4,61
2008	17,7	16,2	10,8	9,7	1,47	4,75
2009	17,9	16,3	10,4	9,8	1,36	4,88
2010	18,0	16,5	10,1	9,9	1,29	5,02
2011	18,2	16,6	9,7	10,0	1,25	5,14
2012	18,3	16,6	9,3	10,1	1,16	5,26
2013	18,4	16,7	9,0	10,1	1,14	5,38
2014	18,5	16,8	8,7	10,2	1,11	5,51

COURSE OF HIV INFECTION

HIV is a lentivirus of the retrovirus family.[3] Two enzymes, reverse transcriptase and viral integrase, incorporate the host's DNA into the virus' mRNA, allowing replication of the virus. The host's Cd4 cells are destroyed, which are important to the immune response process, resulting in an immune deficiency state.

The course of HIV is variable.[4] There is a latent period of about 8-12 weeks following infection, during which there may be an intense viraemia. Seroconversion then occurs, with antibodies to HIV appearing in serum. There is also a rapid fall in viraemia, suggesting that the immunological response has controlled the infection. At this stage one third individuals experience brief illness lasting about 2 weeks. Symptoms include fever, malaise, arthralgia, rash and lymphadenopathy. Then follows as asymptomatic phase of 10-11 years before AIDS develops.[5]

STAGING

HIV can be staged clinically using the WHO staging system. Alternatively it can be staged according to cd4 count.

Table 1: WHO Clinical Staging[5]

CLINICAL STAGE	SYMPTOMS
Stage 1	Asymptomatic Lymphadenopathy
Stage 2	Hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular chelitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Parotid enlargement Herpes zoster Chronic upper respiratory tract infections
Stage 3	Malnutrition Persistent diarrhea Persistent fever Persistent oral condiasis Oral hairy leukoplakia Necrotizing ulcerative gingivitis or periodontisis Lymph node tuberculosis Pulmonary tuberculosis Recurrent bacterial pneumonia Lymphoid interstistial pneumonitis Lung disease (such as brochiectasis) Anemia or chronic thrmobocytopaenia
Stage 4	Severe wasting, stunting, or malnutrition Pneumocystis pneumonia Severe bacterial infections Chronic herpes simplex infection Esophageal candidiasis Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis Extrapulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis Disseminated non-tuberculous mycobacterial infection Chronic cryptosporidiosis (with diarrhoed) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

ANTIRETROVIRAL THERAPY

Currently there are at least 28 antiretroviral drugs approved by the FDA, most falling into 8 mechanistic classes.[6] There are numerous treatment regimes, ranging from standard 3 drug regimens to once a day pills.

Table 2: Classification of Antiretrovirals[7]

DRUG CLASS	EXAMPLES
Nucleoside analogue reverse transcriptase inhibitors[NRTIs] **MOA:**Nucleosides are phosphorylated to form nucleotides and are DNA building blocks, by forming 3' to 5' phosphodiester linkage allowing chain elongation NRTIs and NtRTIs are structural analogues of nucleosides and nucleotides and interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase.	Zidovdine [azt] Didanosine[DDI] Lamivudine [3TC] Stavudine [D4T] Emtricitabine [FTC] Abacavir [ABC] Elvucitabine Apricitabine
Nucleotide reverse transcriptase inhibitors [NtRTI] Similar to above, sometimes regarded as a single drug class	Tenofovir [TDF]
Non nucleoside reverse transcriptase inhibitors[NNRTIs] **MOA**: Non competitive binding directly at a pocket of the p66 subunit of HIV reverse transcriptase.	Nevirapine [nvp] Efavirenz [EFV] Delavirdine [DLV] Etravirine
Protease inhibitors [PI] **MOA**: HIV protease cleaves polypeptide chains to form functional viral proteins. PIs inhibit this enzyme resulting in the release of non-infectious viral proteins with a disorganised structure	Indinavir [IDV] Ritonavir [RTV] Saquinavir [SQV] Nelfinavir [NFV] Lopinavir [LPV] Tiprinavir Darunavir Atazanavir
Fusion inhibitors **MOA:** Relatively new class. Bind to gp41 preventing conformational change necessary for fusion and entry into CD4 cells.	Enfuvirtide [T-20]
CCR5 co-receptor antagonists **MOA**: In order to enter cells, HIV must bind to Cd4 receptors and chemokine co-receptors CCR5 and CCR4. Co-receptor antagonists thus prevent entry of HIV into the host cell	Maraviroc Vicriviroc
Integrase inhibitors **MOA**: Integrase inhibitors target viral integrase, preventing the integration of proviral DNA into human chromosomes	Raltegravir Elvitegravir
Maturation inhibitors **MOA:** These prevent conversion of capsid precursor protein [p25] to the mature capsid protein [p24], thus preventing formation of infectious particles and renders the virus incapable of infecting other cells.	Beviramat

PHARMACOKINETICS AND SIDE EFFECTS OF ARVS [7,8]

Most ARVS are administered orally and have good absorption. This may be affected by gastric ph. They are metabolized by cytochrome P450 system, namely CYP3A and CYP2B6.

Lipophilic drugs such as PI's and NNRTI's are oxidatively metabolized by CYP450 to polar forms for excretion via renal or biliary systems. These drugs can be classified as either inhibitors or inducers of CYP450.[7]
NRTI's are water soluble and renally excreted. "They are prodrugs and require intracellular phosphorylation to be activated. Thus drugs that affect phosphorylation will affect these drugs".

ARV side effects can be broadly classified into categories namely:[8]

1) Mitochondrial toxicity: Lactic acidosis, hepatotoxicity, pancreatitis, peripheral neuropathy.
2) Metabolic: Lipodystrophy, hyperglycaemia, body habitus changes, insulin resistance, osteoporosis.
3) Bone marrow suppression: Pancytopenia.
4) Hypersensitivity reactions: Skin rashes

INDIVIDUAL CLASSES

NRTI

Pharmacokinetics: absorbed enterally-30-60% absorption, with AZT being the only IV preparation.
<10% protein bound. Renally excreted except for Abacavir which undergoes hepatic metabolism. Does not induce cytochrome p450.

S/E: mitochondrial toxicity causing lactic acidosis, pancreatitis, and peripheral neuropathy. Abnormal fat deposition
Zidovudine-high incidence of fatigue, headaches and git disturbances.
Tenofovir: renal impairment, decrease in bone mineral density, GIT intolerance

NNRTI:

Pharmacokinetics: enteral preparations only are well absorbed, highly protein bound. Primarily hepatic metabolism and excretion.
NVP lipophilic, crosses placenta and is excreted in breastmilk. Lead to cytochrome P450 enzyme induction and inhibition, depending on drug used

S/E: All NNRTIs: rash including Stevens-Johnsons syndrome,
EFV: Previously thought to have an association with neural tube defects- controversial- "overall rates of birth defects in infants exposed to EFV, NVP and TDF are similar to those in the general population".[9] Currently included in South African guidelines for pregnant patient. Neuropsychiatric side effects common.
NVP: hepatotoxicity

Protease Inhibitors [PIs]

Pharmacokinetics: enteral preparations only, >86% protein bound. Primarily hepatic metabolism. Extensively metabolized by CYP450. PI's are potent inhibitors of CYP3A4. Ritonavir being the exception, is a potent inhibitor of CYP3A4 and CYP2D6, while being an inducer of CYP1A2 and CYP2C9.

Side effects: Hyperlipidaemia, lipodystrophy, hepatotoxicity, GI intolerance, insulin resistance

Fusion inhibitors

Administered subcutaneously with 84% absorption. 92% protein bound. Used in patients with virological failure

S/E: Neutropaenia, risk of hypersensitivity, eosinophilia

Chemokine co-receptor Antagonists

Enteral preparations 76% protein bound. Mainly hepatic metabolism and renal clearance, large VD

S/E: GIT disturbances, cough, abnormalities in liver function tests

Integrase Inhibitors

Enteral preparations, high fat meals slow absorption
Highly protein bound, no dose adjustment needed in renal or hepatic impairment

S/E: Pruritus and rash, headache, abnormalities in amylase and liver function tests

Maturation Inhibitors

Enteral preparations very highly protein bound. Metabolized by glucuronidation, minor renal clearance

S/E: self-limiting GIT disturbances

FDC [Fixed Dose Combination][10]

There are multiple FDCs currently on the market and in development. The pharmacokinetics and side effect profile of these drugs are the same as the individual drugs themselves.

Some of the current FDCs available:

Atripla/Atrozia - efavirenz +tenofovir +FTC
Eviplera/Complera - Rilpivirine +Tenofovir + FTc
Triumeq - Dolutegravir +Abacavir + 3TC
Stribild - Elvitegravir + Cobicistat + Tenofovir + FTC
Truvada - Tenofovir + FTC
Combivir - AZT +3TC

ARVS IN THE PIPELINE

Cd4 attachment inhibitors[11]:
BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into to CD4 T-cells.

The current trial underway for this drug is AI438011 a Phase IIb, randomized, active-controlled trial. "It is investigating the safety, efficacy and dose response of BMS-663068 versus atazanavir/ritonavir (ATV/r) in treatment-experienced (TE), HIV-1-positive subjects."[11]

At week 24 of the trial the results are the following:
"Mean increases in CD4 T-cell counts across the BMS-663068 arms were consistent with ATV/r, regardless of gender, age and baseline CD4 T-cell count indicating efficacy"[11].

Safety profile: "BMS-663068 was generally well tolerated across all arms, with no related serious adverse events leading to discontinuation and no dose-related safety signals. There were no trends for clinical laboratory abnormalities found These results support further studies into the development of BMS663068".

CCR5/CCR2 co-receptor antagonist[12]:
"Cenicriviroc (CVC), is a once-daily, dual CCR5/CCR2 co- receptor antagonist, and has completed Phase 2b development. It blocks HIV entry but does not allow redistribution into cells".[11] Its side effect profile and efficacy has been compared to EFV in clinical trials.

New NNRTI[13]:
"Doravirine (DOR) is an investigational NNRTI (aka MK- 1439) that retains activity against common NNRTI-resistant mutants".[12] The current week 48 results from the clinical trial underway indicate that when combined with TDF/FTC, it had potent antiviral activity, and is generally safe and well tolerated.

New NtRTI[14]
Tenofovir alafenamide [TAF gs7340] is a new prodrug of tenofovir[TDF] .Current ongoing trial show that TAF results in a 7fold greater intracellular levels of TDF at a smaller dose.

Long Acting Injectables[15];
Rilpivirine LA, a monthly injectable and Caboegravir, administered 3monthly are current in clinical trials. These are possibly the drugs of the future, as they will provide convenient treatment options for patients, and assist with adherence and compliance issues.

CHANGES TO THE SOUTH AFRICAN GUIDELINES [16]

South African guidelines have recently been updated in January 2015. The guidelines are frequently revised and it is advisable that the clinician regularly familiarizes himself with the latest guidelines

The latest guidelines have the following changes/additions[16]:

- General changes to adults and adolescents >15yrs:
    - Early initiation of ARVS, on all patients cd4 <500, prioritizing those with cd4<350 irrespective of clinical stage.
    - Initiation of ARVS in Stage 3 and 4 disease, irrespective of cd4 count.
    - HAART for all patients with Hep B co-infection irrespective of cd4 or clinical stage.
    - HAART for all patients with Tb infection irrespective of cd4 or clinical stage.
    - Routine cryptococcal infection screening for all HIV-infected patients with CD4 <100 cells
    - Use of simplified fixed-dose combinations for ART
    - Harmonised ART regimen across populations, mainly pregnant and breastfeeding women, adolescents and adults

- Pregnant patients;
    - Immediate initiation of lifelong HAART for all HIV positive woman who are pregnant or 1yr post-partum regardless of CD4 count.
    - Use of maternal lifelong HAART to reduce MTCT
    - Use of EFV as part of 1st line regimen, regardless of gestation
    - Repeat HIV testing for all negative women, 3monthly during pregnancy, at delivery and at 6weeks

- Children <5yrs:
    - ART for all children under 5yrs, regardless of CD4 count or clinical stage
    - ART for all children between 5yrs-10yrs with a CD4 < 500 regardless of clinical staging.
    - Immediate initiation of ART for infants with 1st positive HIV PCR while awaiting confirmatory tests

Table 3: What to Start: ART 1st line regimen for Adults & adolescents ≥ 15yrs

POPULATION	DRUG	COMMENTS
Adolescents >15 years and weighing >40kg Adults All TB co-infection All HBV co-infection	TDF + 3TC (or FTC) + EFV provide as fixed-dose combination (FDC)	Replace EFV with NVP in patients: • With significant psychiatric comorbidity or intolerance to EFV • Where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. night shift workers
Adults and adolescents on d4T	Change d4T to TDF (No patient must be on d4T)	Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if d4T well tolerated If VL>1000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40kg	ABC + 3TC + EFV	If adolescent weight <40kg, align with paediatric regimen
CONTRAINDICATION	**SUBSTITUTION DRUG**	**COMMENTS**
Contraindication to EFV: • Significant psychiatric co-morbidity • Intolerance to EFV • Impairment of daily function (shift workers)	TDF + FTC (or 3TC) + NVP or LPV/r	IfCD4 <250 females and <400 males, give NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250 females and ≥400 males, use LPV/r 2 tablets 12 hourly
TDF contraindication: Creatinine clearance of <50 mL/min	ABC+ 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides MDR treatment

Table 4: Second-line regimen for late adolescents and adults [16]

SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
First-line virological failure	**Drugs**	**Comments**
Failing on a TDF-based first-line regimen	AZT + 3TC + LPV/r AZT + **TDF** + 3TC + LPV/r (If HBV co-infected)	If non-adherent, address causes of non-adherence If the VL >1000 copies/mL at any point, intensify adherence and repeat viral load in 2months
Failing on a d4T or AZT-based first line regimen	TDF + 3TC (or FTC) + LPV/r	
SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
Anaemia and renal failure	Switch to ABC	

Table 5: First-line ART regimens in pregnant and breastfeeding women[16]

FIRST-LINE ART REGIMENS		
POPULATION	**DRUGS**	**COMMENTS**
1st ANC visit		
All pregnant women not on ART (any gestational age) All breastfeeding women not on ART	TDF + 3TC (or FTC) + EFV Provide as fixed-dose combination (FDC)	If there is a contraindication to the FDC (Contraindication to TDF: renal insufficiency Contraindication to EFV: active psychiatric illness): start AZT immediately and refer to Boxes 2 and 3
Pregnant women currently on ART	Continue current ART regimen Change to FDC if on individual first-line drugs and virally suppressed and no contraindications to FDC	Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done Patients with confirmed 2nd or 3rd line regimen failure should not breastfeed their infants
2nd ANC visit (1 week later)		
Pregnant women Creatinine ≤85µmol/l and any CD4 cell count	Continue FDC	
Creatinine >85 µmol/l TDF contraindicated	Stop FDC, initiate AZT if Hb ≥7g/dl	High-risk pregnancy: refer urgently for alternate triple therapy within 2 weeks, with dose adjustment if indicated, and investigation of renal dysfunction
Contraindication to EFV (active psychiatric illness)	Continue AZT until initiated on individual drugs TDF+3TC+NVP or LPV/r	Refer urgently for alternate triple therapy CD4 <250cells/µl: NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250cells/µl LPV/r 2 tablets 12 hourly
Unbooked and presents in labour and tests HIV positive	sdNVP + sd Truvada and AZT 3-hourly in labour sdNVP + sd Truvada for C/S Start FDC next day regardless of CD4 cell count	Woman qualifies for lifelong ART Do creatinine and CD4 testing. Woman should get results at the 36 days visit
Emergency caesarean section in an unbooked woman with no ART	Same as above	
Post-Partum		
Mother diagnosed with HIV within 1 year post-partum or still breastfeeding beyond 1 year	Lifelong FDC initiated immediately	

Table 6: Guidelines for Children under 15yrs[16]

CHILD	REGIMEN	COMMENT
Children <3 years or older children weighing <10kg	ABC + 3TC + LPV/r	Doses are based on child's weight and need to be adjusted as the child grows
Children 3-10 years and>10kg Adolescents 10-15 years or <40kg	ABC + 3TC + EFV Children who started on ABC/3TC/LPV/r before 3 years must remain on same regimen at 3yr	Do not exceed maximum dosage If adolescents weight <40kg, align treatment with children's regimen
Children on d4T	Change all d4T to ABC	If VL suppressed: change to ABC If VL>1000 copies/ml, manage as treatment failure If VL 50-1000 copies/ml, consult specialist
Children on DDI	Change all DDI to ABC	Change all regardless of VL

SIGNIFICANT REACTIONS WITH DRUGS RELATED TO ANAESTHESIA [17,18,19,20]

Given that many of South African HIV patients will be presenting for anaesthesia it is important to be aware of the drug- drug interactions that may occur.
Drug interactions can be classified into two broad categories:

1] Anaesthetic agents may induce pharmaco-dynamic changes to affect the efficacy and toxicity of ARVs,

2] Pharmacokinetic effects of ARVs can affect the absorption, distribution, metabolism and elimination of anaesthetic drugs.
Some ARVs may not directly interact with anaesthetic drugs themselves, but with drugs commonly seen as adjuncts or prescribed to patients pre-operatively, eg statins.

A] NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS[NNRTI]:

Interactions:
Delavirdine is an inhibitor, while Nevirapine is an inducer of CYP450. Efavirenz may either induce or inhibit the CYP450 system

Opiods; of particular concern, NVP and Efavirenz may cause sub therapeutic levels of Fentanyl and Alfentanil and the dose may need to be increased. There have also been reports of Methadone withdrawal in patients on NVP.

Benzodiazepines: Although there are no published reports, Efavirenz is contraindicated with Midazolam, Triazolam and ergotamine derivatives. Delavirdine is a potent inhibitor of CYP3A4 and may potentiate the effect of benzodiazepines and are thus best avoided.

Anticonvulsants: Carbamazepine, phenobarbital and phenytoin may significantly reduce NNRTI concentrations and should be replaced by other agents such as Valproic acid.

Anticoagulants: Complex reaction between warfarin and NNRTIs, with tendency for anticoagulant effect to be potentiated.

B] Nucleoside and nucleotide reverse transcriptase inhibitors [NRTI]

Not metabolized by CYP450 system, so minimal drug interactions occur.
No documented reactions with anaesthetic agents.
Concern of interactions with Didanosine with antibiotics. It is formulated as enteric coated capsules or buffered powder for oral solutions. The buffer may affect fluroquinolone and ciprofloxacin.
Tenofovir is nephrotoxic and the concurrent use of other nephrotoxic agents should be avoided.

C] PROTEASE INHIBITORS [PI]

Strong Inhibitors of the cyp450. Ritonavir's effect on multiple CYP450 enyzmes, complicates and increases the number of drug interactions, as it may function as both an inhibitor or inducer.

Benzodiazepines: PIs react with midazolam and diazepam by increasing plasma levels, causing prolonged sedation and depression of respiration

Opiates: Methadone
Impairs Fentanyl and Alfentanil metabolism leading to increased levels and respiratory depression.

Thiopentone and Dexamethasone: decrease PI plasma concentrations

Statins: Myopathies and rhabdomyolysis may occur when PIs interact with statins. Due to this risk, lovastatin and simvastatin are contra-indicated.
Ergot derivatives: contraindicated with Efavirenz due to risk of prolonged vasospasm

D] FUSION INHIBITORS

Enfuvirtide is a 36–amino-acid peptide that does not enter human cells.
To date, no significant drug interactions has been found.

E] CCR5 Co-Receptor Antagonists

Maraviroc (MVC) is a substrate of CYP3A enzymes and P-glycoprotein.
MVC does not inhibit or induce the CYP3A system. It is not known to disrupt the pharmacokinetics of other drugs.

Its concentration can be significantly increased when co administered with strong CYP3A inhibitors (eg, ritonavir).Reduced concentration may occur when coadministered with strong CYP3A inducers (eg, efavirenz, rifampin).

F] INTEGRASE INHIBITORS

Dolutegravir is metabolized by UGT1A1 with only 10–15% metabolized by CYP3A4. It neither induces nor inhibits CYP450 or UGT and therefore clinically significant drug interactions are not expected.

G] MATURATION INHIBITORS

No documented dose adjustments needed for sedatives or analgesics. Beviramat is neither an inducer nor inhibitor and drug interactions are not common.

SUMMARY OF COMMON DRUG INTERACTIONS WITH DRUGS ASSOCIATED WITH ANAESTHESIA [19]

The tables below are courtesy of www.Hivdruginteraction.org.

KEY:
These drugs should not be coadministered ---------- /
Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration /
No clinically significant interaction expected /
There are no clear data, actual or theoretical, to indicate whether an interaction will occur /
Data not available n//a

Table 7: generated via www hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Abacavir	Emtricitabine (FTC)	Lamivudine (3TC)	Stavudine (d4T)
Bupivacaine	◇	◇	◇	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	◇	◇	◇	◇
Ephedrine	◇	□	□	□
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	◇	◇	◇	◇
Propofol	◇	◇	◇	◇
Rocuronium	◇	◇	◇	◇
Sevoflurane	◇	◇	◇	◇
Sufentanil	◇	◇	◇	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Alfentanil	◇	◇	◇	◇
Fentanyl	◇	◇	◇	◇
Morphine	◇	◇	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	◇	◇	◇	◇
Anxiolytics/Hypnotics/ Sedatives	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Diazepam	◇	◇	◇	◇
Midazolam (oral)	◇	◇	◇	◇
Gastrointestinal Agents (anti-emetics)	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Metoclopramide	◇	◇	◇	◇

Table 8: generated via www.hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Lopinavir	Efavirenz	Nevirapine	Tenofovir
Bupivacaine	■	■	■	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	■	■	◇	◇
Ephedrine	◇	◇	◇	■
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	■	■	■	◇
Propofol	■	■	■	◇
Rocuronium	■	■	◇	◇
Sevoflurane	■	◇	◇	◇
Sufentanil	■	■	■	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Alfentanil	■	■	■	◇
Fentanyl	■	■	■	◇
Morphine	■	■	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	■	■	■	◇
Anxiolytics/Hypnotics/ Sedatives	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Diazepam	■	■	■	◇
Midazolam (oral)	●	●	■	◇
Gastrointestinal Agents (anti-emetics)	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Metoclopramide	◇	◇	◇	◇
Ondansetron	■	◇	◇	◇
Steroids	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Dexamethasone	■	■	■	◇

www.hiv-druginteractions.org is a useful website were printable charts of ARV drug interactions can be found allowing ease for the clinician.

ARVS IN THE CRITICALLY ILL [22,23,26]

Patients presenting to the critical care physician may present in 2 different categories:
1] AIDs related opportunistic infections
2] Pathologies unrelated to HIV such as trauma or elective surgery

Concern about administering ARVs in the critically ill is that it may worsen their current clinical condition, due to interactions with other drugs, Immune Reconstitution Syndrome [IRIS] and drug side effects

The pharmacokinetics in the critical care patient are in addition altered, and may lead to sub-therapeutic or supra-therapeutic doses. Most ARVs are available in oral preparations only and need to be crushed and administered via a feeding tube in the ICU patient. Gastro-intestinal absorption may be inconsistent, leading to unpredictable drug levels, creating a risk for drug resistance and toxicity.

Drug-drug interactions are common, with analgesics, antibiotics, antihypertensive, anti-arrhythmic all being implicated.

IRIS occurs after improvement of the immune system with a renewed inflammatory response against new pathogens. It usually occurs in the 1st two weeks after Arv initiation. It may cause a paradoxical and clinical worsening of a condition or unmask a new localized infection.
The critically ill patient is already significantly compromised with poor physiological reserve. In these patients a paradoxical worsening of a condition may have devastating consequences.

There are several mechanisms by which ARVS may improve outcomes in ICU but none have been proven. All evidence for the use of ARVS in ICU is from retrospective studies and expert opinion only. Retrospective chart analysis showed lower mortality in patients receiving HAART.

There are currently no clear guidelines set out for the use of ARV's in ICU. Most of HIV patients coming to ICU will not be on therapy.
Patients previously well and admitted for a non HIV related condition may have therapy postponed.

Patients with long term stays and cd4<200 could potentially benefit from ARVS to prevent other opportunistic infections.
Those with AIDs defining illness should be ideally initiated on ARVS as soon as possible.

Given that the decision to initiate ARV in the critically ill patient is a complex one, each patient should be individualized and the merits and demerits of ARV therapy discussed, before initiating therapy.

CONCLUSION

With advances in antiretroviral therapy, more HIV positive patients are likely to present for elective non HIV related surgery. As we move into the future, we can look forward to exciting developments in ARVs.

The pharmacology and drug interactions can be complex and pose challenging to the anaesthetist. It is therefore important to stay current and continuously update ourselves on newer ARVs and current guidelines available.

To assist the modern day doctor, the South African Department of Health has made all clinical guidelines available freely online……..

And to those who love their apps, the Department has recently announced their new app, HIV Clinical Guide App, sponsored by the openmedicine project.org. It is freely available on Android and Apple devices via App Stores and Google Play.

So happy downloading, and happy learning… together we can contribute to curbing this epidemic.

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No. 18

ARVS FOR THE ANAESTHETIST

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ARVS FOR THE ANAESTHETIST

INTRODUCTION

A PUBMED search for HIV, yields more than 288000 results, yet surprisingly many current day anaesthetists would not be able easily quote the latest ARV guidelines, pleading ignorance, blaming the government and even load shedding for the apparent lack of acknowledge that is freely available.

2014 marked a decade since the Anti-retroviral therapy roll out for South Africa was instituted, with ever changing guidelines and practices, due to better understanding of therapy and greater accessibility to newer drug therapy. The current guidelines have just been released in January 2015.

So where are we a decade later? For the general population at large, this means easier access to ARVs, with HAART being rolled at higher cd4 counts, better screening tools, and fewer opportunistic infections.

For the anaesthetist this has many implications, with the HIV positive population being a dynamic and ever changing one .In the pre and early ARV era, most patients presented to the anaesthetist, with stage 4 disease, for surgery for AIDS related pathology. These patients were ill, and presented confounders for critical care.

Today's HIV population are presenting as "healthy" individuals, for surgery for none HIV related pathologies. Access to ARV therapy has increased life expectancy significantly. The focus of the anaesthetist is shifting from disease related issues, to issues related to ARV – anaesthetic drug interactions, and issues related to side effect profiles.

PREVALENCE

HIV was first discovered in 1981. Today it has reached pandemic proportions. The Southern African sub-region, in particular, is experiencing the most severe epidemics. Statistics according to www.unicef.org[1], reveal that "Nine countries- Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe- have an adult prevalence of over 10%."

As per Statistics SA, "the total number of people living with HIV in South Africa increased from estimated 4.09million in 2002 to 5.51 million in 2014 .An estimated 10.6% of the total population is HIV positive, with approximately one fifth of South African women in their reproductive ages being HIV positive."[2]

Table 1: HIV prevalence estimates & the number of people living with HIV, 2002-2014[2]

YEAR	PREVALENCE				INCIDENCE ADULT 15 - 49	HIV POPULATION (MILLIONS)
	WOMEN 15 - 49	ADULT 15 - 49	YOUTH 15 - 24	TOTAL POPULATION		
2002	16,7	15,8	14,1	9,0	1,64	4,09
2003	16,9	15,9	13,2	9,1	1,64	4,20
2004	17,0	15,9	12,5	9,2	1,69	4,29
2005	17,1	15,9	11,9	9,3	1,73	4,38
2006	17,3	15,9	11,5	9,4	1,69	4,48
2007	17,5	16,0	11,1	9,5	1,59	4,61
2008	17,7	16,2	10,8	9,7	1,47	4,75
2009	17,9	16,3	10,4	9,8	1,36	4,88
2010	18,0	16,5	10,1	9,9	1,29	5,02
2011	18,2	16,6	9,7	10,0	1,25	5,14
2012	18,3	16,6	9,3	10,1	1,16	5,26
2013	18,4	16,7	9,0	10,1	1,14	5,38
2014	18,5	16,8	8,7	10,2	1,11	5,51

COURSE OF HIV INFECTION

HIV is a lentivirus of the retrovirus family.[3] Two enzymes, reverse transcriptase and viral integrase, incorporate the host's DNA into the virus' mRNA, allowing replication of the virus. The host's Cd4 cells are destroyed, which are important to the immune response process, resulting in an immune deficiency state.

The course of HIV is variable.[4] There is a latent period of about 8-12 weeks following infection, during which there may be an intense viraemia. Seroconversion then occurs, with antibodies to HIV appearing in serum. There is also a rapid fall in viraemia, suggesting that the immunological response has controlled the infection. At this stage one third individuals experience brief illness lasting about 2 weeks. Symptoms include fever, malaise, arthralgia, rash and lymphadenopathy. Then follows as asymptomatic phase of 10-11 years before AIDS develops.[5]

STAGING

HIV can be staged clinically using the WHO staging system. Alternatively it can be staged according to cd4 count.

Table 1: WHO Clinical Staging[5]

CLINICAL STAGE	SYMPTOMS
Stage 1	Asymptomatic Lymphadenopathy
Stage 2	Hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular chelitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Parotid enlargement Herpes zoster Chronic upper respiratory tract infections
Stage 3	Malnutrition Persistent diarrhea Persistent fever Persistent oral condiasis Oral hairy leukoplakia Necrotizing ulcerative gingivitis or periodontisis Lymph node tuberculosis Pulmonary tuberculosis Recurrent bacterial pneumonia Lymphoid interstistial pneumonitis Lung disease (such as brochiectasis) Anemia or chronic thrmobocytopaenia
Stage 4	Severe wasting, stunting, or malnutrition Pneumocystis pneumonia Severe bacterial infections Chronic herpes simplex infection Esophageal candidiasis Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis Extrapulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis Disseminated non-tuberculous mycobacterial infection Chronic cryptosporidiosis (with diarrhoed) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

ANTIRETROVIRAL THERAPY

Currently there are at least 28 antiretroviral drugs approved by the FDA, most falling into 8 mechanistic classes.[6] There are numerous treatment regimes, ranging from standard 3 drug regimens to once a day pills.

Table 2: Classification of Antiretrovirals[7]

DRUG CLASS	EXAMPLES
Nucleoside analogue reverse transcriptase inhibitors[NRTIs] **MOA:**Nucleosides are phosphorylated to form nucleotides and are DNA building blocks, by forming 3' to 5' phosphodiester linkage allowing chain elongation NRTIs and NtRTIs are structural analogues of nucleosides and nucleotides and interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase.	Zidovdine [azt] Didanosine[DDI] Lamivudine [3TC] Stavudine [D4T] Emtricitabine [FTC] Abacavir [ABC] Elvucitabine Apricitabine
Nucleotide reverse transcriptase inhibitors [NtRTI] Similar to above, sometimes regarded as a single drug class	Tenofovir [TDF]
Non nucleoside reverse transcriptase inhibitors[NNRTIs] **MOA**: Non competitive binding directly at a pocket of the p66 subunit of HIV reverse transcriptase.	Nevirapine [nvp] Efavirenz [EFV] Delavirdine [DLV] Etravirine
Protease inhibitors [PI] **MOA**: HIV protease cleaves polypeptide chains to form functional viral proteins. PIs inhibit this enzyme resulting in the release of non-infectious viral proteins with a disorganised structure	Indinavir [IDV] Ritonavir [RTV] Saquinavir [SQV] Nelfinavir [NFV] Lopinavir [LPV] Tiprinavir Darunavir Atazanavir
Fusion inhibitors **MOA:** Relatively new class. Bind to gp41 preventing conformational change necessary for fusion and entry into CD4 cells.	Enfuvirtide [T-20]
CCR5 co-receptor antagonists **MOA**: In order to enter cells, HIV must bind to Cd4 receptors and chemokine co-receptors CCR5 and CCR4. Co-receptor antagonists thus prevent entry of HIV into the host cell	Maraviroc Vicriviroc
Integrase inhibitors **MOA**: Integrase inhibitors target viral integrase, preventing the integration of proviral DNA into human chromosomes	Raltegravir Elvitegravir
Maturation inhibitors **MOA:** These prevent conversion of capsid precursor protein [p25] to the mature capsid protein [p24], thus preventing formation of infectious particles and renders the virus incapable of infecting other cells.	Beviramat

PHARMACOKINETICS AND SIDE EFFECTS OF ARVS [7,8]

Most ARVS are administered orally and have good absorption. This may be affected by gastric ph. They are metabolized by cytochrome P450 system, namely CYP3A and CYP2B6.

Lipophilic drugs such as PI's and NNRTI's are oxidatively metabolized by CYP450 to polar forms for excretion via renal or biliary systems. These drugs can be classified as either inhibitors or inducers of CYP450.[7]
NRTI's are water soluble and renally excreted. "They are prodrugs and require intracellular phosphorylation to be activated. Thus drugs that affect phosphorylation will affect these drugs".

ARV side effects can be broadly classified into categories namely:[8]

1) Mitochondrial toxicity: Lactic acidosis, hepatotoxicity, pancreatitis, peripheral neuropathy.
2) Metabolic: Lipodystrophy, hyperglycaemia, body habitus changes, insulin resistance, osteoporosis.
3) Bone marrow suppression: Pancytopenia.
4) Hypersensitivity reactions: Skin rashes

INDIVIDUAL CLASSES

NRTI

Pharmacokinetics: absorbed enterally-30-60% absorption, with AZT being the only IV preparation.
<10% protein bound. Renally excreted except for Abacavir which undergoes hepatic metabolism. Does not induce cytochrome p450.

