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Southern African Journal of HIV Medicine

- Adult ART guidelines
- Abacavir use in Gauteng
- TB/HIV integration in primary care
- Revised ARV drug dosing chart for children and adolescents

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From the Editor

The 20th International AIDS Conference was recently held in July in Washington, DC, USA. South Africa, generally, and the Southern African HIV Clinicians Society, specifically, were well represented, with prominent presentations by senior academics and policy makers. Indeed, following the conference, I have heard several colleagues from around the country comment that 'South Africans were presenting everywhere' at the meeting. The conference theme, 'Turning the Tide Together', reflected a sense of renewed hope in the fight against the HIV epidemic. Research towards a cure for HIV disease received a great deal of attention, while discussions of antiretroviral-based prevention strategies shifted from trials for determining efficacy towards grappling with the practical issues of implementation. Although most of us could not attend the meeting, luckily much of the conference content is downloadable from the website: http://www.aids2012.org.

At the meeting, the International AIDS Society (IAS) inducted a new governing council, including Professor Linda-Gail Bekker from the University of Cape Town (a former Editor of the *Southern African Journal of HIV Medicine*). Congratulations to Linda-Gail on this significant achievement. We look forward to hearing from her on international developments at the IAS in future editions of the Journal.

Closer to home, the Society is preparing for its inaugural conference, to be held in Cape Town from 25 - 28 November 2012. The conference will cover the latest local research on key topics in HIV medicine and service delivery, and a panel of international speakers will present current 'state-of-the-art' in clinical practice. For the conference programme and information on how to register, see: http://www.sahivsoc2012.co.za. We hope to publish conference abstracts and related outputs in an edition of the Journal in early 2013, for those who cannot attend this exciting meeting.

This edition of the Journal features the latest guidelines from the Society on the use of antiretroviral therapy in adults (an update to previous guidelines from 2008). As with many of the Society's recommendations, these guidelines seek to balance best clinical practice with what is realistic and feasible in the range of healthcare settings across the country. Following this, Evans and colleagues[1] present an analysis of the prescribing of abacavir in public facilities across Gauteng Province. Their results provide an interesting real-world counterpoint to the guidelines for ART use – a pause for reflection on how the best-intended guidelines may be translated into clinical practice. Also from Gauteng, a study by Page-Shipp[2] demonstrates the challenges of integrating TB-HIV services in primary care. This article also shows the important insights that can be generated from routinely collected service delivery data. Hopefully, we will see more submissions of this kind of valuable operations research to the Journal. In addition, Moosa[3] assesses the effect of treating depression on ART adherence, with results suggesting that effective therapy (whether pharmacological or psychotherapeutic) can help to improve HIV outcomes over time.

This edition also features two interesting case reports. This first, a report by Patel[4] from Botswana, gives rise to discussion of long-term non-progressors in sub-Saharan Africa – a group of patients who may go undetected and sub-optimally managed in many settings. In the second report, Kibirige[5] presents a case of likely HIV-associated Addison's disease from Uganda, highlighting the difficulty in arriving at a definitive diagnosis where resources for investigation are limited.

Finally, this issue of the Journal includes as a loose insert: a revised dosing chart for paediatric antiretrovirals from the Society. With an accompanying description by Nuttall and Schowalter,[6] this chart is an invaluable resource for clinicians on the ground, and is sure to be a hot commodity. Additional copies are available on request from the Society.

Happy reading.

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Message from the Executive

I am not sure if I am the only one who feels this way, but sometimes I feel we are fighting a losing battle. It seems that the numbers and the challenges are overwhelming. But, something happened in the last few weeks that reminded me never to give up in fighting for the healthcare rights of all South Africans. Michelle Moorehouse, a member of our board, was incensed by an advertisement for Pre-Sex gel. This clearly unregistered product was being manufactured and sold by a doctor in Port Elizabeth. Michelle did not want anyone to buy this gel and to think that they were protected from HIV. She drafted a passionate letter that was sent off to a number of key stakeholders, including the Registrar of Medicine. The

Medicines Control Council (MCC) visited the doctor's rooms, withdrew the product and stopped all sales. Who knows how many lives have been saved as a consequence? Well done to Michelle. We need to fight each battle that comes our way with the same dedication.

On the real prevention front, there has been some good news. The United States Food and Drug Administration (FDA) has registered Truvada for pre-exposure prophylaxis for men and women. Much media frenzy has surrounded this announcement, with the common question: 'Does this mean we can abandon condoms?' There is not going to be a one-size-fits-all for HIV prevention, but each new intervention will contribute in some way.

To all members, members' friends and potential members, please remember that the first Southern African HIV Clinicians Society Conference will be held in Cape Town at the end of this year. Please put the dates 25 - 28 November 2012 into your diaries, register for the conference, and make travel arrangements accordingly.

Francesca Conradie
President
Southern African HIV Clinicians Society
Johannesburg

Update: ARV dosing chart for children and adolescents, 2012

This edition of the *Southern African Journal of HIV Medicine* includes a new Antiretroviral Drug Dosing Chart for Children and Adolescents (2012). The chart was updated by the Southern African HIV Clinicians Society's ARV Dosing Committee,* a sub-group of the Society's Child and Adolescent Committee, and the National Department of Health (DoH). The purpose of the chart is to provide an accurate and reliable antiretroviral therapy (ART) dosing guide for South African practitioners initiating and managing ART in children and adolescents. The chart is intended for doctors, nurses and pharmacists working in the South African public sector.

The 2012 chart serves to update both the Antiretroviral Drug Dosing Chart for Children (2009), which was incorporated into the paediatric treatment guidelines of the DoH (Guidelines for the Management of HIV in Children[1]) in 2010, as well as the Antiretroviral Drug Dosing Chart for Children (2011) which was adopted in the Western Cape province. The 2012 chart represents national paediatric treatment policy.

In this latest revision, the following principles were considered:

- continued use of the standardised World Health Organization (WHO) weight bands[2]
- provision of target doses or dose ranges (mg/kg or mg/m^2)
- use of WHO weight-band dosing recommendations, differing where necessary, based on characteristics of currently available antiretroviral (ARV) drug formulations in the South African public sector, or local evidence-based practice, where possible
- avoidance of dosing any ARV drug below 90% of the target dose or dose range, or higher than 25% above the target dose or dose range, adjusting WHO-recommended dosing if indicated, and taking into account that younger children (beyond the neonatal period) may frequently require relatively higher doses to achieve drug exposures similar to those of older children and adults
- where evidence is available, incorporation of the option of once-daily dosing for treatment simplification, to promote adherence and support harmonisation of paediatric and adult ART regimens
- incorporation of flexibility, wherever practical and available formulations allow, by providing both liquid and solid formulation dosing recommendations for up to a 25 kg body weight, while retaining the principle of moving children from liquid to solid formulations whenever possible
- use of one formulation (either liquid or solid) for any given dose
- avoidance of different morning and evening doses for a given drug, where possible
- use of fractions of tablets (no less than half) only where available tablets are scored, and warning about which tablet formulations are film-coated and must be swallowed whole (not chewed, divided or crushed).

