HIV MANAGEMENT IN PRACTICE

South Africa has the largest HIV epidemic in the world and it is therefore imperative that all health care workers are knowledgeable about the management of HIV/AIDS.

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This article briefly reviews the new South African HIV treatment guidelines for adults and adolescents, children and pregnant women. It focuses on the timing of the initiation of antiretroviral treatment and argues for earlier initiation. It discusses the construction of a treatment regimen and the monitoring thereof, with emphasis on the importance of HIV viral load testing. Finally, it briefly addresses issues around treatment failure and HIV prevention.

The South African (SA) health care system is straining under the enormous burden of HIV/AIDS. According to the 2010 UNAIDS report,[1] approximately 5.6 million South Africans were living with HIV in 2009, making it the largest epidemic in the world. Even though close to 1 million people are currently accessing antiretroviral treatment (ART) in South Africa, it represents fewer than 40% of patients in need of treatment. The UNAIDS report showed an encouraging decrease in incidence among young people in sub-Saharan Africa, yet it is alarming to note that, for every one person started on ART, two more are newly infected.[2]

Given the magnitude of the epidemic, it is imperative that all health care practitioners are comfortable and confident in treating HIV-infected patients. To this end, this article reviews the new SA HIV treatment guidelines and provides practical recommendations for the management of HIV-positive patients in general practice.

Testing

The early diagnosis of HIV with timely initiation of ART is one of the strongest predictors of long-term survival. Mathematical modelling has shown that the life expectancy of HIV-infected patients can approach that of the uninfected population if patients are diagnosed and enter care early.[3] It is therefore paramount that all patients are offered regular HIV testing that can enable timely initiation of treatment.

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Treatment

New SA guidelines[4]

The SA Department of Health released new HIV treatment guidelines for adults and adolescents, children and pregnant women in April 2010. There are nine major changes in the new guidelines (Tables I and II). In summary, these changes are:

- Selective new adult initiation criteria of CD4 <350 cells/µl.
- New paediatric initiation criteria, especially starting ART in all infants under 1 year of age.
- New prevention of mother-to-child transmission (PMTCT) initiation criteria. All pregnant women not qualifying for HAART,

Table I. Initiation criteria and treatment regimens in adults and children

	Adults and adolescents	Pregnant women	Children (<15 years)
Initiation criteria for ART	WHO Stage 4	WHO Stage 3 and 4	All infants <1 year: immediate ART
	CD4 ≤200 cells/µl	CD4 ≤350 cells/µl	1 - 5 years: WHO Stage 3 and 4 CD4% ≤25% or absolute CD4 <750 cells/µl
	TB: CD4 ≤350 cells/µl		5 - 15 years: WHO Stage 4 and CD4 ≤350 cells/µl
	MDR/XDR TB: Any CD4		
First-line ART	TDF, 3TC and NVP or efavirenz (EFV)	TDF, 3TC, NVP	<3 years: ABC, 3TC, lopinavir/ritonavir (LPV/r)
	If no complications on d4T: do not change		≥3 years: ABC, 3TC, EFV
	Contraindication to TDF: AZT	Contraindication to TDF: AZT	If no complications on d4T: do not change
Second-line ART	Failed d4T/AZT-based ART: TDF, 3TC, LPV/r		≥3 years: failed d4T/AZT-based ART: ABC, ddI, LPV/r
	Failed TDF-based ART: AZT, 3TC, LPV/r		≥3 years: failed ABC-based ART: AZT, ddI, LPV/r
			Failed LPV/r or <3 years: refer to specialist
Third-line ART	Refer to specialist		Refer to specialist

i.e. CD4 >350 cells/µl, should be on AZT (zidovudine) from 14 weeks of gestation (or as soon as possible thereafter). During labour, single-dose nevirapine (NVP) is given together with tenofovir and emtricitabine (TDF/FTC) (Truvada) to cover the tail and minimise the chance of resistance to NVP.

- Expedited initiation within 2 weeks in all pregnant women, all patients with CD4 counts <100 cells/µl, WHO Stage 4, all children <1 year of age, and MDR or XDR TB.
- Altered first-line ART for adults, with the introduction of TDF in the place of stavudine (d4T).
- Altered second-line ART for adults, centering on removal of didanosine (ddI) and recycling of lamivudine (3TC).
- Altered first- and second-line ART for children, with the introduction of abacavir (ABC).
- Decreased monitoring (Table II) with no baseline viral load (VL) in adults, decreased VL and CD4 monitoring after the first year, and focused alanine transaminase (ALT), full blood count (FBC) and creatinine clearance in specific regimens only.
- Focus on nurse-initiated treatment.