S/E: mitochondrial toxicity causing lactic acidosis, pancreatitis, and peripheral neuropathy. Abnormal fat deposition
Zidovudine-high incidence of fatigue, headaches and git disturbances.
Tenofovir: renal impairment, decrease in bone mineral density, GIT intolerance

NNRTI:

Pharmacokinetics: enteral preparations only are well absorbed, highly protein bound. Primarily hepatic metabolism and excretion.
NVP lipophilic, crosses placenta and is excreted in breastmilk. Lead to cytochrome P450 enzyme induction and inhibition, depending on drug used

S/E: All NNRTIs: rash including Stevens-Johnsons syndrome,
EFV: Previously thought to have an association with neural tube defects- controversial- "overall rates of birth defects in infants exposed to EFV, NVP and TDF are similar to those in the general population".[9] Currently included in South African guidelines for pregnant patient. Neuropsychiatric side effects common.
NVP: hepatotoxicity

Protease Inhibitors [PIs]

Pharmacokinetics: enteral preparations only, >86% protein bound. Primarily hepatic metabolism. Extensively metabolized by CYP450. PI's are potent inhibitors of CYP3A4. Ritonavir being the exception, is a potent inhibitor of CYP3A4 and CYP2D6, while being an inducer of CYP1A2 and CYP2C9.

Side effects: Hyperlipidaemia, lipodystrophy, hepatotoxicity, GI intolerance, insulin resistance

Fusion inhibitors

Administered subcutaneously with 84% absorption. 92% protein bound. Used in patients with virological failure

S/E: Neutropaenia, risk of hypersensitivity, eosinophilia

Chemokine co-receptor Antagonists

Enteral preparations 76% protein bound. Mainly hepatic metabolism and renal clearance, large VD

S/E: GIT disturbances, cough, abnormalities in liver function tests

Integrase Inhibitors

Enteral preparations, high fat meals slow absorption
Highly protein bound, no dose adjustment needed in renal or hepatic impairment

S/E: Pruritus and rash, headache, abnormalities in amylase and liver function tests

Maturation Inhibitors

Enteral preparations very highly protein bound. Metabolized by glucuronidation, minor renal clearance

S/E: self-limiting GIT disturbances

FDC [Fixed Dose Combination][10]

There are multiple FDCs currently on the market and in development. The pharmacokinetics and side effect profile of these drugs are the same as the individual drugs themselves.

Some of the current FDCs available:

Atripla/Atrozia - efavirenz +tenofovir +FTC
Eviplera/Complera - Rilpivirine +Tenofovir + FTc
Triumeq - Dolutegravir +Abacavir + 3TC
Stribild - Elvitegravir + Cobicistat + Tenofovir + FTC
Truvada - Tenofovir + FTC
Combivir - AZT +3TC

ARVS IN THE PIPELINE

Cd4 attachment inhibitors[11]:
BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into to CD4 T-cells.

The current trial underway for this drug is AI438011 a Phase IIb, randomized, active-controlled trial. "It is investigating the safety, efficacy and dose response of BMS-663068 versus atazanavir/ritonavir (ATV/r) in treatment-experienced (TE), HIV-1-positive subjects."[11]

At week 24 of the trial the results are the following:
"Mean increases in CD4 T-cell counts across the BMS-663068 arms were consistent with ATV/r, regardless of gender, age and baseline CD4 T-cell count indicating efficacy"[11].

Safety profile: "BMS-663068 was generally well tolerated across all arms, with no related serious adverse events leading to discontinuation and no dose-related safety signals. There were no trends for clinical laboratory abnormalities found These results support further studies into the development of BMS663068".

CCR5/CCR2 co-receptor antagonist[12]:
"Cenicriviroc (CVC), is a once-daily, dual CCR5/CCR2 co- receptor antagonist, and has completed Phase 2b development. It blocks HIV entry but does not allow redistribution into cells".[11] Its side effect profile and efficacy has been compared to EFV in clinical trials.

New NNRTI[13]:
"Doravirine (DOR) is an investigational NNRTI (aka MK- 1439) that retains activity against common NNRTI-resistant mutants".[12] The current week 48 results from the clinical trial underway indicate that when combined with TDF/FTC, it had potent antiviral activity, and is generally safe and well tolerated.

New NtRTI[14]
Tenofovir alafenamide [TAF gs7340] is a new prodrug of tenofovir[TDF] .Current ongoing trial show that TAF results in a 7fold greater intracellular levels of TDF at a smaller dose.

Long Acting Injectables[15];
Rilpivirine LA, a monthly injectable and Caboegravir, administered 3monthly are current in clinical trials. These are possibly the drugs of the future, as they will provide convenient treatment options for patients, and assist with adherence and compliance issues.

CHANGES TO THE SOUTH AFRICAN GUIDELINES [16]

South African guidelines have recently been updated in January 2015. The guidelines are frequently revised and it is advisable that the clinician regularly familiarizes himself with the latest guidelines

The latest guidelines have the following changes/additions[16]:

- General changes to adults and adolescents >15yrs:
    - Early initiation of ARVS, on all patients cd4 <500, prioritizing those with cd4<350 irrespective of clinical stage.
    - Initiation of ARVS in Stage 3 and 4 disease, irrespective of cd4 count.
    - HAART for all patients with Hep B co-infection irrespective of cd4 or clinical stage.
    - HAART for all patients with Tb infection irrespective of cd4 or clinical stage.
    - Routine cryptococcal infection screening for all HIV-infected patients with CD4 <100 cells
    - Use of simplified fixed-dose combinations for ART
    - Harmonised ART regimen across populations, mainly pregnant and breastfeeding women, adolescents and adults

- Pregnant patients;
    - Immediate initiation of lifelong HAART for all HIV positive woman who are pregnant or 1yr post-partum regardless of CD4 count.
    - Use of maternal lifelong HAART to reduce MTCT
    - Use of EFV as part of 1st line regimen, regardless of gestation
    - Repeat HIV testing for all negative women, 3monthly during pregnancy, at delivery and at 6weeks

- Children <5yrs:
    - ART for all children under 5yrs, regardless of CD4 count or clinical stage
    - ART for all children between 5yrs-10yrs with a CD4 < 500 regardless of clinical staging.
    - Immediate initiation of ART for infants with 1st positive HIV PCR while awaiting confirmatory tests

Table 3: What to Start: ART 1st line regimen for Adults & adolescents ≥ 15yrs

POPULATION	DRUG	COMMENTS
Adolescents >15 years and weighing >40kg Adults All TB co-infection All HBV co-infection	TDF + 3TC (or FTC) + EFV provide as fixed-dose combination (FDC)	Replace EFV with NVP in patients: • With significant psychiatric comorbidity or intolerance to EFV • Where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. night shift workers
Adults and adolescents on d4T	Change d4T to TDF (No patient must be on d4T)	Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if d4T well tolerated If VL>1000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40kg	ABC + 3TC + EFV	If adolescent weight <40kg, align with paediatric regimen
CONTRAINDICATION	**SUBSTITUTION DRUG**	**COMMENTS**
Contraindication to EFV: • Significant psychiatric co-morbidity • Intolerance to EFV • Impairment of daily function (shift workers)	TDF + FTC (or 3TC) + NVP or LPV/r	IfCD4 <250 females and <400 males, give NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250 females and ≥400 males, use LPV/r 2 tablets 12 hourly
TDF contraindication: Creatinine clearance of <50 mL/min	ABC+ 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides MDR treatment

Table 4: Second-line regimen for late adolescents and adults [16]

SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
First-line virological failure	**Drugs**	**Comments**
Failing on a TDF-based first-line regimen	AZT + 3TC + LPV/r AZT + **TDF** + 3TC + LPV/r (If HBV co-infected)	If non-adherent, address causes of non-adherence If the VL >1000 copies/mL at any point, intensify adherence and repeat viral load in 2months
Failing on a d4T or AZT-based first line regimen	TDF + 3TC (or FTC) + LPV/r	
SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
Anaemia and renal failure	Switch to ABC	

Table 5: First-line ART regimens in pregnant and breastfeeding women[16]

FIRST-LINE ART REGIMENS		
POPULATION	**DRUGS**	**COMMENTS**
1st ANC visit		
All pregnant women not on ART (any gestational age) All breastfeeding women not on ART	TDF + 3TC (or FTC) + EFV Provide as fixed-dose combination (FDC)	If there is a contraindication to the FDC (Contraindication to TDF: renal insufficiency Contraindication to EFV: active psychiatric illness): start AZT immediately and refer to Boxes 2 and 3
Pregnant women currently on ART	Continue current ART regimen Change to FDC if on individual first-line drugs and virally suppressed and no contraindications to FDC	Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done Patients with confirmed 2nd or 3rd line regimen failure should not breastfeed their infants
2nd ANC visit (1 week later)		
Pregnant women Creatinine ≤85µmol/l and any CD4 cell count	Continue FDC	
Creatinine >85 µmol/l TDF contraindicated	Stop FDC, initiate AZT if Hb ≥7g/dl	High-risk pregnancy: refer urgently for alternate triple therapy within 2 weeks, with dose adjustment if indicated, and investigation of renal dysfunction
Contraindication to EFV (active psychiatric illness)	Continue AZT until initiated on individual drugs TDF+3TC+NVP or LPV/r	Refer urgently for alternate triple therapy CD4 <250cells/µl: NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250cells/µl LPV/r 2 tablets 12 hourly
Unbooked and presents in labour and tests HIV positive	sdNVP + sd Truvada and AZT 3-hourly in labour sdNVP + sd Truvada for C/S Start FDC next day regardless of CD4 cell count	Woman qualifies for lifelong ART Do creatinine and CD4 testing. Woman should get results at the 36 days visit
Emergency caesarean section in an unbooked woman with no ART	Same as above	
Post-Partum		
Mother diagnosed with HIV within 1 year post-partum or still breastfeeding beyond 1 year	Lifelong FDC initiated immediately	

Table 6: Guidelines for Children under 15yrs[16]

CHILD	REGIMEN	COMMENT
Children <3 years or older children weighing <10kg	ABC + 3TC + LPV/r	Doses are based on child's weight and need to be adjusted as the child grows
Children 3-10 years and>10kg Adolescents 10-15 years or <40kg	ABC + 3TC + EFV Children who started on ABC/3TC/LPV/r before 3 years must remain on same regimen at 3yr	Do not exceed maximum dosage If adolescents weight <40kg, align treatment with children's regimen
Children on d4T	Change all d4T to ABC	If VL suppressed: change to ABC If VL>1000 copies/ml, manage as treatment failure If VL 50-1000 copies/ml, consult specialist
Children on DDI	Change all DDI to ABC	Change all regardless of VL

SIGNIFICANT REACTIONS WITH DRUGS RELATED TO ANAESTHESIA [17,18,19,20]

Given that many of South African HIV patients will be presenting for anaesthesia it is important to be aware of the drug- drug interactions that may occur.
Drug interactions can be classified into two broad categories:

1] Anaesthetic agents may induce pharmaco-dynamic changes to affect the efficacy and toxicity of ARVs,

2] Pharmacokinetic effects of ARVs can affect the absorption, distribution, metabolism and elimination of anaesthetic drugs.
Some ARVs may not directly interact with anaesthetic drugs themselves, but with drugs commonly seen as adjuncts or prescribed to patients pre-operatively, eg statins.

A] NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS[NNRTI]:

Interactions:
Delavirdine is an inhibitor, while Nevirapine is an inducer of CYP450. Efavirenz may either induce or inhibit the CYP450 system

Opiods; of particular concern, NVP and Efavirenz may cause sub therapeutic levels of Fentanyl and Alfentanil and the dose may need to be increased. There have also been reports of Methadone withdrawal in patients on NVP.

Benzodiazepines: Although there are no published reports, Efavirenz is contraindicated with Midazolam, Triazolam and ergotamine derivatives. Delavirdine is a potent inhibitor of CYP3A4 and may potentiate the effect of benzodiazepines and are thus best avoided.

Anticonvulsants: Carbamazepine, phenobarbital and phenytoin may significantly reduce NNRTI concentrations and should be replaced by other agents such as Valproic acid.

Anticoagulants: Complex reaction between warfarin and NNRTIs, with tendency for anticoagulant effect to be potentiated.

B] Nucleoside and nucleotide reverse transcriptase inhibitors [NRTI]

Not metabolized by CYP450 system, so minimal drug interactions occur.
No documented reactions with anaesthetic agents.
Concern of interactions with Didanosine with antibiotics. It is formulated as enteric coated capsules or buffered powder for oral solutions. The buffer may affect fluroquinolone and ciprofloxacin.
Tenofovir is nephrotoxic and the concurrent use of other nephrotoxic agents should be avoided.

C] PROTEASE INHIBITORS [PI]

Strong Inhibitors of the cyp450. Ritonavir's effect on multiple CYP450 enyzmes, complicates and increases the number of drug interactions, as it may function as both an inhibitor or inducer.

Benzodiazepines: PIs react with midazolam and diazepam by increasing plasma levels, causing prolonged sedation and depression of respiration

Opiates: Methadone
Impairs Fentanyl and Alfentanil metabolism leading to increased levels and respiratory depression.

Thiopentone and Dexamethasone: decrease PI plasma concentrations

Statins: Myopathies and rhabdomyolysis may occur when PIs interact with statins. Due to this risk, lovastatin and simvastatin are contra-indicated.
Ergot derivatives: contraindicated with Efavirenz due to risk of prolonged vasospasm

D] FUSION INHIBITORS

Enfuvirtide is a 36–amino-acid peptide that does not enter human cells.
To date, no significant drug interactions has been found.

E] CCR5 Co-Receptor Antagonists

Maraviroc (MVC) is a substrate of CYP3A enzymes and P-glycoprotein.
MVC does not inhibit or induce the CYP3A system. It is not known to disrupt the pharmacokinetics of other drugs.

Its concentration can be significantly increased when co administered with strong CYP3A inhibitors (eg, ritonavir).Reduced concentration may occur when coadministered with strong CYP3A inducers (eg, efavirenz, rifampin).

F] INTEGRASE INHIBITORS

Dolutegravir is metabolized by UGT1A1 with only 10–15% metabolized by CYP3A4. It neither induces nor inhibits CYP450 or UGT and therefore clinically significant drug interactions are not expected.

G] MATURATION INHIBITORS

No documented dose adjustments needed for sedatives or analgesics. Beviramat is neither an inducer nor inhibitor and drug interactions are not common.

SUMMARY OF COMMON DRUG INTERACTIONS WITH DRUGS ASSOCIATED WITH ANAESTHESIA [19]

The tables below are courtesy of www.Hivdruginteraction.org.

KEY:
These drugs should not be coadministered ---------- /
Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration /
No clinically significant interaction expected /
There are no clear data, actual or theoretical, to indicate whether an interaction will occur /
Data not available n//a

Table 7: generated via www hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Abacavir	Emtricitabine (FTC)	Lamivudine (3TC)	Stavudine (d4T)
Bupivacaine	◇	◇	◇	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	◇	◇	◇	◇
Ephedrine	◇	□	□	□
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	◇	◇	◇	◇
Propofol	◇	◇	◇	◇
Rocuronium	◇	◇	◇	◇
Sevoflurane	◇	◇	◇	◇
Sufentanil	◇	◇	◇	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Alfentanil	◇	◇	◇	◇
Fentanyl	◇	◇	◇	◇
Morphine	◇	◇	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	◇	◇	◇	◇
Anxiolytics/Hypnotics/ Sedatives	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Diazepam	◇	◇	◇	◇
Midazolam (oral)	◇	◇	◇	◇
Gastrointestinal Agents (anti-emetics)	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Metoclopramide	◇	◇	◇	◇

Table 8: generated via www.hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Lopinavir	Efavirenz	Nevirapine	Tenofovir
Bupivacaine	■	■	■	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	■	■	◇	◇
Ephedrine	◇	◇	◇	■
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	■	■	■	◇
Propofol	■	■	■	◇
Rocuronium	■	■	◇	◇
Sevoflurane	■	◇	◇	◇
Sufentanil	■	■	■	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Alfentanil	■	■	■	◇
Fentanyl	■	■	■	◇
Morphine	■	■	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	■	■	■	◇
Anxiolytics/Hypnotics/ Sedatives	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Diazepam	■	■	■	◇
Midazolam (oral)	●	●	■	◇
Gastrointestinal Agents (anti-emetics)	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Metoclopramide	◇	◇	◇	◇
Ondansetron	■	◇	◇	◇
Steroids	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Dexamethasone	■	■	■	◇

www.hiv-druginteractions.org is a useful website were printable charts of ARV drug interactions can be found allowing ease for the clinician.

ARVS IN THE CRITICALLY ILL [22,23,26]

Patients presenting to the critical care physician may present in 2 different categories:
1] AIDs related opportunistic infections
2] Pathologies unrelated to HIV such as trauma or elective surgery

Concern about administering ARVs in the critically ill is that it may worsen their current clinical condition, due to interactions with other drugs, Immune Reconstitution Syndrome [IRIS] and drug side effects

The pharmacokinetics in the critical care patient are in addition altered, and may lead to sub-therapeutic or supra-therapeutic doses. Most ARVs are available in oral preparations only and need to be crushed and administered via a feeding tube in the ICU patient. Gastro-intestinal absorption may be inconsistent, leading to unpredictable drug levels, creating a risk for drug resistance and toxicity.

Drug-drug interactions are common, with analgesics, antibiotics, antihypertensive, anti-arrhythmic all being implicated.

IRIS occurs after improvement of the immune system with a renewed inflammatory response against new pathogens. It usually occurs in the 1st two weeks after Arv initiation. It may cause a paradoxical and clinical worsening of a condition or unmask a new localized infection.
The critically ill patient is already significantly compromised with poor physiological reserve. In these patients a paradoxical worsening of a condition may have devastating consequences.