Significant revisions

Abacavir and lamivudine

- Dosing in the lower weight bands (<10 kg) was considered to be too high in relation to the principles described above, and has therefore been revised slightly to recommend 2 ml twice daily (bd) in the weight band 3.0 - 4.9 kg, and 3 ml bd in the weight band 5.0 - 6.9 kg.
- A liquid formulation option is provided for ≤24.9 kg of body weight. Whereas lamivudine tablets may be divided and, if necessary, crushed for easier ingestion by younger children, currently available abacavir tablets are film-coated and unscored and must be swallowed whole. This has necessitated the recommendation to use only the liquid formulation (in unavoidably large volumes) for the weight band 20.0 - 24.9 kg.
- The option of once-daily dosing is provided for 10 kg and upwards. Although there are no available clinical trial data involving children initiating ART with once-daily dosing of abacavir and lamivudine, the inclusion of this dosing option is supported by pharmacokinetic studies on clinically stable children aged 3 - 12 years with low viral loads, who were switched from twice-daily to once-daily dosing.[3-5] No treatment-limiting toxicity was reported and there was high acceptability and a strong preference for once-daily dosing among children and caregivers. This allows for the option of a once-daily treatment regimen for those children receiving efavirenz in combination with abacavir and lamivudine.

Lopinavir/ritonavir

- Dosing in the lower weight bands (<5 kg) was considered to be too high in relation to the principles described above. Taking this into account and toxicity concerns, doses have been adjusted slightly to 1 ml (80 mg) bd for 3.0 - 4.9 kg and 1.5 ml (120 mg) bd for 5.0 - 9.9 kg.
- The option of tablets in the 10.0 - 13.9 kg weight band has been removed as it is very unlikely that many children in this group would be able to swallow whole tablets, adding to the risk that caregivers may divide or crush these tablets, which must be avoided.
- The dosing for ritonavir boosting with rifampicin-based TB treatment has been adjusted accordingly and simplified to a dose of 1.5 ml (previously 1.2 ml) for the weight band 5.0 - 9.9 kg.

*The Society convened a meeting of paediatric experts on 2 December 2011, chaired by Professor Mark Cotton and Dr Tammy Meyers. The chart principles and major changes were agreed upon at this meeting. A subcommittee of meeting participants, co-ordinated by Laurie Schowalter and comprised of Dr Moherndren Archary, Dr Leon Levin, Dr James Nuttall and Liezl Pienaar, worked in partnership with the national DoH and Paediatric Essential Drug List Committee to finalise changes post meeting.

Efavirenz

- The 2012 chart recommends using 600 mg in children weighing >40 kg (the 2011 chart allowed for use of 600 mg above 35 kg).

Didanosine

- Once-daily dosing has been adopted.

Other

The 2012 chart also includes 2 additional warning statements:

(i) Avoid Kaletra® (LPV/rtv) solution in any full-term infant aged <14 days and any premature infant aged <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice.

(ii) Currently available tablet formulations of abacavir, efavirenz, LPV/rtv (Aluvia®) and AZT are film-coated and must be swallowed whole and **not** chewed, divided or crushed.

The chart is available for download on the Society's website: http://www.sahivsoc.org. A limited number of hard copies are available. To request a copy while there are supplies, email: child_adolescent@sahivsoc.org.

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Guidelines for antiretroviral therapy in adults

by the Southern African HIV Clinicians Society

Graeme Meintjes, Gary Maartens (Chairpersons of the Adult Guidelines Committee), **Andrew Boulle, Francesca Conradie, Eric Goemaere, Eric Hefer, Dave Johnson, Moeketsi Mathe, Yunus Moosa, Regina Osih, Theresa Rossouw, Gilles van Cutsem, Ebrahim Variava, Francois Venter** (Expert Panel Members), **Dave Spencer** (Reviewer), **on behalf of the Southern African HIV Clinicians Society**

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Disclaimer: Specific recommendations provided here are intended only as a guide to clinical therapy, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

These guidelines are intended as an update to those published in the *Southern African Journal of HIV Medicine* in January 2008. Since the release of the previous guidelines, the scale-up of antiretroviral therapy (ART) in Southern Africa has continued to grow. Cohort studies from the region show excellent clinical outcomes; however, ART is still being started late (in advanced disease), resulting in relatively high early mortality rates. New data on antiretroviral (ARV) tolerability in the region and several new ARV drugs have become available. Although currently few in number, some patients in the region are failing protease inhibitor (PI)-based second-line regimens. To address this, guidelines on third-line (or 'salvage') therapy have been expanded.

S Afr J HIV Med 2012;13(3):114-133. DOI:10.7196/SAJHIVMED.862

1. Underlying principles

While many ART guidelines are available internationally, these guidelines have been written to address issues relevant to Southern Africa. The following general principles underpinned the writing process:

- South Africa is a middle-income country whereas certain other countries in the region are low-income countries; therefore, affordability was taken into account.
- Only treatment and diagnostic options available in Southern Africa were included.
- We recognised the need to bridge the gap in treatment recommendations between public and private sector programmes, considering that many patients transition between the 2 sectors for treatment.
- The guidelines are intended to reflect 'best practice' – while it is acknowledged that certain recommendations are aspirational for poorly resourced settings, the unavailability of diagnostic/monitoring tests should not be a barrier to providing ART to those in need.
- There has been a shift to view treatment as a means of HIV prevention. The evidence base for this exists for serodiscordant couples; recommendations in this regard are included in these guidelines and additional data from community studies are awaited.
- References for key new recommendations were included to address the need for supporting evidence.

2. Goals of therapy

The primary goals of ART are to:

- improve quality of life
- reduce HIV-related morbidity and mortality
- provide maximal and durable suppression of viral load
- restore and/or preserve immune function.