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Reasons to start ART earlier

Despite the encouraging changes in the 2010 guidelines, South Africa is still lagging far behind international standards where initiating ART at a CD4 count ≤350 cells/µl is viewed as the 'minimum standard of care'. Professional bodies such as the IAS-USA panel even recommend ART at CD4 counts of up to 500 cells/µl.[5] Delaying the initiation of ART until the CD4 count has dropped below 350 cells/µl has been associated with increased mortality, disease- and treatment-related morbidity, and cost. These are mostly due to the increased frequency and severity of opportunistic disease, malignancies, drug toxicity, drug resistance, and immune reconstitution inflammatory syndrome (IRIS) at low CD4 counts.[6,7]

Selecting an appropriate regimen for your patient

First line

TDF and 3TC/FTC in combination with either NVP or efavirenz (EFV) is an excellent first-line regimen for most adult patients. It is imperative to use TDF in combination with 3TC/FTC in patients with co-existing hepatitis B virus (HBV) infection, and this regimen should be continued even when a treatment switch is made for HIV treatment failure. It therefore seems prudent to request a baseline HBV on all patients, if possible. TDF should however be avoided when the creatinine clearance is below 50 ml/min, in which case AZT can be used if the Hb is more than 8 g/dl. ABC is an alternative to AZT, although there are still questions about its potency at very high VLs and the safety of its cardiac profile. NVP should not be used in combination with TB treatment and should be used with caution in patients with liver disease. It is probably best to monitor female patients with a CD4 >250 cells/µl closely for the development of hepatotoxicity, even though new reports indicate that it may be safe.[8] EFV is best avoided in shift workers and in patients with pre-existing psychiatric disease and drug-dependence because of the central nervous system side-effects.

Second line

A second-line regimen of AZT, 3TC and lopinavir/ritonavir (LPV/r) should be adequate to achieve virological control after failure on the standardised first-line regimen. The FBC should be carefully monitored for anaemia and neutropenia and the glucose and lipid levels should be checked for an extended period of time. After years of treatment, a bone mineral density scan will also be valuable in all patients treated with protease inhibitors (PIs). Most patients failing the second-line regimen have no evidence of PI resistance mutations, thereby highlighting the need for continued adherence counselling for patients on this regimen.

Third line and beyond

The options for a salvage regimen are limited in the public sector and such patients are best referred to a specialist centre. In the private sector, salvage regimens can be tailored according to the specific treatment history and resistance profile of the patient. A combination of a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), a PI and an integrase inhibitor, i.e. etravirine, darunavir and raltegravir, is an attractive, though expensive, option.

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Monitoring on ART

HIV VL and CD4

As a basic principle, chronic virological diseases should be monitored with virological tests, such as VL. A baseline VL has predictive value in terms of the risk of drug resistance, progression of disease, death, occurrence of opportunistic diseases and cancers, and response to therapy.[9] Ongoing VL monitoring provides the earliest evidence of treatment failure and it precedes immunological and clinical failure by months to years. Frequent VL monitoring is of particular use in the first months of treatment and the North American guidelines advise repeating VL 2 - 8 weeks after initiation, every 4 - 8 weeks until suppressed, and then every 3 - 4 months for at least the first year.[5] In the SA public sector, VL monitoring is however very limited. CD4 monitoring is useful to assess the need for ART and to monitor the recovery of the immune system, but is a late indicator of treatment failure.

Expected response to treatment

In most patients the VL will decrease by 1 log by 8 weeks, become undetectable by 6 months and remain undetectable throughout. If this is not the case, increased adherence counselling is warranted, with a repeat VL after 8 weeks. Persistently elevated VL above 50 copies/ml (USA guidelines) or 1 000 copies/ml (SA guidelines) signals treatment failure. Immunological recovery is characterised by a first rapid phase in the first 16 weeks (median rate 25.5 cells/µl/month), followed by a slower second phase from 16 to 48 weeks (median rate 7.7 cells/µl/month). Patients initiating ART with a baseline CD4 cell count <50 cells/µl are less

Table II. Monitoring strategies for adults and children

	All adults and adolescents	Children (<15 years)
Monitoring	VL: months 6, 12 and then annually	VL: at initiation, months 6, 12 and then annually
	CD4: at diagnosis, months 6, 12 and annually	CD4: at initiation, months 6, 12 and annually
	ALT if on NVP: baseline, and then if rash or hepatitis symptoms	ALT if on NVP: baseline, and then if rash or jaundice
	FBC or Hb for all at baseline	FBC for all at baseline
	If on AZT: baseline, months 1, 2, 3 and 6	If on AZT: baseline, months 1, 2, 3 and annually
	Creatinine clearance if on TDF: baseline, months 3, 6 and annually	
	Fasting cholesterol and triglycerides if on LPV/r: month 3	Fasting cholesterol and triglycerides if on LPV/r: baseline and annually