There are several mechanisms by which ARVS may improve outcomes in ICU but none have been proven. All evidence for the use of ARVS in ICU is from retrospective studies and expert opinion only. Retrospective chart analysis showed lower mortality in patients receiving HAART.

There are currently no clear guidelines set out for the use of ARV's in ICU. Most of HIV patients coming to ICU will not be on therapy.
Patients previously well and admitted for a non HIV related condition may have therapy postponed.

Patients with long term stays and cd4<200 could potentially benefit from ARVS to prevent other opportunistic infections.
Those with AIDs defining illness should be ideally initiated on ARVS as soon as possible.

Given that the decision to initiate ARV in the critically ill patient is a complex one, each patient should be individualized and the merits and demerits of ARV therapy discussed, before initiating therapy.

CONCLUSION

With advances in antiretroviral therapy, more HIV positive patients are likely to present for elective non HIV related surgery. As we move into the future, we can look forward to exciting developments in ARVs.

The pharmacology and drug interactions can be complex and pose challenging to the anaesthetist. It is therefore important to stay current and continuously update ourselves on newer ARVs and current guidelines available.

To assist the modern day doctor, the South African Department of Health has made all clinical guidelines available freely online……..

And to those who love their apps, the Department has recently announced their new app, HIV Clinical Guide App, sponsored by the openmedicine project.org. It is freely available on Android and Apple devices via App Stores and Google Play.

So happy downloading, and happy learning… together we can contribute to curbing this epidemic.

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No. 18

ARVS FOR THE ANAESTHETIST

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ARVS FOR THE ANAESTHETIST

INTRODUCTION

A PUBMED search for HIV, yields more than 288000 results, yet surprisingly many current day anaesthetists would not be able easily quote the latest ARV guidelines, pleading ignorance, blaming the government and even load shedding for the apparent lack of acknowledge that is freely available.

2014 marked a decade since the Anti-retroviral therapy roll out for South Africa was instituted, with ever changing guidelines and practices, due to better understanding of therapy and greater accessibility to newer drug therapy. The current guidelines have just been released in January 2015.

So where are we a decade later? For the general population at large, this means easier access to ARVs, with HAART being rolled at higher cd4 counts, better screening tools, and fewer opportunistic infections.

For the anaesthetist this has many implications, with the HIV positive population being a dynamic and ever changing one .In the pre and early ARV era, most patients presented to the anaesthetist, with stage 4 disease, for surgery for AIDS related pathology. These patients were ill, and presented confounders for critical care.

Today's HIV population are presenting as "healthy" individuals, for surgery for none HIV related pathologies. Access to ARV therapy has increased life expectancy significantly. The focus of the anaesthetist is shifting from disease related issues, to issues related to ARV – anaesthetic drug interactions, and issues related to side effect profiles.

PREVALENCE

HIV was first discovered in 1981. Today it has reached pandemic proportions. The Southern African sub-region, in particular, is experiencing the most severe epidemics. Statistics according to www.unicef.org[1], reveal that "Nine countries- Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe- have an adult prevalence of over 10%."

As per Statistics SA, "the total number of people living with HIV in South Africa increased from estimated 4.09million in 2002 to 5.51 million in 2014 .An estimated 10.6% of the total population is HIV positive, with approximately one fifth of South African women in their reproductive ages being HIV positive."[2]

Table 1: HIV prevalence estimates & the number of people living with HIV, 2002-2014[2]

YEAR	PREVALENCE				INCIDENCE ADULT 15 - 49	HIV POPULATION (MILLIONS)
	WOMEN 15 - 49	ADULT 15 - 49	YOUTH 15 - 24	TOTAL POPULATION		
2002	16,7	15,8	14,1	9,0	1,64	4,09
2003	16,9	15,9	13,2	9,1	1,64	4,20
2004	17,0	15,9	12,5	9,2	1,69	4,29
2005	17,1	15,9	11,9	9,3	1,73	4,38
2006	17,3	15,9	11,5	9,4	1,69	4,48
2007	17,5	16,0	11,1	9,5	1,59	4,61
2008	17,7	16,2	10,8	9,7	1,47	4,75
2009	17,9	16,3	10,4	9,8	1,36	4,88
2010	18,0	16,5	10,1	9,9	1,29	5,02
2011	18,2	16,6	9,7	10,0	1,25	5,14
2012	18,3	16,6	9,3	10,1	1,16	5,26
2013	18,4	16,7	9,0	10,1	1,14	5,38
2014	18,5	16,8	8,7	10,2	1,11	5,51

COURSE OF HIV INFECTION

HIV is a lentivirus of the retrovirus family.[3] Two enzymes, reverse transcriptase and viral integrase, incorporate the host's DNA into the virus' mRNA, allowing replication of the virus. The host's Cd4 cells are destroyed, which are important to the immune response process, resulting in an immune deficiency state.

The course of HIV is variable.[4] There is a latent period of about 8-12 weeks following infection, during which there may be an intense viraemia. Seroconversion then occurs, with antibodies to HIV appearing in serum. There is also a rapid fall in viraemia, suggesting that the immunological response has controlled the infection. At this stage one third individuals experience brief illness lasting about 2 weeks. Symptoms include fever, malaise, arthralgia, rash and lymphadenopathy. Then follows as asymptomatic phase of 10-11 years before AIDS develops.[5]

STAGING

HIV can be staged clinically using the WHO staging system. Alternatively it can be staged according to cd4 count.

Table 1: WHO Clinical Staging[5]

CLINICAL STAGE	SYMPTOMS
Stage 1	Asymptomatic Lymphadenopathy
Stage 2	Hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular chelitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Parotid enlargement Herpes zoster Chronic upper respiratory tract infections
Stage 3	Malnutrition Persistent diarrhea Persistent fever Persistent oral condiasis Oral hairy leukoplakia Necrotizing ulcerative gingivitis or periodontisis Lymph node tuberculosis Pulmonary tuberculosis Recurrent bacterial pneumonia Lymphoid interstistial pneumonitis Lung disease (such as brochiectasis) Anemia or chronic thrmobocytopaenia
Stage 4	Severe wasting, stunting, or malnutrition Pneumocystis pneumonia Severe bacterial infections Chronic herpes simplex infection Esophageal candidiasis Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis Extrapulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis Disseminated non-tuberculous mycobacterial infection Chronic cryptosporidiosis (with diarrhoed) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

ANTIRETROVIRAL THERAPY

Currently there are at least 28 antiretroviral drugs approved by the FDA, most falling into 8 mechanistic classes.[6] There are numerous treatment regimes, ranging from standard 3 drug regimens to once a day pills.

Table 2: Classification of Antiretrovirals[7]

DRUG CLASS	EXAMPLES
Nucleoside analogue reverse transcriptase inhibitors[NRTIs] **MOA:**Nucleosides are phosphorylated to form nucleotides and are DNA building blocks, by forming 3' to 5' phosphodiester linkage allowing chain elongation NRTIs and NtRTIs are structural analogues of nucleosides and nucleotides and interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase.	Zidovdine [azt] Didanosine[DDI] Lamivudine [3TC] Stavudine [D4T] Emtricitabine [FTC] Abacavir [ABC] Elvucitabine Apricitabine
Nucleotide reverse transcriptase inhibitors [NtRTI] Similar to above, sometimes regarded as a single drug class	Tenofovir [TDF]
Non nucleoside reverse transcriptase inhibitors[NNRTIs] **MOA**: Non competitive binding directly at a pocket of the p66 subunit of HIV reverse transcriptase.	Nevirapine [nvp] Efavirenz [EFV] Delavirdine [DLV] Etravirine
Protease inhibitors [PI] **MOA**: HIV protease cleaves polypeptide chains to form functional viral proteins. PIs inhibit this enzyme resulting in the release of non-infectious viral proteins with a disorganised structure	Indinavir [IDV] Ritonavir [RTV] Saquinavir [SQV] Nelfinavir [NFV] Lopinavir [LPV] Tiprinavir Darunavir Atazanavir
Fusion inhibitors **MOA:** Relatively new class. Bind to gp41 preventing conformational change necessary for fusion and entry into CD4 cells.	Enfuvirtide [T-20]
CCR5 co-receptor antagonists **MOA**: In order to enter cells, HIV must bind to Cd4 receptors and chemokine co-receptors CCR5 and CCR4. Co-receptor antagonists thus prevent entry of HIV into the host cell	Maraviroc Vicriviroc
Integrase inhibitors **MOA**: Integrase inhibitors target viral integrase, preventing the integration of proviral DNA into human chromosomes	Raltegravir Elvitegravir
Maturation inhibitors **MOA:** These prevent conversion of capsid precursor protein [p25] to the mature capsid protein [p24], thus preventing formation of infectious particles and renders the virus incapable of infecting other cells.	Beviramat

PHARMACOKINETICS AND SIDE EFFECTS OF ARVS [7,8]

Most ARVS are administered orally and have good absorption. This may be affected by gastric ph. They are metabolized by cytochrome P450 system, namely CYP3A and CYP2B6.

Lipophilic drugs such as PI's and NNRTI's are oxidatively metabolized by CYP450 to polar forms for excretion via renal or biliary systems. These drugs can be classified as either inhibitors or inducers of CYP450.[7]
NRTI's are water soluble and renally excreted. "They are prodrugs and require intracellular phosphorylation to be activated. Thus drugs that affect phosphorylation will affect these drugs".

ARV side effects can be broadly classified into categories namely:[8]

1) Mitochondrial toxicity: Lactic acidosis, hepatotoxicity, pancreatitis, peripheral neuropathy.
2) Metabolic: Lipodystrophy, hyperglycaemia, body habitus changes, insulin resistance, osteoporosis.
3) Bone marrow suppression: Pancytopenia.
4) Hypersensitivity reactions: Skin rashes

INDIVIDUAL CLASSES

NRTI

Pharmacokinetics: absorbed enterally-30-60% absorption, with AZT being the only IV preparation.
<10% protein bound. Renally excreted except for Abacavir which undergoes hepatic metabolism. Does not induce cytochrome p450.

S/E: mitochondrial toxicity causing lactic acidosis, pancreatitis, and peripheral neuropathy. Abnormal fat deposition
Zidovudine-high incidence of fatigue, headaches and git disturbances.
Tenofovir: renal impairment, decrease in bone mineral density, GIT intolerance

NNRTI:

Pharmacokinetics: enteral preparations only are well absorbed, highly protein bound. Primarily hepatic metabolism and excretion.
NVP lipophilic, crosses placenta and is excreted in breastmilk. Lead to cytochrome P450 enzyme induction and inhibition, depending on drug used

S/E: All NNRTIs: rash including Stevens-Johnsons syndrome,
EFV: Previously thought to have an association with neural tube defects- controversial- "overall rates of birth defects in infants exposed to EFV, NVP and TDF are similar to those in the general population".[9] Currently included in South African guidelines for pregnant patient. Neuropsychiatric side effects common.
NVP: hepatotoxicity

Protease Inhibitors [PIs]

Pharmacokinetics: enteral preparations only, >86% protein bound. Primarily hepatic metabolism. Extensively metabolized by CYP450. PI's are potent inhibitors of CYP3A4. Ritonavir being the exception, is a potent inhibitor of CYP3A4 and CYP2D6, while being an inducer of CYP1A2 and CYP2C9.

Side effects: Hyperlipidaemia, lipodystrophy, hepatotoxicity, GI intolerance, insulin resistance

Fusion inhibitors

Administered subcutaneously with 84% absorption. 92% protein bound. Used in patients with virological failure

S/E: Neutropaenia, risk of hypersensitivity, eosinophilia

Chemokine co-receptor Antagonists

Enteral preparations 76% protein bound. Mainly hepatic metabolism and renal clearance, large VD

S/E: GIT disturbances, cough, abnormalities in liver function tests

Integrase Inhibitors

Enteral preparations, high fat meals slow absorption
Highly protein bound, no dose adjustment needed in renal or hepatic impairment

S/E: Pruritus and rash, headache, abnormalities in amylase and liver function tests

Maturation Inhibitors

Enteral preparations very highly protein bound. Metabolized by glucuronidation, minor renal clearance

S/E: self-limiting GIT disturbances

FDC [Fixed Dose Combination][10]

There are multiple FDCs currently on the market and in development. The pharmacokinetics and side effect profile of these drugs are the same as the individual drugs themselves.

Some of the current FDCs available:

Atripla/Atrozia - efavirenz +tenofovir +FTC
Eviplera/Complera - Rilpivirine +Tenofovir + FTc
Triumeq - Dolutegravir +Abacavir + 3TC
Stribild - Elvitegravir + Cobicistat + Tenofovir + FTC
Truvada - Tenofovir + FTC
Combivir - AZT +3TC

ARVS IN THE PIPELINE

Cd4 attachment inhibitors[11]:
BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into to CD4 T-cells.

The current trial underway for this drug is AI438011 a Phase IIb, randomized, active-controlled trial. "It is investigating the safety, efficacy and dose response of BMS-663068 versus atazanavir/ritonavir (ATV/r) in treatment-experienced (TE), HIV-1-positive subjects."[11]

At week 24 of the trial the results are the following:
"Mean increases in CD4 T-cell counts across the BMS-663068 arms were consistent with ATV/r, regardless of gender, age and baseline CD4 T-cell count indicating efficacy"[11].

Safety profile: "BMS-663068 was generally well tolerated across all arms, with no related serious adverse events leading to discontinuation and no dose-related safety signals. There were no trends for clinical laboratory abnormalities found These results support further studies into the development of BMS663068".

CCR5/CCR2 co-receptor antagonist[12]:
"Cenicriviroc (CVC), is a once-daily, dual CCR5/CCR2 co- receptor antagonist, and has completed Phase 2b development. It blocks HIV entry but does not allow redistribution into cells".[11] Its side effect profile and efficacy has been compared to EFV in clinical trials.

New NNRTI[13]:
"Doravirine (DOR) is an investigational NNRTI (aka MK- 1439) that retains activity against common NNRTI-resistant mutants".[12] The current week 48 results from the clinical trial underway indicate that when combined with TDF/FTC, it had potent antiviral activity, and is generally safe and well tolerated.

New NtRTI[14]
Tenofovir alafenamide [TAF gs7340] is a new prodrug of tenofovir[TDF] .Current ongoing trial show that TAF results in a 7fold greater intracellular levels of TDF at a smaller dose.

Long Acting Injectables[15];
Rilpivirine LA, a monthly injectable and Caboegravir, administered 3monthly are current in clinical trials. These are possibly the drugs of the future, as they will provide convenient treatment options for patients, and assist with adherence and compliance issues.