These goals are achieved by completely suppressing viral replication for as long as possible using well-tolerated and sustainable treatment. With prolonged viral suppression, the CD4 lymphocyte count usually increases, which is accompanied by partial restoration of pathogen-specific immune function. For most patients, this results in a dramatic reduction in the risk of HIV-associated morbidity and mortality. It is still unclear whether immune function ever returns to full normality. Long-term cohorts will provide answers, but for now, and for practical purposes, clinicians should treat patients who adhere to ART with the anticipation of a near-normal life expectancy.

3. Standard of care

Maximally suppressive ART regimens should be used to obtain the best results and to prevent resistance. In the region, non-suppressive regimens such as mono/dual nucleoside reverse transcriptase inhibitor (NRTI) therapies have historically been used. The initiation of such therapies is now strongly discouraged. However, non-suppressive regimens have a role in the prevention of mother-to-child transmission (PMTCT) and in post-exposure prophylaxis (PEP) for healthcare workers following occupational exposure. Furthermore, they are probably effective following sexual exposure. For further guidance:

Southern African HIV Clinicians Society. Post-exposure prophylaxis. *Southern African Journal of HIV Medicine* 2008;9:36-45.

4. Classes of ARV agents and their mechanisms of action

The most commonly used ARV agents in the region inhibit 1 of 3 key HIV enzymes that are required by the virus for intracellular replication (Table 1):

- reverse transcriptase – essential for completion of the early stages of HIV replication
- protease – required for the assembly and maturation of fully-infectious viral progeny
- integrase – required for the integration of proviral DNA into the host chromosomal DNA.

5. ARV agents currently available in Southern Africa (Table 2)

5.1 Notes

Different fixed-dose drug combinations are increasingly being made available. The oldest combination is zidovudine (AZT)/lamivudine (3TC), but a number of other 2 - 3 fixed-dose combinations are now available in Southern Africa. These reduce the burden of multiple pills and improve adherence. However, side-effects remain as described in Table 2.

Low-dose ritonavir is used to 'boost' the concentration of other PIs. It is always used with lopinavir (LPV) (fixed-dose combination) and saquinavir (SQV) and is strongly encouraged with other PIs. The following PIs are recommended for use: LPV/ritonavir (LPV/r), atazanavir/ritonavir (ATV/r) and darunavir/ritonavir (DRV/r). Patients receiving older PIs (e.g. SQV and indinavir) should be switched to these (consult an expert if the patient's viral load is not suppressed). We recommend against regimens containing dual ritonavir-boosted PIs, as there is no evidence for superior efficacy[1] and significant side-effects are likely.

Combinations to be avoided include: *(i)* AZT plus d4T (antagonism); *(ii)* tenofovir (TDF) plus didanosine (ddI) (associated with poorer virological and immunological responses and increased toxicity); and *(iii)* D4T plus ddI (associated with a very high risk for mitochondrial toxicities such as lactic acidosis and peripheral neuropathy).

6. Indications for starting ART

Indications for ART initiation are summarised in Table 3. ART initiation is never an emergency, unless used for PEP or PMTCT. However, patients with profound immunosuppression are at significant risk of opportunistic illnesses, and should be assessed rapidly and initiated on ART as soon as adherence is assured. The following investigations are recommended prior to initiating ART:

- alanine transaminase (ALT)
- full blood count (FBC)
- serum creatinine and calculate creatinine clearance: avoid TDF if creatinine clearance is <50 ml/min; other NRTIs, except abacavir (ABC), require dose adjustment if creatinine clearance is <50 ml/min (see the modified Cockgraft-Gault equation – Table 9)
- urinalysis for proteinuria
- hepatitis B surface antigen
- CD4 count.

Where feasible, a serum or plasma cryptococcal antigen test should be performed in patients starting ART with a CD4 count <100 cells/µl, to screen for early cryptococcal disease and to initiate pre-emptive treatment if needed. In addition, a baseline HIV viral load should be performed where feasible.

ART should be deferred until patients are prepared to commit to long-term treatment and maintaining good treatment adherence. However, efforts should be made to avoid lengthy indecision that may result in avoidable clinical deterioration and death.

Table 1. Classes of ARV agents

Class	Abbreviation	Mechanism of action	Specific action
Nucleoside and nucleotide reverse transcriptase inhibitors	NRTIs and NtRTIs	Reverse transcriptase inhibition	Nucleic acid analogues that mimic the normal building blocks of DNA, preventing transcription of viral RNA to DNA
Non-nucleoside reverse transcriptase inhibitors	NNRTIs	Reverse transcriptase inhibition	Small compounds shaped to fit into the genomic HIV binding site of reverse transcriptase and directly inhibit its action
Protease inhibitors	PIs	Protease inhibition	Inhibit the final maturation stages of HIV replication, resulting in the formation of non-infective viral particles
Entry inhibitors*	-	Entry inhibition	Bind to viral gp41 or host cell CD4 or chemokine (CCR5) receptors
Integrase inhibitors (also termed integrase strand transfer inhibitors)	InSTIs	Inhibit viral integration	Prevent the transfer of proviral DNA strands into the host chromosomal DNA

* Not yet available in Southern Africa.

ARV = antiretroviral; DNA = deoxyribonucleic acid; RNA = ribonucleic acid.

Table 2. Dose and common adverse drug reactions of ARV agents available in Southern Africa

