UNAIDS estimated that, at the end of 2009, there were 33.4 million people worldwide who were living with HIV or AIDS, with an estimated 5.6 million of these people in South Africa. Although South Africa has the largest antiretroviral programme in the world, it also has the highest incidence of infected patients and access to treatment is low. At the end of 2009, only 37% of those infected with the virus in South Africa were receiving treatment for HIV according to the latest WHO guidelines.1

Since the start of the epidemic in sub-Saharan Africa, the in-hospital occupancy of HIV-positive patients has risen from 6% in 1990 to 43% in 2005. These admissions have resulted in longer hospital stays with more intensive medical care.2

The pathologies related to ICU admissions can be divided into three categories:
1) AIDS-related opportunistic infections (such as Pneumocystis jirovecii pneumonia, PCP)
2) Factors related to the long-term survival of HIV, or the use of antiretroviral therapy (cardiac disease, hypersensitivity syndromes and mitochondrial dysfunction).
3) Pathologies with no link to HIV (trauma and elective surgery).

Respiratory disease remains the leading cause of ICU admission despite the introduction of antiretroviral therapy.3

Eligibility for treatment

According to the South African guidelines for adults and adolescents,4 the following patients are eligible for antiretrovirals:

- CD4 <200 cells/µl irrespective of clinical stage.
- CD4 <350 cells/µl in patients with tuberculosis or pregnant women.
- WHO stage IV regardless of the CD4 count.
- Multi-drug resistant tuberculosis (MDR) or extensively drug resistant tuberculosis (XDR).

Full WHO guidelines:
- Patients with CD4 count <350 cells/µl.
- All patients with tuberculosis.
- WHO stage IV.

There is increasing evidence that earlier initiation of antiretrovirals within weeks of treatment of an opportunistic infection is beneficial.5 The SAPIT trial suggests that initiation of antiretrovirals should commence within two to four weeks of commencement of tuberculosis treatment in patients with CD4 count < 200 cells/µl.6 These studies were done in moderately ill patients. There are currently no trials in critically ill patients.

The only evidence available for the use of antiretrovirals in ICU is from retrospective studies. In a retrospective review of 58 patients in San Francisco admitted with PCP between 1996 and 2001, six were receiving antiretroviral therapy and continued, and six were initiated on highly active antiretroviral therapy (HAART). The mortality was lower (25% vs. 63%) for patients receiving antiretroviral therapy. These patients had the same severity of illness and baseline characteristics.3,7

Another retrospective review of 278 HIV-positive patients admitted to ICU at the Universidade de Sao Paulo, Brazil between 1996-2006, aimed to determine what factors were associated with ICU and six-month survival. The use of HAART in ICU in
these patients was shown to be a negative predictor of mortality, especially if administered within four days of admission.8

There are several mechanisms by which HAART may improve outcomes in ICU, but none of these have been proven. The activation of CD4 cells by an acute infectious illness may increase HIV viraemia by stimulating replication of the HIV virus in blood and tissue. Pro-inflammatory cytokines, such as TNF-α, increase binding of NF-κB to the HIV long-terminal repeat region and enhance HIV replication.9 In addition, there is an acute drop in CD4 count in critically ill patients.10 HAART may also decrease the incidence of opportunistic infections.5,7

There is a concern that the administration of antiretrovirals in critically ill patients may worsen their clinical condition through drug interactions, toxic side-effects and immune reconstitution inflammatory syndrome (iIRIS). In addition, the altered pharmacokinetics in critically ill patients may result in subtherapeutic or supratherapeutic drug levels, putting patients at risk for the development of drug resistance and drug toxicity respectively.

Potential problems with introduction of antiretrovirals in ICU administration

- Most of the drugs are only available for oral administration as tablets and capsules.2,7,11 Enfurvitide, an entry inhibitor, is administered subcutaneously, it is very expensive, and there are no reports of its use in ICU. There is a parenteral form of zidovudine. Tablets can be crushed, and capsules opened and administered via a feeding tube. Oral feeding is sometimes contraindicated in critically ill patients making antiretroviral administration impossible.