Table III. Most common causes of treatment failure	
Non-adherence	Variable aetiology, but mostly caused by denial of diagnosis, religious beliefs of cure, hiding of medication from family and friends, lack of support system, lack of transport, pill fatigue, side-effects and frequent travelling
Previous ART	PMTCT in the form of mono- or dual therapy within the last 2 years Multiple previous ART regimens
Concomitant treatment	Prescription drugs that interfere with ART, e.g. proton pump blockers and PIs Over-the-counter drugs, e.g. St John's wort Alternative remedies such as herbs and special teas and coffees Immune boosters, e.g. '123', African Potato Extract™ and Stameta™ Products claimed to cure HIV, e.g. *ubejani*
Co-morbid conditions	Psychiatric conditions, especially depression, and alcohol and substance abuse
Malabsorption	Chronic diarrhoea and vomiting Induced vomiting and 'cleansing' as part of cultural rituals
Rare	Primary HIV resistance Re-infection Metabolic or genetic abnormalities that interfere with absorption or metabolism of drugs

likely to attain a CD4 cell count of 200 cells/µl at 48 weeks, although such a low baseline count does not preclude immune recovery. Failure to reconstitute the immune system is also associated with older age, lower baseline plasma VL, and a VL >400 copies/ml at any time during treatment. There is no need for a treatment change if immune recovery is incomplete, but the VL is suppressed. These patients should however be evaluated for an underlying opportunistic infection or malignancy.[10]

Clinical assessment – back to basics

- Observations
  - Weight – excellent indication of progress and can warn of impending problems such as lactic acidosis, opportunistic infections and malignancies.
  - Pulse – no patient should be considered stable on treatment until the pulse rate is below 100 beats/minute.
  - Respiratory rate – can alert to infections (such as *Pneumocystis jiroveci* pneumonia) and complications (such as lactic acidosis and renal failure).
  - Urine dipstick – warns of new-onset glucosuria and nephrotoxicity caused by HIV, ART and other treatment.
- Always examine – a thorough clinical examination should always be done before initiating ART, monthly for the first 6 months of treatment, and then at least 3 times a year.
- All that coughs is not TB! TB should always be suspected and excluded with acid-fast bacilli and culture of all obtainable fluids and lymph nodes. Infections, e.g. atypical bacteria and non-tuberculous mycobacteria; malignancies, e.g. lymphoma, Kaposi's sarcoma and lung carcinoma; and inflammatory conditions, e.g. sarcoidosis and rheumatoid arthritis, might present in a similar fashion.
- The 4Cs of chronic disease management:[11]
  - compliance – some form of adherence measurement
  - complaints – always evaluate complaints
  - complications – look for adverse effects of treatment
  - control – HIV VL.

Principles of management of treatment failure (Table III)

- Establish possible cause.
- Address cause.
- Selection of next regimen.

Duration of failure

Resistance mutations occur step-wise. Resistance usually first develops to the NNRTIs, such as NVP and EFV – and 3TC. Resistance to TDF takes a little longer to develop. Due to natural polymorphisms in subtype C infection – the major subtype in South Africa – only one mutation is needed for resistance to TDF to occur,[12] and if treatment has failed for longer than 6 months, resistance to all drugs should be assumed. Whenever treatment failure occurs and resistance testing is not available, all the drugs should be changed at the same time.

Previous drug history

It is vital that a thorough treatment history is taken. Resistance testing can only determine resistance to the drugs the patient is currently taking. It does not indicate anything about the previous medication, as the resistance mutations are most likely archived and not evident in the blood. They will however re-emerge when the drugs are restarted.

Resistance testing

Ideally a genotype should always be performed when a patient fails therapy. It has tremendous value in identifying patients with no resistance mutations where a switch to second line will be unnecessary. It is also invaluable when a patient has failed multiple regimens. It is however an expensive test and not freely available.

Prevention

Last year saw the release of promising results in the field of microbicides, with the 1% TDF gel preventing 39% of HIV infections.[13] We also know that circumcision is protective, at least for men. The current most promising prevention strategy seems to be ART, with the 'Partners in Prevention HSV/HIV Transmission Study' showing a 92% reduction (adjusted incidence rate ratio 0.08, 95% CI 0.00 - 0.57, p=0.004) in HIV transmission in discordant couples (where one partner is HIV positive and one HIV negative).[14]

Conclusion

There are many promising new developments in the field of HIV/AIDS and the possibility now exists to offer patients a productive and healthy life, despite their HIV diagnosis.

References available at www.cmej.org.za

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- Diagnose and treat HIV as early as possible.
- Patients who start ART early, while still asymptomatic, can have a virtually normal life expectancy.
- Always do basic observations and examine your patient.
- Remember the four Cs of chronic disease management.
- All patients, regardless of baseline CD4 count, can achieve immune reconstitution, although patients with a CD4 <50 cells/µl are less likely to do so.
- HIV VL is the most accurate way to monitor treatment response.
- When drugs are changed for reasons of toxicity, it should first be determined that the VL is undetectable before a single drug substitution is made.
- When drugs are changed for reasons of virological failure, at least 2 (and preferably all 3) of the drugs need to be changed.
- Always determine and address the reason/s for treatment failure before switching therapy.
- ART is a very effective method of preventing HIV transmission between discordant couples.