Generic name	Class of drug*	Recommended dosage	Common or severe adverse drug reactions†
Zidovudine (AZT)	NRTI	300 mg 12-hourly	**Bone marrow suppression**, gastro-intestinal (GI) upset, headache, myopathy, **hyperlactataemia**/steatohepatitis (medium potential), lipo-atrophy
Didanosine (ddI)	NRTI	400 mg daily (250 mg daily if <60 kg) taken on an empty stomach (enteric coated formulation preferred)	Peripheral neuropathy, **pancreatitis**, nausea, diarrhoea, **hyperlactataemia**/steatohepatitis (high potential)
Lamivudine (3TC)	NRTI	150 mg 12-hourly or 300 mg daily	**Anaemia (pure red cell aplasia)** (rare), **hyperlactataemia**/ steatohepatitis (very low potential)
Stavudine (D4T)	NRTI	30 mg 12-hourly Note: higher doses for >60 kg no longer recommended due to toxicity	Peripheral neuropathy, lipo-atrophy, **hyperlactataemia**/ steatohepatitis (high potential), **pancreatitis, HIV-associated neuromuscular weakness syndrome (HANWS)** (rare), dyslipidaemia
Abacavir (ABC)	NRTI	300 mg 12-hourly or 600 mg daily	**Hypersensitivity reaction**, **hyperlactataemia**/ steatohepatitis (very low potential)
Tenofovir (TDF)	NtRTI	300 mg daily	**Renal failure**, tubular wasting syndrome, reduced bone mineral density, **hyperlactataemia**/steatohepatitis (very low potential)
Emtricitabine (FTC)	NRTI	200 mg daily	Palmar hyperpigmentation, **hyperlactataemia**/ steatohepatitis (very low potential)
Nevirapine (NVP)	NNRTI	200 mg daily for 14 days then 200 mg 12-hourly	**Rash**, **hepatitis**
Efavirenz (EFV)	NNRTI	600 mg at night	Central nervous system symptoms (vivid dreams, problems with concentration, confusion, mood disturbance, psychosis), **rash, hepatitis,** gynaecomastia
Etravirine (ETV)	NNRTI	200 mg 12-hourly	**Rash, hepatitis**
Indinavir (IDV) (rarely used)	PI	800 mg 12-hourly with 100 mg ritonavir 12-hourly No food restrictions Maintain high fluid intake	Kidney stones, unconjugated hyperbilirubinaemia (visible jaundice in minority of patients), GI disturbances, hair loss, hyperglycaemia, headache, dyslipidaemia
Atazanavir (ATV)	PI	400 mg daily (only if ART-naive) or 300 mg with ritonavir 100 mg daily (preferable) With TDF 300/100 mg daily and with EFV 400/100 mg daily	Unconjugated hyperbilirubinaemia (visible jaundice in minority of patients), dyslipidaemia (low potential), renal stones (rare), hepatitis
Lopinavir/ritonavir (LPV/r)	Boosted PI	400/100 mg 12-hourly or 800/200 mg daily (only if PI-naive).	GI upset, dyslipidaemia, hepatitis
Darunavir (DRV)	PI	600 mg 12-hourly with 100 mg ritonavir 12-hourly or 800/100 mg daily (only if PI-naive)	GI upset, rash, dyslipidaemia, hepatitis Contains sulphonamide moiety (use with caution in patients with sulpha allergy)
Saquinavir (SQV) (hard gel formulation, rarely used)	PI	1 000 mg with 100 mg ritonavir 12-hourly, or 1 600 mg with 100 mg ritonavir daily (only if PI-naive) Take with a fatty meal, or up to 2 hours after meal	GI disturbance (mild), hepatitis, hyperglycaemia, dyslipidaemia
Raltegravir (RAL)	InSTI	400 mg 12-hourly	**Rash** (rare), headache, GI upset

*All protease inhibitors (PIs) may be associated with cardiac conduction abnormalities (especially PR prolongation). This seldom results in clinically significant effects, but caution should be taken when co-prescribing other drugs that cause delayed cardiac conduction, such as macrolides.

†Life-threatening reactions are indicated in bold.

NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; InSTI = integrase inhibitor (integrase strand transfer inhibitor).

6.1 Rationale for these guidelines

6.1.1 CD4 threshold

A randomised trial in Haiti demonstrated reduced mortality and incident tuberculosis (TB) in patients starting ART at a CD4 threshold <350 cells/µl (compared with patients waiting to start therapy at <200 cells/µl).[2] Some observational data suggest that reduced morbidity and mortality are associated with starting ART even earlier (at CD4 thresholds of 500 cells/µl or above that).[3-6] However, these data are derived from retrospective studies with methodological issues and probable residual confounding. If there is benefit to patients starting ART at CD4 counts >350 cells/µl, the benefit is likely to be small, since HIV-related events at high CD4 counts are rare. A randomised controlled trial (RCT) (HPTN052) showed reduced morbidity but not mortality associated with starting ART at a CD4 count of 350 - 550 cells/µl (compared with <250 cells/µl).[7] However, again, the absolute benefits were small. Definitive evidence regarding earlier ART initiation is awaited from an ongoing RCT, the START study (http://clinicaltrials.gov/ct2/show/NCT00867048).

6.1.2 Treating WHO stage 3

Many observational studies have shown that TB (the most common World Health Organization (WHO) stage 3 condition associated with HIV) accelerates HIV disease progression and increases mortality.[8] We advise that an episode of HIV-associated TB (i.e. TB diagnosed at the time of seropositive HIV test) is a sufficient criterion for ART, but not remote episodes of TB when the patient's HIV status was unknown.

6.1.3 Serodiscordant couples

The HPTN052 trial showed that treating the HIV-infected partner in a serodiscordant relationship with ART was associated with a 96% reduction in transmission risk to the uninfected partner.[7]

6.2 Starting ART in patients with TB

Decisions regarding the timing of ART in patients with TB should be made on the basis of the CD4 count:

- **CD4 count ≤50 cells/µl:** ART should be regarded as urgent, and the aim should be to start therapy after 2 weeks of TB treatment. Three RCTs[9-11] have demonstrated that this approach reduces AIDS progression and mortality. It is advised to commence ART **after** it is clear that the patient's TB symptoms are improving and that TB therapy is tolerated.
- **CD4 count >50 cells/µl:** ART should be delayed until after the intensive phase of TB treatment (2 months) **unless** the patient has other serious HIV-related conditions (e.g. Kaposi's sarcoma or HIV encephalopathy). The longer delay before commencing ART in this group is expected to reduce the risk of shared toxicity (as the patient will then be receiving fewer TB drugs) and to reduce the risk of the immune reconstitution inflammatory syndrome (IRIS) (section 15). The RCTs did not show a higher risk of AIDS progression/mortality in this group when ART initiation was delayed until 2 months after starting TB treatment.[9-11]
- There are important drug interactions and shared side-effects when ART is co-administered with TB therapy (section 13.1).

Table 3. Indications for ART*

Clinical diagnoses (irrespective of CD4 count)	
WHO clinical stage 3 and 4†	ART recommended
Other severe HIV-related disorders, e.g.:‡ Immune thrombocytopenia Thrombotic thrombocytopenic purpura Polymyositis Lymphocytic interstitial pneumonitis	ART recommended
Non HIV-related disorders:§ Malignancies (excluding localised malignancies) Hepatitis B¶ Hepatitis C	ART recommended
Any condition requiring long-term immunosuppressive therapy	ART recommended
CD4 counts	
<350 cells/µl	ART recommended
>350 cells/µl	Defer ART
HIV-infected partner in serodiscordant relationship	
Regardless of CD4 count or clinical diagnoses	Offer ART and discuss safe sex (discussion must involve both partners)

*Note that EITHER listed clinical diagnoses OR CD4 strata would be an indication for ART.

†See Appendix.

‡Specialist input required. Note that this list is not exhaustive – any other severe HIV-related disorder should be considered an indication for ART.