CHANGES TO THE SOUTH AFRICAN GUIDELINES [16]

South African guidelines have recently been updated in January 2015. The guidelines are frequently revised and it is advisable that the clinician regularly familiarizes himself with the latest guidelines

The latest guidelines have the following changes/additions[16]:

- General changes to adults and adolescents >15yrs:
    - Early initiation of ARVS, on all patients cd4 <500, prioritizing those with cd4<350 irrespective of clinical stage.
    - Initiation of ARVS in Stage 3 and 4 disease, irrespective of cd4 count.
    - HAART for all patients with Hep B co-infection irrespective of cd4 or clinical stage.
    - HAART for all patients with Tb infection irrespective of cd4 or clinical stage.
    - Routine cryptococcal infection screening for all HIV-infected patients with CD4 <100 cells
    - Use of simplified fixed-dose combinations for ART
    - Harmonised ART regimen across populations, mainly pregnant and breastfeeding women, adolescents and adults

- Pregnant patients;
    - Immediate initiation of lifelong HAART for all HIV positive woman who are pregnant or 1yr post-partum regardless of CD4 count.
    - Use of maternal lifelong HAART to reduce MTCT
    - Use of EFV as part of 1st line regimen, regardless of gestation
    - Repeat HIV testing for all negative women, 3monthly during pregnancy, at delivery and at 6weeks

- Children <5yrs:
    - ART for all children under 5yrs, regardless of CD4 count or clinical stage
    - ART for all children between 5yrs-10yrs with a CD4 < 500 regardless of clinical staging.
    - Immediate initiation of ART for infants with 1st positive HIV PCR while awaiting confirmatory tests

Table 3: What to Start: ART 1st line regimen for Adults & adolescents ≥ 15yrs

POPULATION	DRUG	COMMENTS
Adolescents >15 years and weighing >40kg Adults All TB co-infection All HBV co-infection	TDF + 3TC (or FTC) + EFV provide as fixed-dose combination (FDC)	Replace EFV with NVP in patients: • With significant psychiatric comorbidity or intolerance to EFV • Where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. night shift workers
Adults and adolescents on d4T	Change d4T to TDF (No patient must be on d4T)	Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if d4T well tolerated If VL>1000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40kg	ABC + 3TC + EFV	If adolescent weight <40kg, align with paediatric regimen
CONTRAINDICATION	**SUBSTITUTION DRUG**	**COMMENTS**
Contraindication to EFV: • Significant psychiatric co-morbidity • Intolerance to EFV • Impairment of daily function (shift workers)	TDF + FTC (or 3TC) + NVP or LPV/r	IfCD4 <250 females and <400 males, give NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250 females and ≥400 males, use LPV/r 2 tablets 12 hourly
TDF contraindication: Creatinine clearance of <50 mL/min	ABC+ 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides MDR treatment

Table 4: Second-line regimen for late adolescents and adults [16]

SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
First-line virological failure	**Drugs**	**Comments**
Failing on a TDF-based first-line regimen	AZT + 3TC + LPV/r AZT + **TDF** + 3TC + LPV/r (If HBV co-infected)	If non-adherent, address causes of non-adherence If the VL >1000 copies/mL at any point, intensify adherence and repeat viral load in 2months
Failing on a d4T or AZT-based first line regimen	TDF + 3TC (or FTC) + LPV/r	
SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
Anaemia and renal failure	Switch to ABC	

Table 5: First-line ART regimens in pregnant and breastfeeding women[16]

FIRST-LINE ART REGIMENS		
POPULATION	**DRUGS**	**COMMENTS**
1st ANC visit		
All pregnant women not on ART (any gestational age) All breastfeeding women not on ART	TDF + 3TC (or FTC) + EFV Provide as fixed-dose combination (FDC)	If there is a contraindication to the FDC (Contraindication to TDF: renal insufficiency Contraindication to EFV: active psychiatric illness): start AZT immediately and refer to Boxes 2 and 3
Pregnant women currently on ART	Continue current ART regimen Change to FDC if on individual first-line drugs and virally suppressed and no contraindications to FDC	Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done Patients with confirmed 2nd or 3rd line regimen failure should not breastfeed their infants
2nd ANC visit (1 week later)		
Pregnant women Creatinine ≤85µmol/l and any CD4 cell count	Continue FDC	
Creatinine >85 µmol/l TDF contraindicated	Stop FDC, initiate AZT if Hb ≥7g/dl	High-risk pregnancy: refer urgently for alternate triple therapy within 2 weeks, with dose adjustment if indicated, and investigation of renal dysfunction
Contraindication to EFV (active psychiatric illness)	Continue AZT until initiated on individual drugs TDF+3TC+NVP or LPV/r	Refer urgently for alternate triple therapy CD4 <250cells/µl: NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250cells/µl LPV/r 2 tablets 12 hourly
Unbooked and presents in labour and tests HIV positive	sdNVP + sd Truvada and AZT 3-hourly in labour sdNVP + sd Truvada for C/S Start FDC next day regardless of CD4 cell count	Woman qualifies for lifelong ART Do creatinine and CD4 testing. Woman should get results at the 36 days visit
Emergency caesarean section in an unbooked woman with no ART	Same as above	
Post-Partum		
Mother diagnosed with HIV within 1 year post-partum or still breastfeeding beyond 1 year	Lifelong FDC initiated immediately	

Table 6: Guidelines for Children under 15yrs[16]

CHILD	REGIMEN	COMMENT
Children <3 years or older children weighing <10kg	ABC + 3TC + LPV/r	Doses are based on child's weight and need to be adjusted as the child grows
Children 3-10 years and>10kg Adolescents 10-15 years or <40kg	ABC + 3TC + EFV Children who started on ABC/3TC/LPV/r before 3 years must remain on same regimen at 3yr	Do not exceed maximum dosage If adolescents weight <40kg, align treatment with children's regimen
Children on d4T	Change all d4T to ABC	If VL suppressed: change to ABC If VL>1000 copies/ml, manage as treatment failure If VL 50-1000 copies/ml, consult specialist
Children on DDI	Change all DDI to ABC	Change all regardless of VL

SIGNIFICANT REACTIONS WITH DRUGS RELATED TO ANAESTHESIA [17,18,19,20]

Given that many of South African HIV patients will be presenting for anaesthesia it is important to be aware of the drug- drug interactions that may occur.
Drug interactions can be classified into two broad categories:

1] Anaesthetic agents may induce pharmaco-dynamic changes to affect the efficacy and toxicity of ARVs,

2] Pharmacokinetic effects of ARVs can affect the absorption, distribution, metabolism and elimination of anaesthetic drugs.
Some ARVs may not directly interact with anaesthetic drugs themselves, but with drugs commonly seen as adjuncts or prescribed to patients pre-operatively, eg statins.

A] NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS[NNRTI]:

Interactions:
Delavirdine is an inhibitor, while Nevirapine is an inducer of CYP450. Efavirenz may either induce or inhibit the CYP450 system

Opiods; of particular concern, NVP and Efavirenz may cause sub therapeutic levels of Fentanyl and Alfentanil and the dose may need to be increased. There have also been reports of Methadone withdrawal in patients on NVP.

Benzodiazepines: Although there are no published reports, Efavirenz is contraindicated with Midazolam, Triazolam and ergotamine derivatives. Delavirdine is a potent inhibitor of CYP3A4 and may potentiate the effect of benzodiazepines and are thus best avoided.

Anticonvulsants: Carbamazepine, phenobarbital and phenytoin may significantly reduce NNRTI concentrations and should be replaced by other agents such as Valproic acid.

Anticoagulants: Complex reaction between warfarin and NNRTIs, with tendency for anticoagulant effect to be potentiated.

B] Nucleoside and nucleotide reverse transcriptase inhibitors [NRTI]

Not metabolized by CYP450 system, so minimal drug interactions occur.
No documented reactions with anaesthetic agents.
Concern of interactions with Didanosine with antibiotics. It is formulated as enteric coated capsules or buffered powder for oral solutions. The buffer may affect fluroquinolone and ciprofloxacin.
Tenofovir is nephrotoxic and the concurrent use of other nephrotoxic agents should be avoided.

C] PROTEASE INHIBITORS [PI]

Strong Inhibitors of the cyp450. Ritonavir's effect on multiple CYP450 enyzmes, complicates and increases the number of drug interactions, as it may function as both an inhibitor or inducer.

Benzodiazepines: PIs react with midazolam and diazepam by increasing plasma levels, causing prolonged sedation and depression of respiration

Opiates: Methadone
Impairs Fentanyl and Alfentanil metabolism leading to increased levels and respiratory depression.

Thiopentone and Dexamethasone: decrease PI plasma concentrations

Statins: Myopathies and rhabdomyolysis may occur when PIs interact with statins. Due to this risk, lovastatin and simvastatin are contra-indicated.
Ergot derivatives: contraindicated with Efavirenz due to risk of prolonged vasospasm

D] FUSION INHIBITORS

Enfuvirtide is a 36–amino-acid peptide that does not enter human cells.
To date, no significant drug interactions has been found.

E] CCR5 Co-Receptor Antagonists

Maraviroc (MVC) is a substrate of CYP3A enzymes and P-glycoprotein.
MVC does not inhibit or induce the CYP3A system. It is not known to disrupt the pharmacokinetics of other drugs.

Its concentration can be significantly increased when co administered with strong CYP3A inhibitors (eg, ritonavir).Reduced concentration may occur when coadministered with strong CYP3A inducers (eg, efavirenz, rifampin).

F] INTEGRASE INHIBITORS

Dolutegravir is metabolized by UGT1A1 with only 10–15% metabolized by CYP3A4. It neither induces nor inhibits CYP450 or UGT and therefore clinically significant drug interactions are not expected.

G] MATURATION INHIBITORS

No documented dose adjustments needed for sedatives or analgesics. Beviramat is neither an inducer nor inhibitor and drug interactions are not common.

SUMMARY OF COMMON DRUG INTERACTIONS WITH DRUGS ASSOCIATED WITH ANAESTHESIA [19]

The tables below are courtesy of www.Hivdruginteraction.org.

KEY:
These drugs should not be coadministered ---------- /
Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration /
No clinically significant interaction expected /
There are no clear data, actual or theoretical, to indicate whether an interaction will occur /
Data not available n//a

Table 7: generated via www hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Abacavir	Emtricitabine (FTC)	Lamivudine (3TC)	Stavudine (d4T)
Bupivacaine	◇	◇	◇	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	◇	◇	◇	◇
Ephedrine	◇	□	□	□
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	◇	◇	◇	◇
Propofol	◇	◇	◇	◇
Rocuronium	◇	◇	◇	◇
Sevoflurane	◇	◇	◇	◇
Sufentanil	◇	◇	◇	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Alfentanil	◇	◇	◇	◇
Fentanyl	◇	◇	◇	◇
Morphine	◇	◇	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	◇	◇	◇	◇
Anxiolytics/Hypnotics/ Sedatives	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Diazepam	◇	◇	◇	◇
Midazolam (oral)	◇	◇	◇	◇
Gastrointestinal Agents (anti-emetics)	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Metoclopramide	◇	◇	◇	◇

Table 8: generated via www.hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Lopinavir	Efavirenz	Nevirapine	Tenofovir
Bupivacaine	■	■	■	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	■	■	◇	◇
Ephedrine	◇	◇	◇	■
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	■	■	■	◇
Propofol	■	■	■	◇
Rocuronium	■	■	◇	◇
Sevoflurane	■	◇	◇	◇
Sufentanil	■	■	■	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Alfentanil	■	■	■	◇
Fentanyl	■	■	■	◇
Morphine	■	■	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	■	■	■	◇
Anxiolytics/Hypnotics/ Sedatives	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Diazepam	■	■	■	◇
Midazolam (oral)	●	●	■	◇
Gastrointestinal Agents (anti-emetics)	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Metoclopramide	◇	◇	◇	◇
Ondansetron	■	◇	◇	◇
Steroids	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Dexamethasone	■	■	■	◇

www.hiv-druginteractions.org is a useful website were printable charts of ARV drug interactions can be found allowing ease for the clinician.

ARVS IN THE CRITICALLY ILL [22,23,26]

Patients presenting to the critical care physician may present in 2 different categories:
1] AIDs related opportunistic infections
2] Pathologies unrelated to HIV such as trauma or elective surgery

Concern about administering ARVs in the critically ill is that it may worsen their current clinical condition, due to interactions with other drugs, Immune Reconstitution Syndrome [IRIS] and drug side effects

The pharmacokinetics in the critical care patient are in addition altered, and may lead to sub-therapeutic or supra-therapeutic doses. Most ARVs are available in oral preparations only and need to be crushed and administered via a feeding tube in the ICU patient. Gastro-intestinal absorption may be inconsistent, leading to unpredictable drug levels, creating a risk for drug resistance and toxicity.

Drug-drug interactions are common, with analgesics, antibiotics, antihypertensive, anti-arrhythmic all being implicated.

IRIS occurs after improvement of the immune system with a renewed inflammatory response against new pathogens. It usually occurs in the 1st two weeks after Arv initiation. It may cause a paradoxical and clinical worsening of a condition or unmask a new localized infection.
The critically ill patient is already significantly compromised with poor physiological reserve. In these patients a paradoxical worsening of a condition may have devastating consequences.

There are several mechanisms by which ARVS may improve outcomes in ICU but none have been proven. All evidence for the use of ARVS in ICU is from retrospective studies and expert opinion only. Retrospective chart analysis showed lower mortality in patients receiving HAART.

There are currently no clear guidelines set out for the use of ARV's in ICU. Most of HIV patients coming to ICU will not be on therapy.
Patients previously well and admitted for a non HIV related condition may have therapy postponed.

Patients with long term stays and cd4<200 could potentially benefit from ARVS to prevent other opportunistic infections.
Those with AIDs defining illness should be ideally initiated on ARVS as soon as possible.

Given that the decision to initiate ARV in the critically ill patient is a complex one, each patient should be individualized and the merits and demerits of ARV therapy discussed, before initiating therapy.

CONCLUSION

With advances in antiretroviral therapy, more HIV positive patients are likely to present for elective non HIV related surgery. As we move into the future, we can look forward to exciting developments in ARVs.

The pharmacology and drug interactions can be complex and pose challenging to the anaesthetist. It is therefore important to stay current and continuously update ourselves on newer ARVs and current guidelines available.

To assist the modern day doctor, the South African Department of Health has made all clinical guidelines available freely online……..

And to those who love their apps, the Department has recently announced their new app, HIV Clinical Guide App, sponsored by the openmedicine project.org. It is freely available on Android and Apple devices via App Stores and Google Play.

So happy downloading, and happy learning… together we can contribute to curbing this epidemic.

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No. 18

ARVS FOR THE ANAESTHETIST

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ARVS FOR THE ANAESTHETIST

INTRODUCTION

A PUBMED search for HIV, yields more than 288000 results, yet surprisingly many current day anaesthetists would not be able easily quote the latest ARV guidelines, pleading ignorance, blaming the government and even load shedding for the apparent lack of acknowledge that is freely available.

2014 marked a decade since the Anti-retroviral therapy roll out for South Africa was instituted, with ever changing guidelines and practices, due to better understanding of therapy and greater accessibility to newer drug therapy. The current guidelines have just been released in January 2015.

So where are we a decade later? For the general population at large, this means easier access to ARVs, with HAART being rolled at higher cd4 counts, better screening tools, and fewer opportunistic infections.

For the anaesthetist this has many implications, with the HIV positive population being a dynamic and ever changing one .In the pre and early ARV era, most patients presented to the anaesthetist, with stage 4 disease, for surgery for AIDS related pathology. These patients were ill, and presented confounders for critical care.

Today's HIV population are presenting as "healthy" individuals, for surgery for none HIV related pathologies. Access to ARV therapy has increased life expectancy significantly. The focus of the anaesthetist is shifting from disease related issues, to issues related to ARV – anaesthetic drug interactions, and issues related to side effect profiles.

PREVALENCE

HIV was first discovered in 1981. Today it has reached pandemic proportions. The Southern African sub-region, in particular, is experiencing the most severe epidemics. Statistics according to www.unicef.org[1], reveal that "Nine countries- Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe- have an adult prevalence of over 10%."

As per Statistics SA, "the total number of people living with HIV in South Africa increased from estimated 4.09million in 2002 to 5.51 million in 2014 .An estimated 10.6% of the total population is HIV positive, with approximately one fifth of South African women in their reproductive ages being HIV positive."[2]

Table 1: HIV prevalence estimates & the number of people living with HIV, 2002-2014[2]

YEAR	PREVALENCE				INCIDENCE ADULT 15 - 49	HIV POPULATION (MILLIONS)
	WOMEN 15 - 49	ADULT 15 - 49	YOUTH 15 - 24	TOTAL POPULATION		
2002	16,7	15,8	14,1	9,0	1,64	4,09
2003	16,9	15,9	13,2	9,1	1,64	4,20
2004	17,0	15,9	12,5	9,2	1,69	4,29
2005	17,1	15,9	11,9	9,3	1,73	4,38
2006	17,3	15,9	11,5	9,4	1,69	4,48
2007	17,5	16,0	11,1	9,5	1,59	4,61
2008	17,7	16,2	10,8	9,7	1,47	4,75
2009	17,9	16,3	10,4	9,8	1,36	4,88
2010	18,0	16,5	10,1	9,9	1,29	5,02
2011	18,2	16,6	9,7	10,0	1,25	5,14
2012	18,3	16,6	9,3	10,1	1,16	5,26
2013	18,4	16,7	9,0	10,1	1,14	5,38
2014	18,5	16,8	8,7	10,2	1,11	5,51

COURSE OF HIV INFECTION

HIV is a lentivirus of the retrovirus family.[3] Two enzymes, reverse transcriptase and viral integrase, incorporate the host's DNA into the virus' mRNA, allowing replication of the virus. The host's Cd4 cells are destroyed, which are important to the immune response process, resulting in an immune deficiency state.

The course of HIV is variable.[4] There is a latent period of about 8-12 weeks following infection, during which there may be an intense viraemia. Seroconversion then occurs, with antibodies to HIV appearing in serum. There is also a rapid fall in viraemia, suggesting that the immunological response has controlled the infection. At this stage one third individuals experience brief illness lasting about 2 weeks. Symptoms include fever, malaise, arthralgia, rash and lymphadenopathy. Then follows as asymptomatic phase of 10-11 years before AIDS develops.[5]

STAGING

HIV can be staged clinically using the WHO staging system. Alternatively it can be staged according to cd4 count.

Table 1: WHO Clinical Staging[5]

CLINICAL STAGE	SYMPTOMS
Stage 1	Asymptomatic Lymphadenopathy
Stage 2	Hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular chelitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Parotid enlargement Herpes zoster Chronic upper respiratory tract infections
Stage 3	Malnutrition Persistent diarrhea Persistent fever Persistent oral condiasis Oral hairy leukoplakia Necrotizing ulcerative gingivitis or periodontisis Lymph node tuberculosis Pulmonary tuberculosis Recurrent bacterial pneumonia Lymphoid interstistial pneumonitis Lung disease (such as brochiectasis) Anemia or chronic thrmobocytopaenia
Stage 4	Severe wasting, stunting, or malnutrition Pneumocystis pneumonia Severe bacterial infections Chronic herpes simplex infection Esophageal candidiasis Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis Extrapulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis Disseminated non-tuberculous mycobacterial infection Chronic cryptosporidiosis (with diarrhoed) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

ANTIRETROVIRAL THERAPY

Currently there are at least 28 antiretroviral drugs approved by the FDA, most falling into 8 mechanistic classes.[6] There are numerous treatment regimes, ranging from standard 3 drug regimens to once a day pills.