- Gastrointestinal absorption in critically ill patients is often inconsistent, leading to unpredictable drug levels, and tests to measure levels of antiretroviral drugs are not freely available. Such inconsistencies in the administration of drugs make the development of drug resistance in this setting a possibility. Some antiretrovirals require the interruption of enteral feeds for optimal absorption, while others should be taken with food. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) have a longer half-life than other antiretrovirals, and the discontinuation of a treatment schedule involving an NNRTI may result in the development of drug resistance due to “monotherapy”.2,7,11

- All nucleoside reverse transcriptase inhibitors (NRTIs) (with the exception of abacavir) need to be dose adjusted in renal failure, and all the NNRTIs and protease inhibitors will require dose adjustment in hepatic failure.2,7

Drug interactions

Drug interactions are common with antiretroviral medication. All protease inhibitors inhibit the cytochrome P450 system, and efavirenz is a mixed enzyme inducer and enzyme inhibitor.11 The effects of benzodiazepines, amiodarone, calcium-channel blockers, methadone and sildanefil, may be greatly enhanced in the presence of these antiretroviral drugs. Similarly, macrolides, azaoles and rifamycins are also cytochrome P450 enzyme inducers and may result in subtherapeutic drug concentrations, increasing the potential for drug resistance.

Side-effects

Mitochondrial dysfunction

Mitochondrial dysfunction can occur with the use of any NRTI. In addition to reverse transcriptase, the nucleoside analogues have a high affinity for human DNA polymerase-β (DNA repair) and mitochondrial DNA polymerase-β. The impairment of oxidative phosphorylation, due to the inhibition of DNA polymerase-β, causes pyruvate to be shifted to lactate production, preventing ATP production, beta-oxidation of fatty acids and removal of free radicals resulting in oxidative stress. Triglycerides accumulate in the liver, causing hepatic steatosis and decreasing lactic acid clearance.12

Different cell types have different oxidative phosphorylation thresholds below which cellular dysfunction occurs, and each drug has a different affinity for DNA polymerase. Consequently, certain NRTIs are more likely to cause mitochondrial dysfunction. In addition, certain drugs target certain organs, depending on the concentrations of thymidine kinase which phosphorylate NRTIs.

Clinical presentation depends on the target organ involved.

- Lactic acidosis usually occurs after patients have been on an NRTI for six months, but has been described as early as two months on treatment, although this is very unusual. Severe cases carry a 30-60% mortality. There are many additional causes of lactic acidosis in critically ill patients and it may be difficult to determine whether the lactic acidosis is NRTI-induced. If antiretroviral-induced lactic acidosis...
is being considered as a diagnosis, the NRTI must be stopped and supportive care initiated. The most common antiretrovirals implicated are didanosine and stavudine.\(^{11,12}\)

- **Proximal myopathy, with the use of zidovudine.** The myopathy is associated with an elevated creatinine phosphokinase and, in rare cases, an elevated lactate.\(^{12}\)

- **Peripheral neuropathy, which is usually sensory, and commonly caused by stavudine and didanosine.**\(^{12}\) Weakness caused by the proximal myopathy and peripheral neuropathy may be compounded in a critically ill patient by the use of steroids and muscle relaxants.

- **Pancreatitis is uncommon, and is usually accompanied by lactic acidosis.** Stavudine and didanosine are the culprit drugs.\(^{12}\)

- **Bone marrow suppression associated with zidovudine.** This is usually only an issue in the first few months of treatment.\(^{12}\)

- **Hepatic steatosis and hepatic failure has been reported in patients using stavudine, zidovudine, didanosine, and the protease inhibitors as a consequence of triglyceride accumulation in the liver.**\(^{12}\)

### Hypersensitivity reactions

Abacavir and nevirapine can both cause severe hypersensitivity reactions.\(^{2,7}\) Complications to abacavir are commonly seen after 10-14 days of treatment. The patient presents with a fever, rash, nausea and vomiting. This may progress to hypotension, an acute interstitial pneumonia with respiratory failure, hepatic necrosis with liver failure, and toxic epidermal necrolysis. Patients develop a severe anaphylactic reaction to rechallenge. The drug should be stopped and supportive care initiated.

Nevirapine toxicity was initially thought to occur in patients at higher CD4 counts, but is now thought to occur at any immunological level. It can also cause a severe hypersensitivity reaction, fulminant hepatic necrosis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Rechallenge with the drug is contraindicated.