§Specialist input required. Other disorders that may benefit from improvement in immune function should also be considered as an indication to start ART. Also, given that untreated HIV appears to be a risk factor for vascular disease, patients with symptomatic vascular disease or diabetes mellitus can be considered for earlier ART.

¶Hepatitis B that qualifies for specific anti-hepatitis B therapy (see section 13.5 for criteria and recommended ART regimens).

- When ART is commenced, patients should be warned that TB symptoms or signs may temporarily worsen and new features may occur in the first 3 months as a result of TB-IRIS.
- Unless contra-indicated, cotrimoxazole prophylaxis should be initiated in patients with HIV-associated TB.
- Patients with TB meningitis (TBM) starting ART immediately or at 2 months following diagnosis were shown to have similar high mortality, with more complications in the former.[12] We recommend starting ART 2 - 8 weeks after TBM diagnosis.

6.3 Starting ART in patients with other opportunistic diseases/infections

For patients with cryptococcal meningitis (CM), the optimal time to start ART is currently unclear. The high risk of mortality prior to ART and the mortality risk associated with intracranial cryptococcal IRIS need to be balanced, and published studies have shown conflicting results.[13,14] The Cryptococcal Optimal ART Timing (COAT) trial was recently stopped early by the Data and Safety Monitoring Board because of excess mortality in patients who started ART in hospital 1 - 2 weeks after CM diagnosis compared with those starting 5 - 6 weeks after diagnosis. The final results of this trial are awaited. In the interim, we recommend starting ART around 4 weeks after antifungal treatment (preferably amphotericin B-based) is started.

In patients with other infections (e.g. pneumocystis pneumonia or bacterial pneumonia) and who have a CD4 count <200 cells/µl, clinicians should aim to start ART within 2 weeks of starting treatment for that infection. In patients with severe Kaposi's sarcoma and lymphoma, ART counselling should be expedited and ART should be started as soon as possible.

Refer to supplementary material: 'Starting ART in hospital' and 'High-risk patients'.

6.4 Patient readiness for ART

Patient readiness for therapy is as important as the medical indications for commencing therapy.

- The patient must demonstrate insight and must have established the ability to attend reliably.
- Conventionally, ART is not started at the first visit. Usually, 2 - 3 visits staggered closely together are required before ART is started, to accommodate counselling. Prolonged delays in starting ART should be avoided. ART should be delayed only if concerns about adherence are severe enough to outweigh the risk of HIV disease progression.
- The patient should be provided with information on the following:
  - ART is life-long therapy
  - the importance of 100% adherence
  - ART side-effects and what to do and who to contact if serious side-effects occur.
- Active depression or substance abuse should be dealt with.
- A personal treatment plan should be formulated for each patient, specifying drug storage, strategies for missed doses and how to integrate taking medication into daily routine. The patient must be made aware of scheduling in terms of clinical follow-up.
- Disclosure of HIV status (to a partner and/or other household members) should be strongly encouraged. This has been shown to be an important determinant of treatment adherence and assists in the provision of patient-directed support. Disclosure also identifies exposed contacts for screening and support. This issue needs to be handled sensitively in situations where disclosure may have harmful consequences, particularly for women.
- The patient should be encouraged to join a support group and/or identify a treatment 'buddy'. However, neither disclosure nor support group participation are prerequisites for good adherence in all patients.
- Clinicians should ensure that they have the contact details of each patient and their treatment 'buddy'.
- Counselling should cover safe-sex practices and address issues related to reproductive health (i.e. family planning, contraception, condom use, pregnancy and PMTCT).

Refer to supplementary material: 'Common misconceptions regarding ART' and 'Adherence interventions'.

6.5 ART in primary infection

There is insufficient evidence to recommend ART for primary infection. There are compelling reasons to defer therapy, including lack of proven efficacy, drug toxicity, and the potential for drug resistance. Patients with severe primary infection progress more rapidly, which is an indication for careful follow-up. ART in primary infection should be considered in a properly conducted research study, or in the presence of very severe symptoms (e.g. meningo-encephalitis), which are rare. Consultation with an expert treater is advised.

7. Initial ARV regimens for the previously untreated patient

In accordance with international recommendations, we recommend the use of a non-nucleoside reverse transcriptase inhibitor (NNRTI) and 2 NRTIs (a safe dual NRTI combination) as the first-line ART regimen. In comparison with PIs, NNRTIs are better tolerated in the long term and are at least as potent when combined with an appropriate dual NRTI combination.[15] We do not recommend PI or integrase inhibitor (integrase strand transfer inhibitor (InSTI)) use in first-line therapy, unless dictated by intolerance or NNRTI contra-indications.

Either NVP or efavirenz (EFV) may be selected as the NNRTI. EFV is the preferred NNRTI. NVP should be selected for women in the first trimester of pregnancy or those who intend to fall pregnant (section 13.2). Owing to its neuropsychiatric side-effects, EFV should be avoided in those with active psychiatric illness, shift workers and those operating heavy machinery or vehicles. NVP should be avoided in women with a CD4 count >250 cells/µl and men with a CD4 count >400 cells/µl initiating ART for the first time, because of the increased risk of rash-associated hepatitis. It should be noted, however, that this side-effect can occur at any CD4 count. Clinicians should consider avoiding NVP in patients who may encounter difficulties getting rapid medical attention should rash or hepatitis symptoms occur. NVP should also be avoided in patients with pre-existent liver disease. When both NVP and EFV are contra-indicated, raltegravir (RAL) or a PI could be substituted. Any patient starting an NNRTI should be told to report a rash, jaundice or symptoms of hepatitis immediately.

Any of the following 2-drug NRTI combinations are recommended for use with the NNRTI:

- 3TC plus TDF, AZT or ABC
- emtricitabine (FTC) – a cytidine analogue very similar to 3TC – that is combined with TDF in a fixed-dose combination or with the addition of EFV as a triple-drug combination pill.

TDF is the favoured NRTI to use with 3TC (or FTC). Selection will depend on affordability and co-morbidity (e.g. patients with

a creatinine clearance <50 ml/min should not start TDF). If TDF is unavailable or contra-indicated, AZT should be used, provided that haemoglobin (Hb) is >10 g/dl. A large clinical trial comparing ABC- v. TDF-containing first-line regimens showed lower rates of virological suppression with ABC in patients with a baseline viral load >100 000 copies/ml.[16] Similar findings were demonstrated in a second study,[17] but not confirmed in another.[18] ABC is more costly and unavailable in most public sector programmes and has been associated with an increased risk of myocardial infarction (MI) in some, but not all, cohort studies.[19,20] The association with MI was not confirmed in a meta-analysis of RCTs.[21] Nevertheless, caution is recommended when considering ABC for patients at significant risk of ischaemic heart disease or with established ischaemic heart disease. ABC is an option to consider in chronic renal failure where TDF and AZT (because of anaemia) cannot be used.