Table 2: Classification of Antiretrovirals[7]

DRUG CLASS	EXAMPLES
Nucleoside analogue reverse transcriptase inhibitors[NRTIs] **MOA:**Nucleosides are phosphorylated to form nucleotides and are DNA building blocks, by forming 3' to 5' phosphodiester linkage allowing chain elongation NRTIs and NtRTIs are structural analogues of nucleosides and nucleotides and interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase.	Zidovdine [azt] Didanosine[DDI] Lamivudine [3TC] Stavudine [D4T] Emtricitabine [FTC] Abacavir [ABC] Elvucitabine Apricitabine
Nucleotide reverse transcriptase inhibitors [NtRTI] Similar to above, sometimes regarded as a single drug class	Tenofovir [TDF]
Non nucleoside reverse transcriptase inhibitors[NNRTIs] **MOA**: Non competitive binding directly at a pocket of the p66 subunit of HIV reverse transcriptase.	Nevirapine [nvp] Efavirenz [EFV] Delavirdine [DLV] Etravirine
Protease inhibitors [PI] **MOA**: HIV protease cleaves polypeptide chains to form functional viral proteins. PIs inhibit this enzyme resulting in the release of non-infectious viral proteins with a disorganised structure	Indinavir [IDV] Ritonavir [RTV] Saquinavir [SQV] Nelfinavir [NFV] Lopinavir [LPV] Tiprinavir Darunavir Atazanavir
Fusion inhibitors **MOA:** Relatively new class. Bind to gp41 preventing conformational change necessary for fusion and entry into CD4 cells.	Enfuvirtide [T-20]
CCR5 co-receptor antagonists **MOA**: In order to enter cells, HIV must bind to Cd4 receptors and chemokine co-receptors CCR5 and CCR4. Co-receptor antagonists thus prevent entry of HIV into the host cell	Maraviroc Vicriviroc
Integrase inhibitors **MOA**: Integrase inhibitors target viral integrase, preventing the integration of proviral DNA into human chromosomes	Raltegravir Elvitegravir
Maturation inhibitors **MOA:** These prevent conversion of capsid precursor protein [p25] to the mature capsid protein [p24], thus preventing formation of infectious particles and renders the virus incapable of infecting other cells.	Beviramat

PHARMACOKINETICS AND SIDE EFFECTS OF ARVS [7,8]

Most ARVS are administered orally and have good absorption. This may be affected by gastric ph. They are metabolized by cytochrome P450 system, namely CYP3A and CYP2B6.

Lipophilic drugs such as PI's and NNRTI's are oxidatively metabolized by CYP450 to polar forms for excretion via renal or biliary systems. These drugs can be classified as either inhibitors or inducers of CYP450.[7]
NRTI's are water soluble and renally excreted. "They are prodrugs and require intracellular phosphorylation to be activated. Thus drugs that affect phosphorylation will affect these drugs".

ARV side effects can be broadly classified into categories namely:[8]

1) Mitochondrial toxicity: Lactic acidosis, hepatotoxicity, pancreatitis, peripheral neuropathy.
2) Metabolic: Lipodystrophy, hyperglycaemia, body habitus changes, insulin resistance, osteoporosis.
3) Bone marrow suppression: Pancytopenia.
4) Hypersensitivity reactions: Skin rashes

INDIVIDUAL CLASSES

NRTI

Pharmacokinetics: absorbed enterally-30-60% absorption, with AZT being the only IV preparation.
<10% protein bound. Renally excreted except for Abacavir which undergoes hepatic metabolism. Does not induce cytochrome p450.

S/E: mitochondrial toxicity causing lactic acidosis, pancreatitis, and peripheral neuropathy. Abnormal fat deposition
Zidovudine-high incidence of fatigue, headaches and git disturbances.
Tenofovir: renal impairment, decrease in bone mineral density, GIT intolerance

NNRTI:

Pharmacokinetics: enteral preparations only are well absorbed, highly protein bound. Primarily hepatic metabolism and excretion.
NVP lipophilic, crosses placenta and is excreted in breastmilk. Lead to cytochrome P450 enzyme induction and inhibition, depending on drug used

S/E: All NNRTIs: rash including Stevens-Johnsons syndrome,
EFV: Previously thought to have an association with neural tube defects- controversial- "overall rates of birth defects in infants exposed to EFV, NVP and TDF are similar to those in the general population".[9] Currently included in South African guidelines for pregnant patient. Neuropsychiatric side effects common.
NVP: hepatotoxicity

Protease Inhibitors [PIs]

Pharmacokinetics: enteral preparations only, >86% protein bound. Primarily hepatic metabolism. Extensively metabolized by CYP450. PI's are potent inhibitors of CYP3A4. Ritonavir being the exception, is a potent inhibitor of CYP3A4 and CYP2D6, while being an inducer of CYP1A2 and CYP2C9.

Side effects: Hyperlipidaemia, lipodystrophy, hepatotoxicity, GI intolerance, insulin resistance

Fusion inhibitors

Administered subcutaneously with 84% absorption. 92% protein bound. Used in patients with virological failure

S/E: Neutropaenia, risk of hypersensitivity, eosinophilia

Chemokine co-receptor Antagonists

Enteral preparations 76% protein bound. Mainly hepatic metabolism and renal clearance, large VD

S/E: GIT disturbances, cough, abnormalities in liver function tests

Integrase Inhibitors

Enteral preparations, high fat meals slow absorption
Highly protein bound, no dose adjustment needed in renal or hepatic impairment

S/E: Pruritus and rash, headache, abnormalities in amylase and liver function tests

Maturation Inhibitors

Enteral preparations very highly protein bound. Metabolized by glucuronidation, minor renal clearance

S/E: self-limiting GIT disturbances

FDC [Fixed Dose Combination][10]

There are multiple FDCs currently on the market and in development. The pharmacokinetics and side effect profile of these drugs are the same as the individual drugs themselves.

Some of the current FDCs available:

Atripla/Atrozia - efavirenz +tenofovir +FTC
Eviplera/Complera - Rilpivirine +Tenofovir + FTc
Triumeq - Dolutegravir +Abacavir + 3TC
Stribild - Elvitegravir + Cobicistat + Tenofovir + FTC
Truvada - Tenofovir + FTC
Combivir - AZT +3TC

ARVS IN THE PIPELINE

Cd4 attachment inhibitors[11]:
BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into to CD4 T-cells.

The current trial underway for this drug is AI438011 a Phase IIb, randomized, active-controlled trial. "It is investigating the safety, efficacy and dose response of BMS-663068 versus atazanavir/ritonavir (ATV/r) in treatment-experienced (TE), HIV-1-positive subjects."[11]

At week 24 of the trial the results are the following:
"Mean increases in CD4 T-cell counts across the BMS-663068 arms were consistent with ATV/r, regardless of gender, age and baseline CD4 T-cell count indicating efficacy"[11].

Safety profile: "BMS-663068 was generally well tolerated across all arms, with no related serious adverse events leading to discontinuation and no dose-related safety signals. There were no trends for clinical laboratory abnormalities found These results support further studies into the development of BMS663068".

CCR5/CCR2 co-receptor antagonist[12]:
"Cenicriviroc (CVC), is a once-daily, dual CCR5/CCR2 co- receptor antagonist, and has completed Phase 2b development. It blocks HIV entry but does not allow redistribution into cells".[11] Its side effect profile and efficacy has been compared to EFV in clinical trials.

New NNRTI[13]:
"Doravirine (DOR) is an investigational NNRTI (aka MK- 1439) that retains activity against common NNRTI-resistant mutants".[12] The current week 48 results from the clinical trial underway indicate that when combined with TDF/FTC, it had potent antiviral activity, and is generally safe and well tolerated.

New NtRTI[14]
Tenofovir alafenamide [TAF gs7340] is a new prodrug of tenofovir[TDF] .Current ongoing trial show that TAF results in a 7fold greater intracellular levels of TDF at a smaller dose.

Long Acting Injectables[15];
Rilpivirine LA, a monthly injectable and Caboegravir, administered 3monthly are current in clinical trials. These are possibly the drugs of the future, as they will provide convenient treatment options for patients, and assist with adherence and compliance issues.

CHANGES TO THE SOUTH AFRICAN GUIDELINES [16]

South African guidelines have recently been updated in January 2015. The guidelines are frequently revised and it is advisable that the clinician regularly familiarizes himself with the latest guidelines

The latest guidelines have the following changes/additions[16]:

- General changes to adults and adolescents >15yrs:
    - Early initiation of ARVS, on all patients cd4 <500, prioritizing those with cd4<350 irrespective of clinical stage.
    - Initiation of ARVS in Stage 3 and 4 disease, irrespective of cd4 count.
    - HAART for all patients with Hep B co-infection irrespective of cd4 or clinical stage.
    - HAART for all patients with Tb infection irrespective of cd4 or clinical stage.
    - Routine cryptococcal infection screening for all HIV-infected patients with CD4 <100 cells
    - Use of simplified fixed-dose combinations for ART
    - Harmonised ART regimen across populations, mainly pregnant and breastfeeding women, adolescents and adults

- Pregnant patients;
    - Immediate initiation of lifelong HAART for all HIV positive woman who are pregnant or 1yr post-partum regardless of CD4 count.
    - Use of maternal lifelong HAART to reduce MTCT
    - Use of EFV as part of 1st line regimen, regardless of gestation
    - Repeat HIV testing for all negative women, 3monthly during pregnancy, at delivery and at 6weeks

- Children <5yrs:
    - ART for all children under 5yrs, regardless of CD4 count or clinical stage
    - ART for all children between 5yrs-10yrs with a CD4 < 500 regardless of clinical staging.
    - Immediate initiation of ART for infants with 1st positive HIV PCR while awaiting confirmatory tests

Table 3: What to Start: ART 1st line regimen for Adults & adolescents ≥ 15yrs

POPULATION	DRUG	COMMENTS
Adolescents >15 years and weighing >40kg Adults All TB co-infection All HBV co-infection	TDF + 3TC (or FTC) + EFV provide as fixed-dose combination (FDC)	Replace EFV with NVP in patients: • With significant psychiatric comorbidity or intolerance to EFV • Where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. night shift workers
Adults and adolescents on d4T	Change d4T to TDF (No patient must be on d4T)	Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if d4T well tolerated If VL>1000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40kg	ABC + 3TC + EFV	If adolescent weight <40kg, align with paediatric regimen
CONTRAINDICATION	**SUBSTITUTION DRUG**	**COMMENTS**
Contraindication to EFV: • Significant psychiatric co-morbidity • Intolerance to EFV • Impairment of daily function (shift workers)	TDF + FTC (or 3TC) + NVP or LPV/r	IfCD4 <250 females and <400 males, give NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250 females and ≥400 males, use LPV/r 2 tablets 12 hourly
TDF contraindication: Creatinine clearance of <50 mL/min	ABC+ 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides MDR treatment

Table 4: Second-line regimen for late adolescents and adults [16]

SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
First-line virological failure	**Drugs**	**Comments**
Failing on a TDF-based first-line regimen	AZT + 3TC + LPV/r AZT + **TDF** + 3TC + LPV/r (If HBV co-infected)	If non-adherent, address causes of non-adherence If the VL >1000 copies/mL at any point, intensify adherence and repeat viral load in 2months
Failing on a d4T or AZT-based first line regimen	TDF + 3TC (or FTC) + LPV/r	
SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
Anaemia and renal failure	Switch to ABC	

Table 5: First-line ART regimens in pregnant and breastfeeding women[16]

FIRST-LINE ART REGIMENS		
POPULATION	**DRUGS**	**COMMENTS**
1st ANC visit		
All pregnant women not on ART (any gestational age) All breastfeeding women not on ART	TDF + 3TC (or FTC) + EFV Provide as fixed-dose combination (FDC)	If there is a contraindication to the FDC (Contraindication to TDF: renal insufficiency Contraindication to EFV: active psychiatric illness): start AZT immediately and refer to Boxes 2 and 3
Pregnant women currently on ART	Continue current ART regimen Change to FDC if on individual first-line drugs and virally suppressed and no contraindications to FDC	Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done Patients with confirmed 2nd or 3rd line regimen failure should not breastfeed their infants
2nd ANC visit (1 week later)		
Pregnant women Creatinine ≤85µmol/l and any CD4 cell count	Continue FDC	
Creatinine >85 µmol/l TDF contraindicated	Stop FDC, initiate AZT if Hb ≥7g/dl	High-risk pregnancy: refer urgently for alternate triple therapy within 2 weeks, with dose adjustment if indicated, and investigation of renal dysfunction
Contraindication to EFV (active psychiatric illness)	Continue AZT until initiated on individual drugs TDF+3TC+NVP or LPV/r	Refer urgently for alternate triple therapy CD4 <250cells/µl: NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250cells/µl LPV/r 2 tablets 12 hourly
Unbooked and presents in labour and tests HIV positive	sdNVP + sd Truvada and AZT 3-hourly in labour sdNVP + sd Truvada for C/S Start FDC next day regardless of CD4 cell count	Woman qualifies for lifelong ART Do creatinine and CD4 testing. Woman should get results at the 36 days visit
Emergency caesarean section in an unbooked woman with no ART	Same as above	
Post-Partum		
Mother diagnosed with HIV within 1 year post-partum or still breastfeeding beyond 1 year	Lifelong FDC initiated immediately	

Table 6: Guidelines for Children under 15yrs[16]

CHILD	REGIMEN	COMMENT
Children <3 years or older children weighing <10kg	ABC + 3TC + LPV/r	Doses are based on child's weight and need to be adjusted as the child grows
Children 3-10 years and>10kg Adolescents 10-15 years or <40kg	ABC + 3TC + EFV Children who started on ABC/3TC/LPV/r before 3 years must remain on same regimen at 3yr	Do not exceed maximum dosage If adolescents weight <40kg, align treatment with children's regimen
Children on d4T	Change all d4T to ABC	If VL suppressed: change to ABC If VL>1000 copies/ml, manage as treatment failure If VL 50-1000 copies/ml, consult specialist
Children on DDI	Change all DDI to ABC	Change all regardless of VL

SIGNIFICANT REACTIONS WITH DRUGS RELATED TO ANAESTHESIA [17,18,19,20]

Given that many of South African HIV patients will be presenting for anaesthesia it is important to be aware of the drug- drug interactions that may occur.
Drug interactions can be classified into two broad categories:

1] Anaesthetic agents may induce pharmaco-dynamic changes to affect the efficacy and toxicity of ARVs,

2] Pharmacokinetic effects of ARVs can affect the absorption, distribution, metabolism and elimination of anaesthetic drugs.
Some ARVs may not directly interact with anaesthetic drugs themselves, but with drugs commonly seen as adjuncts or prescribed to patients pre-operatively, eg statins.

A] NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS[NNRTI]:

Interactions:
Delavirdine is an inhibitor, while Nevirapine is an inducer of CYP450. Efavirenz may either induce or inhibit the CYP450 system

Opiods; of particular concern, NVP and Efavirenz may cause sub therapeutic levels of Fentanyl and Alfentanil and the dose may need to be increased. There have also been reports of Methadone withdrawal in patients on NVP.

Benzodiazepines: Although there are no published reports, Efavirenz is contraindicated with Midazolam, Triazolam and ergotamine derivatives. Delavirdine is a potent inhibitor of CYP3A4 and may potentiate the effect of benzodiazepines and are thus best avoided.

Anticonvulsants: Carbamazepine, phenobarbital and phenytoin may significantly reduce NNRTI concentrations and should be replaced by other agents such as Valproic acid.

Anticoagulants: Complex reaction between warfarin and NNRTIs, with tendency for anticoagulant effect to be potentiated.

B] Nucleoside and nucleotide reverse transcriptase inhibitors [NRTI]

Not metabolized by CYP450 system, so minimal drug interactions occur.
No documented reactions with anaesthetic agents.
Concern of interactions with Didanosine with antibiotics. It is formulated as enteric coated capsules or buffered powder for oral solutions. The buffer may affect fluroquinolone and ciprofloxacin.
Tenofovir is nephrotoxic and the concurrent use of other nephrotoxic agents should be avoided.

C] PROTEASE INHIBITORS [PI]

Strong Inhibitors of the cyp450. Ritonavir's effect on multiple CYP450 enyzmes, complicates and increases the number of drug interactions, as it may function as both an inhibitor or inducer.

Benzodiazepines: PIs react with midazolam and diazepam by increasing plasma levels, causing prolonged sedation and depression of respiration

Opiates: Methadone
Impairs Fentanyl and Alfentanil metabolism leading to increased levels and respiratory depression.

Thiopentone and Dexamethasone: decrease PI plasma concentrations

Statins: Myopathies and rhabdomyolysis may occur when PIs interact with statins. Due to this risk, lovastatin and simvastatin are contra-indicated.
Ergot derivatives: contraindicated with Efavirenz due to risk of prolonged vasospasm

D] FUSION INHIBITORS

Enfuvirtide is a 36–amino-acid peptide that does not enter human cells.
To date, no significant drug interactions has been found.

E] CCR5 Co-Receptor Antagonists

Maraviroc (MVC) is a substrate of CYP3A enzymes and P-glycoprotein.
MVC does not inhibit or induce the CYP3A system. It is not known to disrupt the pharmacokinetics of other drugs.