### Liver toxicity

Liver toxicity has been described with saquinavir, ritonavir, tenofovir and efavirenz. If a tenofovir-based regimen is stopped in a patient with hepatitis B, acute flare of hepatitis is possible, as tenofovir is a potent suppressor of hepatitis B, and should be interrupted only in the most severe circumstances. Fatal cases of these interruption flares have been described.\(^{13}\)

### Renal toxicity

Cases of acute tubular necrosis resulting in end-stage renal failure have been described with the use of tenofovir, although almost all the NRTIs have been associated with decreases in creatinine clearance. The use of tenofovir is contra-indicated in patients with renal failure, and caution should be used in patients with decreased creatinine clearance.\(^{14}\) NRTIs should be appropriately dose-adjusted. There have been reports of interstitial nephritis in patients with the use of ritonavir and indinavir.

### Immune reconstitution inflammatory syndrome

IRIS results from an improvement in the immune system with a renewed inflammatory response against new pathogens. There are two types. Paradoxical IRIS is the clinical worsening of a condition after the initiation of antiretrovirals. Unmasking IRIS is a new localised infection in a patient who has been adequately screened for opportunistic infections before the initiation of treatment. The incidence is 10-15% for all causes, with an incidence of 7-40% in patients with tuberculosis.

IRIS commonly manifests between two weeks to six months after the initiation of antiretrovirals, but may occur after several years. However, the most common presentations occur in the first two months of therapy and can be dramatic. The implicated infectious pathogen depends on the underlying opportunistic infection burden. In critically ill patients whose physiological reserve is already significantly compromised, paradoxical worsening of a condition may have devastating consequences. In a patient who clinically deteriorates after antiretrovirals have been initiated, it is important to rule out other causes of clinical deterioration.

Treatment of IRIS involves treating the underlying condition and steroids.\(^{15}\) There is only evidence from one randomised control trial for the management of TB-IRIS. This trial from South Africa involved 110 patients with mild/moderate tuberculosis (cold abscesses, lymph nodes, pleural effusions and pulmonary infiltrates) and did not include critically ill patients. Patients who received prednisone 1.5 mg/kg/day for two weeks followed by prednisone 0.75 mg/kg/day for two weeks had a
quicker improvement in symptom scores, resolution of pulmonary infiltrate, and reduction in CRP.

Montelukast and nonsteroidal anti-inflammatory drugs have also been successfully used in the treatment of IRIS, but evidence for this is anecdotal. The discontinuation of antiretrovirals in IRIS is rarely necessary, but may be considered in patients with life-threatening presentations, such as airway compromise.

In the San Francisco cohort (1996-2006) of 278 patients, 18.1% had adverse reactions to antiretrovirals:
- Haematologic 8.8% (zidovudine);
- Pancreatitis 2% (stavudine);
- Lactic acidosis 2.9%.

All adverse reactions required a change in drug regimen. Three patients with tuberculosis developed IRIS, but none required a change of regimen.6

Compliance

Compliance after discharge from ICU is an important issue but, with adequate counselling, the risks of non-compliance should be minimised.

Testing

If knowledge of the HIV status influences the differential diagnosis, diagnostic decisions and treatment decisions, a case can be made for testing a patient without consent. However, the clinician should consult local guidelines and get ethical advice before proceeding. Using the CD4 count as a guide to determine HIV status is not a good idea, as HIV-negative patients experience a reduction in CD4 counts acutely in the setting of critical illness, even below 100 cells/µl.

Conclusion

If a patient is receiving antiretrovirals with adequate viral suppression (lower than the detectable limit), and no contraindication to continuing the antiretroviral regimen in ICU, that patient should continue current therapy.

The majority of HIV-positive patients admitted to ICU are not on therapy. If the patient is admitted for a condition that is not HIV-related, antiretroviral therapy can probably be postponed. However, if the patient has a CD4 count < 200 cells/µl with a protracted ICU stay, antiretrovirals should be initiated to prevent the development of opportunistic infections. Finally, in those patients admitted to ICU with an AIDS-defining illness, antiretrovirals should be initiated as soon as possible.

References

1. UNAIDS. http://www.unaids.com