D4T is a cheaper option than TDF, AZT and ABC, but it is considerably more toxic. Most public sector programmes in Southern Africa have discontinued D4T in first-line ART. Nonetheless, there is still a role for D4T in selected patients, when it is used in the short term in patients with contra-indications to other NRTIs. A common example is a patient with renal dysfunction and anaemia at baseline who could be started on D4T for 3 - 6 months and then switched to AZT or TDF depending on resolution of the anaemia and/or renal dysfunction. In addition, if there is a need for concomitant nephrotoxic medications, e.g. aminoglycosides to treat multidrug resistant (MDR)-TB, D4T (or AZT or ABC) is preferable to TDF during the period of exposure to the other nephrotoxic medication. Patients usually tolerate short-term D4T well. Severe D4T side-effects, such as hyperlactataemia, lipo-atrophy and other mitochondrial toxicity, typically occur after 4 - 6 months, although peripheral neuropathy can develop earlier.

We favour regimens that include fixed-dose combinations and allow once-daily dosing (refer to Table 2 for doses and common side-effects).

8. Laboratory monitoring for ART efficacy

8.1 Viral loads

Viral loads should be performed:

- at baseline (before commencing ART, where possible)
- at 3 months after the commencement of ART (This early viral load is desirable to detect adherence problems early before resistance develops. A small number of patients who start with a very high viral load may not be fully suppressed at 3 months despite 100% adherence, but such patients would have had a >2 log drop in viral load from baseline; therefore, the 3-month result should be interpreted in relation to the baseline viral load. All patients who have a detectable viral load at 3 months should receive additional adherence interventions.)
- at 6 months thereafter and then every 6 months (in patients who are virologically suppressed (undetectable viral load) for longer than 12 months and who demonstrate reliable adherence and follow-up, it may be acceptable to reduce the frequency of viral load monitoring to annually)
- if viral load is >50 copies/ml, then repeat measurement in 3 months, after an adherence intervention.

8.1.1 Notes

(*i*) A viral load >50 copies/ml while receiving ART should be an indication for **urgent** action to improve adherence. A subsequent ART change must be considered if there is not complete viral suppression at the subsequent 3-month follow-up viral load (see section 10 - 'Indications for changing ART').

(*ii*) Viral load monitoring is key to the success of ART. Decisions to change ART made on the basis of virological failure, rather than on clinical or immunologic failure alone, result in better patient outcomes. If the viral load is undetectable, then the virus cannot mutate and develop resistance. A sustained viral load of <50 copies/ml is associated with the most durable virological benefit.

8.2 CD4+ counts

CD4 counts should be performed every 6 months. In patients being monitored with viral loads once the CD4 count is >200 cells/µl, provided that the viral load is suppressed, routine CD4 testing could be stopped as it adds little to management. This is expert opinion rather than being evidence-based. However, if virological or clinical failure occurs, then a CD4 count should be repeated as it may influence management decisions.

9. Defining ART failure

In resource-limited settings where viral loads are unavailable, the WHO has devised criteria for defining ART failure on the basis of CD4 count responses or clinical disease progression. Studies have shown that switching ART regimens using these criteria results in a significant proportion of patients switching very late (with progressive accumulation of resistant mutations) and switching inappropriately (as the CD4 count response may be poor, despite optimal virological suppression).[22]

9.1 Virological criteria for treatment success

Treatment success is defined by:

- a decline in viral load of at least 2 log from pre-treatment levels 3 months after initiating ART
- a decline in viral load to <50 RNA copies/ml within 6 months of commencing ART and sustained thereafter.

9.2 Virological criteria for treatment failure

Treatment failure is defined by a confirmed HIV viral load of >1 000 copies/ml in 2 measurements taken 1 - 3 months apart. Several factors can influence the measurement of HIV viral load. The decision to alter ART should therefore be based on the results of repeat testing after 1 - 3 months following intensive adherence counselling. Inadequate patient adherence to the prescribed regimen remains the most common reason for treatment failure. Other important causes include: prior use of single-dose NVP for PMTCT, especially when ART is initiated within 6 months of the PMTCT dose; drug interactions that decrease ART concentrations; and transmitted drug resistance, which is currently uncommon in the region (<5%).[23]

9.3 CD4 response

Typically, the CD4 count increases rapidly in the first month of ART, by approximately 75 - 100 cells/µl, with a more gradual rise thereafter (50 - 100 cells/µl/year).[24] Most, but not all, patients achieve a CD4 count >500 cells/µl after several years of ART, provided that the viral load remains suppressed.[25-27] However, CD4 responses are highly variable and may fail to increase despite virological suppression, in about 10 - 20% of patients.[28,29] Such patients have a delayed or absent CD4 response to ART despite viral suppression, which is termed an 'immunological discordant response to ART'. Certain studies suggest

that older patients are at higher risk. There is no evidence that such patients benefit from a change in ART regimen; therefore, the same regimen should be continued. Cotrimoxazole prophylaxis should be continued if the CD4 count remains <200 cells/µl and isoniazid (INH) prophylaxis should be considered. There is evidence that the prognosis of such patients is worse than in those who have a CD4 response, but better than that of patients not receiving ART. If such patients are clinically unwell, TB or lymphoma should be considered as the cause of persistent CD4 lymphopaenia.

CD4 counts may continue to rise or remain stable in the presence of incomplete viral suppression (which will result in the emergence of drug resistance) until the viral load is high (approximately 10 000 copies/ml and above).[30]

10. Indications for changing ART

Individual ART drugs may be substituted in the event of toxicity (section 14), provided that the viral load is suppressed or ART was initiated within the preceding 6 months. Changing the first-line ART regimen to a second-line regimen is a major step. The drugs used in second-line regimens are often not as well tolerated and are more expensive, usually with limited options for subsequent treatment owing to cost. For this reason, clinicians tend to switch to second-line ART after a prolonged period of virological failure, which will cause a progressive increase in the accumulation of resistant mutations. This reduces the efficacy of second-line and subsequent regimens. If the viral load is >1 000 copies/ml, it is essential to step up adherence interventions, as discussed above. Once the viral load is confirmed on a second specimen to be >1 000 copies/ml despite adherence, the patient should be switched to a second-line regimen without undue delay. In summary, we advise a switch to a second-line regimen when 2 viral load measurements have been >1 000 copies/ml, preferably with the measurements taken 3 months apart with at least 4 weeks of an intensified adherence intervention in between. In patients with low CD4 counts (<100 cells/µl), this process should be expedited.