Its concentration can be significantly increased when co administered with strong CYP3A inhibitors (eg, ritonavir).Reduced concentration may occur when coadministered with strong CYP3A inducers (eg, efavirenz, rifampin).

F] INTEGRASE INHIBITORS

Dolutegravir is metabolized by UGT1A1 with only 10–15% metabolized by CYP3A4. It neither induces nor inhibits CYP450 or UGT and therefore clinically significant drug interactions are not expected.

G] MATURATION INHIBITORS

No documented dose adjustments needed for sedatives or analgesics. Beviramat is neither an inducer nor inhibitor and drug interactions are not common.

SUMMARY OF COMMON DRUG INTERACTIONS WITH DRUGS ASSOCIATED WITH ANAESTHESIA [19]

The tables below are courtesy of www.Hivdruginteraction.org.

KEY:
These drugs should not be coadministered ---------- /
Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration /
No clinically significant interaction expected /
There are no clear data, actual or theoretical, to indicate whether an interaction will occur /
Data not available n//a

Table 7: generated via www hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Abacavir	Emtricitabine (FTC)	Lamivudine (3TC)	Stavudine (d4T)
Bupivacaine	◇	◇	◇	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	◇	◇	◇	◇
Ephedrine	◇	□	□	□
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	◇	◇	◇	◇
Propofol	◇	◇	◇	◇
Rocuronium	◇	◇	◇	◇
Sevoflurane	◇	◇	◇	◇
Sufentanil	◇	◇	◇	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Alfentanil	◇	◇	◇	◇
Fentanyl	◇	◇	◇	◇
Morphine	◇	◇	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	◇	◇	◇	◇
Anxiolytics/Hypnotics/ Sedatives	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Diazepam	◇	◇	◇	◇
Midazolam (oral)	◇	◇	◇	◇
Gastrointestinal Agents (anti-emetics)	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Metoclopramide	◇	◇	◇	◇

Table 8: generated via www.hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Lopinavir	Efavirenz	Nevirapine	Tenofovir
Bupivacaine	■	■	■	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	■	■	◇	◇
Ephedrine	◇	◇	◇	■
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	■	■	■	◇
Propofol	■	■	■	◇
Rocuronium	■	■	◇	◇
Sevoflurane	■	◇	◇	◇
Sufentanil	■	■	■	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Alfentanil	■	■	■	◇
Fentanyl	■	■	■	◇
Morphine	■	■	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	■	■	■	◇
Anxiolytics/Hypnotics/ Sedatives	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Diazepam	■	■	■	◇
Midazolam (oral)	●	●	■	◇
Gastrointestinal Agents (anti-emetics)	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Metoclopramide	◇	◇	◇	◇
Ondansetron	■	◇	◇	◇
Steroids	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Dexamethasone	■	■	■	◇

www.hiv-druginteractions.org is a useful website were printable charts of ARV drug interactions can be found allowing ease for the clinician.

ARVS IN THE CRITICALLY ILL [22,23,26]

Patients presenting to the critical care physician may present in 2 different categories:
1] AIDs related opportunistic infections
2] Pathologies unrelated to HIV such as trauma or elective surgery

Concern about administering ARVs in the critically ill is that it may worsen their current clinical condition, due to interactions with other drugs, Immune Reconstitution Syndrome [IRIS] and drug side effects

The pharmacokinetics in the critical care patient are in addition altered, and may lead to sub-therapeutic or supra-therapeutic doses. Most ARVs are available in oral preparations only and need to be crushed and administered via a feeding tube in the ICU patient. Gastro-intestinal absorption may be inconsistent, leading to unpredictable drug levels, creating a risk for drug resistance and toxicity.

Drug-drug interactions are common, with analgesics, antibiotics, antihypertensive, anti-arrhythmic all being implicated.

IRIS occurs after improvement of the immune system with a renewed inflammatory response against new pathogens. It usually occurs in the 1st two weeks after Arv initiation. It may cause a paradoxical and clinical worsening of a condition or unmask a new localized infection.
The critically ill patient is already significantly compromised with poor physiological reserve. In these patients a paradoxical worsening of a condition may have devastating consequences.

There are several mechanisms by which ARVS may improve outcomes in ICU but none have been proven. All evidence for the use of ARVS in ICU is from retrospective studies and expert opinion only. Retrospective chart analysis showed lower mortality in patients receiving HAART.

There are currently no clear guidelines set out for the use of ARV's in ICU. Most of HIV patients coming to ICU will not be on therapy.
Patients previously well and admitted for a non HIV related condition may have therapy postponed.

Patients with long term stays and cd4<200 could potentially benefit from ARVS to prevent other opportunistic infections.
Those with AIDs defining illness should be ideally initiated on ARVS as soon as possible.

Given that the decision to initiate ARV in the critically ill patient is a complex one, each patient should be individualized and the merits and demerits of ARV therapy discussed, before initiating therapy.

CONCLUSION

With advances in antiretroviral therapy, more HIV positive patients are likely to present for elective non HIV related surgery. As we move into the future, we can look forward to exciting developments in ARVs.

The pharmacology and drug interactions can be complex and pose challenging to the anaesthetist. It is therefore important to stay current and continuously update ourselves on newer ARVs and current guidelines available.

To assist the modern day doctor, the South African Department of Health has made all clinical guidelines available freely online……..

And to those who love their apps, the Department has recently announced their new app, HIV Clinical Guide App, sponsored by the openmedicine project.org. It is freely available on Android and Apple devices via App Stores and Google Play.

So happy downloading, and happy learning… together we can contribute to curbing this epidemic.

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No. 18

ARVS FOR THE ANAESTHETIST

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ARVS FOR THE ANAESTHETIST

INTRODUCTION

A PUBMED search for HIV, yields more than 288000 results, yet surprisingly many current day anaesthetists would not be able easily quote the latest ARV guidelines, pleading ignorance, blaming the government and even load shedding for the apparent lack of acknowledge that is freely available.

2014 marked a decade since the Anti-retroviral therapy roll out for South Africa was instituted, with ever changing guidelines and practices, due to better understanding of therapy and greater accessibility to newer drug therapy. The current guidelines have just been released in January 2015.

So where are we a decade later? For the general population at large, this means easier access to ARVs, with HAART being rolled at higher cd4 counts, better screening tools, and fewer opportunistic infections.

For the anaesthetist this has many implications, with the HIV positive population being a dynamic and ever changing one .In the pre and early ARV era, most patients presented to the anaesthetist, with stage 4 disease, for surgery for AIDS related pathology. These patients were ill, and presented confounders for critical care.

Today's HIV population are presenting as "healthy" individuals, for surgery for none HIV related pathologies. Access to ARV therapy has increased life expectancy significantly. The focus of the anaesthetist is shifting from disease related issues, to issues related to ARV – anaesthetic drug interactions, and issues related to side effect profiles.

PREVALENCE

HIV was first discovered in 1981. Today it has reached pandemic proportions. The Southern African sub-region, in particular, is experiencing the most severe epidemics. Statistics according to www.unicef.org[1], reveal that "Nine countries- Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe- have an adult prevalence of over 10%."

As per Statistics SA, "the total number of people living with HIV in South Africa increased from estimated 4.09million in 2002 to 5.51 million in 2014 .An estimated 10.6% of the total population is HIV positive, with approximately one fifth of South African women in their reproductive ages being HIV positive."[2]

Table 1: HIV prevalence estimates & the number of people living with HIV, 2002-2014[2]

YEAR	PREVALENCE				INCIDENCE ADULT 15 - 49	HIV POPULATION (MILLIONS)
	WOMEN 15 - 49	ADULT 15 - 49	YOUTH 15 - 24	TOTAL POPULATION		
2002	16,7	15,8	14,1	9,0	1,64	4,09
2003	16,9	15,9	13,2	9,1	1,64	4,20
2004	17,0	15,9	12,5	9,2	1,69	4,29
2005	17,1	15,9	11,9	9,3	1,73	4,38
2006	17,3	15,9	11,5	9,4	1,69	4,48
2007	17,5	16,0	11,1	9,5	1,59	4,61
2008	17,7	16,2	10,8	9,7	1,47	4,75
2009	17,9	16,3	10,4	9,8	1,36	4,88
2010	18,0	16,5	10,1	9,9	1,29	5,02
2011	18,2	16,6	9,7	10,0	1,25	5,14
2012	18,3	16,6	9,3	10,1	1,16	5,26
2013	18,4	16,7	9,0	10,1	1,14	5,38
2014	18,5	16,8	8,7	10,2	1,11	5,51

COURSE OF HIV INFECTION

HIV is a lentivirus of the retrovirus family.[3] Two enzymes, reverse transcriptase and viral integrase, incorporate the host's DNA into the virus' mRNA, allowing replication of the virus. The host's Cd4 cells are destroyed, which are important to the immune response process, resulting in an immune deficiency state.

The course of HIV is variable.[4] There is a latent period of about 8-12 weeks following infection, during which there may be an intense viraemia. Seroconversion then occurs, with antibodies to HIV appearing in serum. There is also a rapid fall in viraemia, suggesting that the immunological response has controlled the infection. At this stage one third individuals experience brief illness lasting about 2 weeks. Symptoms include fever, malaise, arthralgia, rash and lymphadenopathy. Then follows as asymptomatic phase of 10-11 years before AIDS develops.[5]

STAGING

HIV can be staged clinically using the WHO staging system. Alternatively it can be staged according to cd4 count.

Table 1: WHO Clinical Staging[5]

CLINICAL STAGE	SYMPTOMS
Stage 1	Asymptomatic Lymphadenopathy
Stage 2	Hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular chelitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Parotid enlargement Herpes zoster Chronic upper respiratory tract infections
Stage 3	Malnutrition Persistent diarrhea Persistent fever Persistent oral condiasis Oral hairy leukoplakia Necrotizing ulcerative gingivitis or periodontisis Lymph node tuberculosis Pulmonary tuberculosis Recurrent bacterial pneumonia Lymphoid interstistial pneumonitis Lung disease (such as brochiectasis) Anemia or chronic thrmobocytopaenia
Stage 4	Severe wasting, stunting, or malnutrition Pneumocystis pneumonia Severe bacterial infections Chronic herpes simplex infection Esophageal candidiasis Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis Extrapulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis Disseminated non-tuberculous mycobacterial infection Chronic cryptosporidiosis (with diarrhoed) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

ANTIRETROVIRAL THERAPY

Currently there are at least 28 antiretroviral drugs approved by the FDA, most falling into 8 mechanistic classes.[6] There are numerous treatment regimes, ranging from standard 3 drug regimens to once a day pills.

Table 2: Classification of Antiretrovirals[7]

DRUG CLASS	EXAMPLES
Nucleoside analogue reverse transcriptase inhibitors[NRTIs] **MOA:**Nucleosides are phosphorylated to form nucleotides and are DNA building blocks, by forming 3' to 5' phosphodiester linkage allowing chain elongation NRTIs and NtRTIs are structural analogues of nucleosides and nucleotides and interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase.	Zidovdine [azt] Didanosine[DDI] Lamivudine [3TC] Stavudine [D4T] Emtricitabine [FTC] Abacavir [ABC] Elvucitabine Apricitabine
Nucleotide reverse transcriptase inhibitors [NtRTI] Similar to above, sometimes regarded as a single drug class	Tenofovir [TDF]
Non nucleoside reverse transcriptase inhibitors[NNRTIs] **MOA**: Non competitive binding directly at a pocket of the p66 subunit of HIV reverse transcriptase.	Nevirapine [nvp] Efavirenz [EFV] Delavirdine [DLV] Etravirine
Protease inhibitors [PI] **MOA**: HIV protease cleaves polypeptide chains to form functional viral proteins. PIs inhibit this enzyme resulting in the release of non-infectious viral proteins with a disorganised structure	Indinavir [IDV] Ritonavir [RTV] Saquinavir [SQV] Nelfinavir [NFV] Lopinavir [LPV] Tiprinavir Darunavir Atazanavir
Fusion inhibitors **MOA:** Relatively new class. Bind to gp41 preventing conformational change necessary for fusion and entry into CD4 cells.	Enfuvirtide [T-20]
CCR5 co-receptor antagonists **MOA**: In order to enter cells, HIV must bind to Cd4 receptors and chemokine co-receptors CCR5 and CCR4. Co-receptor antagonists thus prevent entry of HIV into the host cell	Maraviroc Vicriviroc
Integrase inhibitors **MOA**: Integrase inhibitors target viral integrase, preventing the integration of proviral DNA into human chromosomes	Raltegravir Elvitegravir
Maturation inhibitors **MOA:** These prevent conversion of capsid precursor protein [p25] to the mature capsid protein [p24], thus preventing formation of infectious particles and renders the virus incapable of infecting other cells.	Beviramat

PHARMACOKINETICS AND SIDE EFFECTS OF ARVS [7,8]

Most ARVS are administered orally and have good absorption. This may be affected by gastric ph. They are metabolized by cytochrome P450 system, namely CYP3A and CYP2B6.

Lipophilic drugs such as PI's and NNRTI's are oxidatively metabolized by CYP450 to polar forms for excretion via renal or biliary systems. These drugs can be classified as either inhibitors or inducers of CYP450.[7]
NRTI's are water soluble and renally excreted. "They are prodrugs and require intracellular phosphorylation to be activated. Thus drugs that affect phosphorylation will affect these drugs".

ARV side effects can be broadly classified into categories namely:[8]

1) Mitochondrial toxicity: Lactic acidosis, hepatotoxicity, pancreatitis, peripheral neuropathy.
2) Metabolic: Lipodystrophy, hyperglycaemia, body habitus changes, insulin resistance, osteoporosis.
3) Bone marrow suppression: Pancytopenia.
4) Hypersensitivity reactions: Skin rashes

INDIVIDUAL CLASSES

NRTI

Pharmacokinetics: absorbed enterally-30-60% absorption, with AZT being the only IV preparation.
<10% protein bound. Renally excreted except for Abacavir which undergoes hepatic metabolism. Does not induce cytochrome p450.

S/E: mitochondrial toxicity causing lactic acidosis, pancreatitis, and peripheral neuropathy. Abnormal fat deposition
Zidovudine-high incidence of fatigue, headaches and git disturbances.
Tenofovir: renal impairment, decrease in bone mineral density, GIT intolerance

NNRTI:

Pharmacokinetics: enteral preparations only are well absorbed, highly protein bound. Primarily hepatic metabolism and excretion.
NVP lipophilic, crosses placenta and is excreted in breastmilk. Lead to cytochrome P450 enzyme induction and inhibition, depending on drug used

S/E: All NNRTIs: rash including Stevens-Johnsons syndrome,
EFV: Previously thought to have an association with neural tube defects- controversial- "overall rates of birth defects in infants exposed to EFV, NVP and TDF are similar to those in the general population".[9] Currently included in South African guidelines for pregnant patient. Neuropsychiatric side effects common.
NVP: hepatotoxicity

Protease Inhibitors [PIs]

Pharmacokinetics: enteral preparations only, >86% protein bound. Primarily hepatic metabolism. Extensively metabolized by CYP450. PI's are potent inhibitors of CYP3A4. Ritonavir being the exception, is a potent inhibitor of CYP3A4 and CYP2D6, while being an inducer of CYP1A2 and CYP2C9.

Side effects: Hyperlipidaemia, lipodystrophy, hepatotoxicity, GI intolerance, insulin resistance

Fusion inhibitors

Administered subcutaneously with 84% absorption. 92% protein bound. Used in patients with virological failure

S/E: Neutropaenia, risk of hypersensitivity, eosinophilia

Chemokine co-receptor Antagonists

Enteral preparations 76% protein bound. Mainly hepatic metabolism and renal clearance, large VD

S/E: GIT disturbances, cough, abnormalities in liver function tests

Integrase Inhibitors

Enteral preparations, high fat meals slow absorption
Highly protein bound, no dose adjustment needed in renal or hepatic impairment

S/E: Pruritus and rash, headache, abnormalities in amylase and liver function tests

Maturation Inhibitors

Enteral preparations very highly protein bound. Metabolized by glucuronidation, minor renal clearance

S/E: self-limiting GIT disturbances

FDC [Fixed Dose Combination][10]

There are multiple FDCs currently on the market and in development. The pharmacokinetics and side effect profile of these drugs are the same as the individual drugs themselves.

Some of the current FDCs available:

Atripla/Atrozia - efavirenz +tenofovir +FTC
Eviplera/Complera - Rilpivirine +Tenofovir + FTc
Triumeq - Dolutegravir +Abacavir + 3TC
Stribild - Elvitegravir + Cobicistat + Tenofovir + FTC
Truvada - Tenofovir + FTC
Combivir - AZT +3TC

ARVS IN THE PIPELINE

Cd4 attachment inhibitors[11]:
BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into to CD4 T-cells.

The current trial underway for this drug is AI438011 a Phase IIb, randomized, active-controlled trial. "It is investigating the safety, efficacy and dose response of BMS-663068 versus atazanavir/ritonavir (ATV/r) in treatment-experienced (TE), HIV-1-positive subjects."[11]

At week 24 of the trial the results are the following:
"Mean increases in CD4 T-cell counts across the BMS-663068 arms were consistent with ATV/r, regardless of gender, age and baseline CD4 T-cell count indicating efficacy"[11].

Safety profile: "BMS-663068 was generally well tolerated across all arms, with no related serious adverse events leading to discontinuation and no dose-related safety signals. There were no trends for clinical laboratory abnormalities found These results support further studies into the development of BMS663068".

CCR5/CCR2 co-receptor antagonist[12]:
"Cenicriviroc (CVC), is a once-daily, dual CCR5/CCR2 co- receptor antagonist, and has completed Phase 2b development. It blocks HIV entry but does not allow redistribution into cells".[11] Its side effect profile and efficacy has been compared to EFV in clinical trials.

New NNRTI[13]:
"Doravirine (DOR) is an investigational NNRTI (aka MK- 1439) that retains activity against common NNRTI-resistant mutants".[12] The current week 48 results from the clinical trial underway indicate that when combined with TDF/FTC, it had potent antiviral activity, and is generally safe and well tolerated.

New NtRTI[14]
Tenofovir alafenamide [TAF gs7340] is a new prodrug of tenofovir[TDF] .Current ongoing trial show that TAF results in a 7fold greater intracellular levels of TDF at a smaller dose.

Long Acting Injectables[15];
Rilpivirine LA, a monthly injectable and Caboegravir, administered 3monthly are current in clinical trials. These are possibly the drugs of the future, as they will provide convenient treatment options for patients, and assist with adherence and compliance issues.

CHANGES TO THE SOUTH AFRICAN GUIDELINES [16]

South African guidelines have recently been updated in January 2015. The guidelines are frequently revised and it is advisable that the clinician regularly familiarizes himself with the latest guidelines

The latest guidelines have the following changes/additions[16]:

- General changes to adults and adolescents >15yrs:
    - Early initiation of ARVS, on all patients cd4 <500, prioritizing those with cd4<350 irrespective of clinical stage.
    - Initiation of ARVS in Stage 3 and 4 disease, irrespective of cd4 count.
    - HAART for all patients with Hep B co-infection irrespective of cd4 or clinical stage.
    - HAART for all patients with Tb infection irrespective of cd4 or clinical stage.
    - Routine cryptococcal infection screening for all HIV-infected patients with CD4 <100 cells
    - Use of simplified fixed-dose combinations for ART
    - Harmonised ART regimen across populations, mainly pregnant and breastfeeding women, adolescents and adults

- Pregnant patients;
    - Immediate initiation of lifelong HAART for all HIV positive woman who are pregnant or 1yr post-partum regardless of CD4 count.
    - Use of maternal lifelong HAART to reduce MTCT
    - Use of EFV as part of 1st line regimen, regardless of gestation
    - Repeat HIV testing for all negative women, 3monthly during pregnancy, at delivery and at 6weeks

- Children <5yrs:
    - ART for all children under 5yrs, regardless of CD4 count or clinical stage
    - ART for all children between 5yrs-10yrs with a CD4 < 500 regardless of clinical staging.
    - Immediate initiation of ART for infants with 1st positive HIV PCR while awaiting confirmatory tests

Table 3: What to Start: ART 1st line regimen for Adults & adolescents ≥ 15yrs

POPULATION	DRUG	COMMENTS
Adolescents >15 years and weighing >40kg Adults All TB co-infection All HBV co-infection	TDF + 3TC (or FTC) + EFV provide as fixed-dose combination (FDC)	Replace EFV with NVP in patients: • With significant psychiatric comorbidity or intolerance to EFV • Where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. night shift workers
Adults and adolescents on d4T	Change d4T to TDF (No patient must be on d4T)	Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if d4T well tolerated If VL>1000 copies/mL, manage as treatment failure and consider switching to second line
Adolescents <15 years or weight <40kg	ABC + 3TC + EFV	If adolescent weight <40kg, align with paediatric regimen
CONTRAINDICATION	**SUBSTITUTION DRUG**	**COMMENTS**
Contraindication to EFV: • Significant psychiatric co-morbidity • Intolerance to EFV • Impairment of daily function (shift workers)	TDF + FTC (or 3TC) + NVP or LPV/r	IfCD4 <250 females and <400 males, give NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250 females and ≥400 males, use LPV/r 2 tablets 12 hourly
TDF contraindication: Creatinine clearance of <50 mL/min	ABC+ 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides MDR treatment

Table 4: Second-line regimen for late adolescents and adults [16]

SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
First-line virological failure	**Drugs**	**Comments**
Failing on a TDF-based first-line regimen	AZT + 3TC + LPV/r AZT + **TDF** + 3TC + LPV/r (If HBV co-infected)	If non-adherent, address causes of non-adherence If the VL >1000 copies/mL at any point, intensify adherence and repeat viral load in 2months
Failing on a d4T or AZT-based first line regimen	TDF + 3TC (or FTC) + LPV/r	
SECOND-LINE REGIMEN: ADOLESCENTS ≥15 YEARS AND ADULTS		
Anaemia and renal failure	Switch to ABC	

Table 5: First-line ART regimens in pregnant and breastfeeding women[16]

FIRST-LINE ART REGIMENS		
POPULATION	**DRUGS**	**COMMENTS**
1st ANC visit		
All pregnant women not on ART (any gestational age) All breastfeeding women not on ART	TDF + 3TC (or FTC) + EFV Provide as fixed-dose combination (FDC)	If there is a contraindication to the FDC (Contraindication to TDF: renal insufficiency Contraindication to EFV: active psychiatric illness): start AZT immediately and refer to Boxes 2 and 3
Pregnant women currently on ART	Continue current ART regimen Change to FDC if on individual first-line drugs and virally suppressed and no contraindications to FDC	Check a VL as soon as pregnancy diagnosed, regardless of when the last VL was done Patients with confirmed 2nd or 3rd line regimen failure should not breastfeed their infants
2nd ANC visit (1 week later)		
Pregnant women Creatinine ≤85µmol/l and any CD4 cell count	Continue FDC	
Creatinine >85 µmol/l TDF contraindicated	Stop FDC, initiate AZT if Hb ≥7g/dl	High-risk pregnancy: refer urgently for alternate triple therapy within 2 weeks, with dose adjustment if indicated, and investigation of renal dysfunction
Contraindication to EFV (active psychiatric illness)	Continue AZT until initiated on individual drugs TDF+3TC+NVP or LPV/r	Refer urgently for alternate triple therapy CD4 <250cells/µl: NVP 200mg daily for 2 weeks, then 200mg BD CD4 ≥250cells/µl LPV/r 2 tablets 12 hourly
Unbooked and presents in labour and tests HIV positive	sdNVP + sd Truvada and AZT 3-hourly in labour sdNVP + sd Truvada for C/S Start FDC next day regardless of CD4 cell count	Woman qualifies for lifelong ART Do creatinine and CD4 testing. Woman should get results at the 36 days visit
Emergency caesarean section in an unbooked woman with no ART	Same as above	
Post-Partum		
Mother diagnosed with HIV within 1 year post-partum or still breastfeeding beyond 1 year	Lifelong FDC initiated immediately	

Table 6: Guidelines for Children under 15yrs[16]

CHILD	REGIMEN	COMMENT
Children <3 years or older children weighing <10kg	ABC + 3TC + LPV/r	Doses are based on child's weight and need to be adjusted as the child grows
Children 3-10 years and>10kg Adolescents 10-15 years or <40kg	ABC + 3TC + EFV Children who started on ABC/3TC/LPV/r before 3 years must remain on same regimen at 3yr	Do not exceed maximum dosage If adolescents weight <40kg, align treatment with children's regimen
Children on d4T	Change all d4T to ABC	If VL suppressed: change to ABC If VL>1000 copies/ml, manage as treatment failure If VL 50-1000 copies/ml, consult specialist
Children on DDI	Change all DDI to ABC	Change all regardless of VL

SIGNIFICANT REACTIONS WITH DRUGS RELATED TO ANAESTHESIA [17,18,19,20]

Given that many of South African HIV patients will be presenting for anaesthesia it is important to be aware of the drug- drug interactions that may occur.
Drug interactions can be classified into two broad categories:

1] Anaesthetic agents may induce pharmaco-dynamic changes to affect the efficacy and toxicity of ARVs,

2] Pharmacokinetic effects of ARVs can affect the absorption, distribution, metabolism and elimination of anaesthetic drugs.
Some ARVs may not directly interact with anaesthetic drugs themselves, but with drugs commonly seen as adjuncts or prescribed to patients pre-operatively, eg statins.

A] NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS[NNRTI]:

Interactions:
Delavirdine is an inhibitor, while Nevirapine is an inducer of CYP450. Efavirenz may either induce or inhibit the CYP450 system

Opiods; of particular concern, NVP and Efavirenz may cause sub therapeutic levels of Fentanyl and Alfentanil and the dose may need to be increased. There have also been reports of Methadone withdrawal in patients on NVP.

Benzodiazepines: Although there are no published reports, Efavirenz is contraindicated with Midazolam, Triazolam and ergotamine derivatives. Delavirdine is a potent inhibitor of CYP3A4 and may potentiate the effect of benzodiazepines and are thus best avoided.

Anticonvulsants: Carbamazepine, phenobarbital and phenytoin may significantly reduce NNRTI concentrations and should be replaced by other agents such as Valproic acid.

Anticoagulants: Complex reaction between warfarin and NNRTIs, with tendency for anticoagulant effect to be potentiated.

B] Nucleoside and nucleotide reverse transcriptase inhibitors [NRTI]

Not metabolized by CYP450 system, so minimal drug interactions occur.
No documented reactions with anaesthetic agents.
Concern of interactions with Didanosine with antibiotics. It is formulated as enteric coated capsules or buffered powder for oral solutions. The buffer may affect fluroquinolone and ciprofloxacin.
Tenofovir is nephrotoxic and the concurrent use of other nephrotoxic agents should be avoided.

C] PROTEASE INHIBITORS [PI]

Strong Inhibitors of the cyp450. Ritonavir's effect on multiple CYP450 enyzmes, complicates and increases the number of drug interactions, as it may function as both an inhibitor or inducer.

Benzodiazepines: PIs react with midazolam and diazepam by increasing plasma levels, causing prolonged sedation and depression of respiration

Opiates: Methadone
Impairs Fentanyl and Alfentanil metabolism leading to increased levels and respiratory depression.

Thiopentone and Dexamethasone: decrease PI plasma concentrations

Statins: Myopathies and rhabdomyolysis may occur when PIs interact with statins. Due to this risk, lovastatin and simvastatin are contra-indicated.
Ergot derivatives: contraindicated with Efavirenz due to risk of prolonged vasospasm

D] FUSION INHIBITORS

Enfuvirtide is a 36–amino-acid peptide that does not enter human cells.
To date, no significant drug interactions has been found.

E] CCR5 Co-Receptor Antagonists

Maraviroc (MVC) is a substrate of CYP3A enzymes and P-glycoprotein.
MVC does not inhibit or induce the CYP3A system. It is not known to disrupt the pharmacokinetics of other drugs.

Its concentration can be significantly increased when co administered with strong CYP3A inhibitors (eg, ritonavir).Reduced concentration may occur when coadministered with strong CYP3A inducers (eg, efavirenz, rifampin).

F] INTEGRASE INHIBITORS

Dolutegravir is metabolized by UGT1A1 with only 10–15% metabolized by CYP3A4. It neither induces nor inhibits CYP450 or UGT and therefore clinically significant drug interactions are not expected.

G] MATURATION INHIBITORS

No documented dose adjustments needed for sedatives or analgesics. Beviramat is neither an inducer nor inhibitor and drug interactions are not common.

SUMMARY OF COMMON DRUG INTERACTIONS WITH DRUGS ASSOCIATED WITH ANAESTHESIA [19]

The tables below are courtesy of www.Hivdruginteraction.org.

KEY:
These drugs should not be coadministered ---------- /
Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration /
No clinically significant interaction expected /
There are no clear data, actual or theoretical, to indicate whether an interaction will occur /
Data not available n//a

Table 7: generated via www hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Abacavir	Emtricitabine (FTC)	Lamivudine (3TC)	Stavudine (d4T)
Bupivacaine	◇	◇	◇	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	◇	◇	◇	◇
Ephedrine	◇	□	□	□
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	◇	◇	◇	◇
Propofol	◇	◇	◇	◇
Rocuronium	◇	◇	◇	◇
Sevoflurane	◇	◇	◇	◇
Sufentanil	◇	◇	◇	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Alfentanil	◇	◇	◇	◇
Fentanyl	◇	◇	◇	◇
Morphine	◇	◇	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	◇	◇	◇	◇
Anxiolytics/Hypnotics/ Sedatives	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Diazepam	◇	◇	◇	◇
Midazolam (oral)	◇	◇	◇	◇
Gastrointestinal Agents (anti-emetics)	**Abacavir**	**Emtricitabine (FTC)**	**Lamivudine (3TC)**	**Stavudine (d4T)**
Metoclopramide	◇	◇	◇	◇

Table 8: generated via www.hiv-druginteractions.org

Anaesthetics and Muscle Relaxants	Lopinavir	Efavirenz	Nevirapine	Tenofovir
Bupivacaine	■	■	■	◇
Cisatracurium	◇	◇	◇	◇
Desflurane	◇	◇	◇	◇
Dexmedetomidine	■	■	◇	◇
Ephedrine	◇	◇	◇	■
Halothane	◇	◇	◇	◇
Isoflurane	◇	◇	◇	◇
Ketamine	■	■	■	◇
Propofol	■	■	■	◇
Rocuronium	■	■	◇	◇
Sevoflurane	■	◇	◇	◇
Sufentanil	■	■	■	◇
Suxamethonium (Succinylcholine)	◇	◇	◇	◇
Thiopental	◇	◇	◇	◇
Analgesics	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Alfentanil	■	■	■	◇
Fentanyl	■	■	■	◇
Morphine	■	■	◇	◇
Paracetamol (Acetaminophen)	◇	◇	◇	◇
Pethidine (Meperidine)	■	■	■	◇
Anxiolytics/Hypnotics/ Sedatives	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Diazepam	■	■	■	◇
Midazolam (oral)	●	●	■	◇
Gastrointestinal Agents (anti-emetics)	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Metoclopramide	◇	◇	◇	◇
Ondansetron	■	◇	◇	◇
Steroids	**Lopinavir**	**Efavirenz**	**Nevirapine**	**Tenofovir**
Dexamethasone	■	■	■	◇

www.hiv-druginteractions.org is a useful website were printable charts of ARV drug interactions can be found allowing ease for the clinician.

ARVS IN THE CRITICALLY ILL [22,23,26]

Patients presenting to the critical care physician may present in 2 different categories:
1] AIDs related opportunistic infections
2] Pathologies unrelated to HIV such as trauma or elective surgery

Concern about administering ARVs in the critically ill is that it may worsen their current clinical condition, due to interactions with other drugs, Immune Reconstitution Syndrome [IRIS] and drug side effects

The pharmacokinetics in the critical care patient are in addition altered, and may lead to sub-therapeutic or supra-therapeutic doses. Most ARVs are available in oral preparations only and need to be crushed and administered via a feeding tube in the ICU patient. Gastro-intestinal absorption may be inconsistent, leading to unpredictable drug levels, creating a risk for drug resistance and toxicity.

Drug-drug interactions are common, with analgesics, antibiotics, antihypertensive, anti-arrhythmic all being implicated.

IRIS occurs after improvement of the immune system with a renewed inflammatory response against new pathogens. It usually occurs in the 1st two weeks after Arv initiation. It may cause a paradoxical and clinical worsening of a condition or unmask a new localized infection.
The critically ill patient is already significantly compromised with poor physiological reserve. In these patients a paradoxical worsening of a condition may have devastating consequences.

There are several mechanisms by which ARVS may improve outcomes in ICU but none have been proven. All evidence for the use of ARVS in ICU is from retrospective studies and expert opinion only. Retrospective chart analysis showed lower mortality in patients receiving HAART.

There are currently no clear guidelines set out for the use of ARV's in ICU. Most of HIV patients coming to ICU will not be on therapy.
Patients previously well and admitted for a non HIV related condition may have therapy postponed.

Patients with long term stays and cd4<200 could potentially benefit from ARVS to prevent other opportunistic infections.
Those with AIDs defining illness should be ideally initiated on ARVS as soon as possible.

Given that the decision to initiate ARV in the critically ill patient is a complex one, each patient should be individualized and the merits and demerits of ARV therapy discussed, before initiating therapy.

CONCLUSION

With advances in antiretroviral therapy, more HIV positive patients are likely to present for elective non HIV related surgery. As we move into the future, we can look forward to exciting developments in ARVs.

The pharmacology and drug interactions can be complex and pose challenging to the anaesthetist. It is therefore important to stay current and continuously update ourselves on newer ARVs and current guidelines available.

To assist the modern day doctor, the South African Department of Health has made all clinical guidelines available freely online……..

And to those who love their apps, the Department has recently announced their new app, HIV Clinical Guide App, sponsored by the openmedicine project.org. It is freely available on Android and Apple devices via App Stores and Google Play.

So happy downloading, and happy learning… together we can contribute to curbing this epidemic.

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