Some patients have persistently detectable viral loads at low levels (200 - 1 000 copies/ml). If patients have low level viraemia for a prolonged period (>1 year) or persistently low CD4 counts (<100 cells/µl) together with low-level viraemia despite adherence interventions, they should be switched to second-line ART.

10.1 Second-line ART

The following ritonavir-boosted PIs are recommended in conjunction with 2 NRTIs (Table 2):

- ATV/r
- LPV/r
- DRV/r (it is preferable to save this drug for third-line therapy, further discussed below).

Indinavir (IDV) is significantly more toxic than other PIs. SQV is less robust in terms of resistance than the 3 options listed. IDV and SQV confer no benefit over other options, and are therefore not recommended.

Boosting involves the addition of low-dose ritonavir, which inhibits PI metabolism, thereby boosting PI plasma concentration and prolonging its half-life. LPV is co-formulated with ritonavir in a heat-stable tablet (Aluvia) and is the best option in patients without a refrigerator (other PIs require ritonavir boosting with a separate ritonavir capsule that ideally requires refrigeration, although ritonavir capsules are stable at room temperature for 30 days). We recommend against the use of unboosted PIs.

If a patient was receiving a first-line combination of 2 NRTIs and a PI (boosted or unboosted), it is best to discuss the choice of second-line regimen with an experienced treater and consider a genotype resistance test. Second-line NNRTI plus NRTI regimens are often not effective in such patients because of NRTI mutations, while boosted PI regimens in second-line ART may remain effective. Decisions are therefore best guided by resistance testing.

10.2 Selecting second-line dual NRTIs

Because boosted PIs are robust drugs (i.e. resistance develops slowly) in PI-naive patients, it is very likely that virological suppression will be achieved with good adherence, even if the 2 NRTIs used in second-line are partially compromised by NRTI resistance mutations (Tables 4 and 5).[31]

Certain NRTI combinations are contra-indicated for toxicity reasons (e.g. d4T plus ddI, or TDF plus ddI). TDF plus ABC is not recommended for second-line ART, as these agents share several resistance mutations. NRTI combinations advised for second-line regimens include either AZT plus 3TC, or TDF plus 3TC (FTC can be substituted in place of 3TC), depending on the likely mutational profile selected during the patient's first-line NRTI combination.

Even if 3TC (or FTC) is used in a failed first-line regimen and may, therefore, have selected for the M184V mutation which confers resistance to the agent, 3TC (or FTC) can be re-used in second-line therapy because of the capacity of the M184V mutation to partially restore susceptibility to AZT, d4T and TDF in the presence of thymidine analogue mutations (TAMs), and to partially restore susceptibility to TDF in the presence of the K65R mutation. The M184V mutation also reduces the replicative capacity of the virus.

Ideally, a resistance test should be performed at first-line failure to ensure that the patient does indeed have resistance (and the virus is not 'wild-type') and to guide choices of second-line and future regimens. However, in many settings in the region, this is unaffordable and/or unavailable.

11. Patients who return after defaulting therapy

We recommend restarting the same regimen if patients return to care after defaulting therapy and repeating HIV viral load measurements after 3 months; switching to a second-line regimen should be considered if the viral load is not suppressed at this point. If a patient is receiving first-line therapy, AZT could be substituted for D4T. However, we do not recommend substituting TDF, because, if the patient has pre-existing NNRTI and 3TC resistance, TDF resistance may rapidly result compromising its efficacy in second-line therapy. If a patient has multiple episodes of interruption, and, particularly, if they are beyond the first year of ART, then many clinicians would consider switching the patient to a second-line regimen, making the assumption that the multiple interruptions resulted in first-line resistance. Reasons for defaulting should be addressed and adherence support increased. Performing a resistance test after the patient has been off ART for longer than 4 weeks is of limited value as many resistance mutations are overtaken by wild-type when ART is stopped.

12. Drug interactions

There are many important drug interactions between ARV agents and other medications, as well as between certain ARV agents themselves. These interactions occur because of metabolism of ARV drugs by cytochrome P450 in the liver and intestine and induction or inhibition by

Table 4. Mutations selected by first-line NRTI combinations*

First-line NRTIs	NRTI mutations selected
3TC or FTC	Select for M184V, which compromises both 3TC and FTC, and slightly impairs the activity of ABC and ddI, but increases susceptibility to AZT, D4T and TDF
AZT	Selects for thymidine analogue mutations (TAMs) which may compromise all NRTIs†
D4T	Selects for TAMs which may compromise all NRTIs In a minority of patients, D4T may select for K65R which compromises TDF, ABC and ddI, but increases susceptibility to AZT
TDF	Selects for K65R which compromises TDF, ABC and ddI, but increases susceptibility to AZT
ABC	Selects for L74V which compromises ABC and ddI May also select for K65R which compromises TDF, ABC and ddI, but increases susceptibility to AZT Selects for Y115F which decreases its susceptibility

*These mutations accumulate with time – the longer the patient has virological failure, the more of these mutations are likely to be selected.

†The presence of ≥3 TAMs, including M41L and L210W, confer intermediate- to high-level TDF resistance.

TAMs = thymidine analogue mutations; NRTI = nucleoside reverse transcriptase inhibitor; 3TC = lamivudine; FTC = emtricitabine; AZT = zidovudine; D4T = stavudine; TDF = tenofovir; ABC = abacavir.

Table 5. Choice of second-line NRTIs in relation to first-line NRTIs used

First-line NRTIs used	Second-line NRTI combination advised
AZT plus 3TC	TDF plus 3TC*
D4T plus 3TC	TDF plus 3TC* (preferably genotype first, given the increased risk of K65R on D4T in subtype C)[32]
TDF plus 3TC*	AZT plus 3TC
ABC plus 3TC	AZT plus 3TC

*3TC is interchangeable with FTC.

NRTI = nucleoside reverse transcriptase inhibitor; AZT = zidovudine; 3TC = lamivudine; D4T = stavudine; TDF = tenofovir; ABC = abacavir; FTC = emtricitabine.

ARVs of this and other enzyme systems and drug transporters. Certain of these drug interactions are discussed in these guidelines (e.g. the interaction between rifampicin and NNRTIs, PIs and RAL). The list of all potential drug interactions is, however, very long and therefore beyond the scope of this document. Knowledge of drug interactions is constantly evolving. Clinicians are advised to consult the package inserts of ARV agents and concomitant medication to assess for drug interactions and the following websites, which provide up-to-date information on drug interactions and the actions required to account for them:

- University of Liverpool Drug Interactions Charts: http://www.hiv-druginteractions.org
- University of Cape Town Medicines Information Centre ARV interactions table: http://www.mic.uct.ac.za/?page_id=47

We advise that clinicians assess for potential drug interactions whenever patients start or switch to a new ARV drugs or regimens, and start new concomitant medications. In addition, herbal medications may also have interactions with ARVs.

13. ART in special populations

13.1 TB

The ART regimen should be modified if necessary for compatibility with rifampicin – a critical component of the TB regimen that substantially reduces the risk of relapse after completing TB treatment. EFV is the preferred NNRTI for use with rifampicin. NVP is an alternative in patients with contra-indications for EFV (e.g. psychosis), but it carries a higher risk of hepatitis and virological failure when used with rifampicin.

The plasma concentrations of all boosted PIs are reduced to sub-therapeutic ranges with rifampicin. Dose adjustment of some PIs can overcome this induction (Table 6), but there is a risk of hepatotoxicity. The patient will require counselling and ALT should be monitored frequently. An alternative approach is to replace rifampicin with rifabutin. However, rifabutin is expensive and not currently available at public sector TB clinics. Also, rifabutin is not co-formulated with other TB drugs such as rifampicin, and the evidence base for rifabutin in the treatment of TB is much less substantial than that for rifampicin.[33] There is also uncertainty regarding the optimal dose of rifabutin with boosted PIs; current guidelines recommend 150 mg on alternate days. Rifabutin may be considered in patients not tolerating co-treatment with ART and rifampicin-based antitubercular therapy (e.g. patients unable to tolerate the increased LPV/r dose) or in ART-experienced patients on an ART regimen that is not compatible with rifampicin (e.g. those on third-line ART with DRV/r). Rifabutin doses may require adjustment (Table 8). If rifabutin is unavailable and adjusted doses of PIs are poorly tolerated in patients on second-line ART, double-dose RAL (800 mg 12-hourly) may be substituted for the PI or triple NRTI therapy may be considered. Triple NRTI ART is, however, inferior to conventional ART and RAL is less robust than a PI in second-line therapy. Nevertheless, short-term use over 6 months is probably preferable to treating TB without rifampicin, which has a high risk of failure or relapse. ART and TB medication share many side-effects (Table 7).

Table 6. ART interactions with rifampicin and recommendations for co-administration

Class	ARV agent	Interaction	Dose of ART drug with rifampicin
NRTIs	All in class	No significant pharmacokinetic interactions	No dose adjustment required
NNRTIs	EFV	Mild reduction in EFV concentrations In some patients, EFV concentrations may increase	No dose adjustment required (600 mg nocte)
	NVP	Moderate reduction in NVP concentrations	Use standard dosing, but omit the lead-in dose phase and start 200 mg NVP 12-hourly
	ETV	Marked reduction in ETV concentrations	Do not prescribe concomitantly
PIs	LPV/r	LPV plasma concentrations significantly decreased	The preferable strategy is to double the dose of LPV/r to 800/200 mg 12-hourly Alternatively, add 300 mg ritonavir 12-hourly to standard dose of 2 tablets 12-hourly of LPV/r There is an increased risk of hepatotoxicity with these strategies These dose adjustments can be made gradually over 1 - 2 weeks*
	SQV/ r	SQV concentrations are significantly decreased	400 mg SQV plus 400 mg ritonavir 12-hourly Increased risk of hepatotoxicity
	All other PIs	Marked reduction in PI concentrations	Do not prescribe concomitantly
InSTI	RAL	Marked reduction in concentrations	Double the dose of RAL to 800 mg 12-hourly

*The double dosing regimen is preferred as it is better tolerated. Dose adjustments should be continued for 2 weeks after rifampicin is stopped.

ART = antiretroviral therapy; ARV = antiretroviral; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; InSTI = Integrase inhibitor (integrase strand transfer inhibitor); EFV = efavirenz; NVP = nevirapine; LPV = lopinavir; LPV/r = lopinavir/ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; RAL = raltegravir.

Table 7. Shared side-effects of TB treatment and ART

Side-effects	ART	TB treatment
Nausea	AZT, ddI, PIs	Pyrazinamide, ethionamide
Hepatitis	NVP, EFV, PIs (NRTIs can cause steatohepatitis)	Rifampicin, isoniazid, pyrazinamide and many second-line drugs including quinolones
Peripheral neuropathy	D4T, ddI	Isoniazid, ethionamide, terizidone/cycloserine
Renal impairment	TDF	Aminoglycosides
Rash	NVP, EFV, RAL	Rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin and many second-line drugs including quinolones
Neuropsychiatric	EFV	Terizidone/cycloserine, quinolones, isoniazid

AZT = zidovudine; ddI = didanosine; PIs = protease inhibitors; NVP = nevirapine; EFV = efavirenz; NRTIs = nucleoside reverse transcriptase inhibitors; D4T = stavudine; TDF = tenofovir.

Table 8. Dosing of ARVs and rifabutin when prescribed concomitantly

ARV	ARV dose change	Rifabutin dose
EFV	None	Increase to 450 mg/day
NVP	None	300 mg/day
ATV or ritonavir-boosted PIs	None	Decrease to 150 mg every second day

ARV = antiretroviral; EFV = efavirenz; NVP = nevirapine; ATV = atazanavir; PIs = protease inhibitors.

13.2 Pregnancy

AIDS is the most frequent cause of death in pregnant women in many Southern African countries,[34] and is a significant cause of morbidity and mortality in children born to HIV-infected women. Even where children are born HIV-negative, their mortality is significantly increased. Traditionally, the focus on HIV and pregnancy has centred on the transmission of HIV to children. This has lead to complex regimens to address concerns about efficacy and resistance. These guidelines attempt where possible to simplify this approach, to decrease transmission in both pregnant and breastfeeding mothers, and facilitate the continuum of care.

13.2.1 NNRTI and PI choice in pregnancy

- EFV has been shown to be teratogenic in primates, resulting in craniofacial abnormalities in exposed offspring. There have been

isolated human case reports of myelomeningocele (neural tube defects) in infants following intra-uterine exposure to EFV. The drug is classified by the United States Food and Drug Administration (FDA) as a category D drug, meaning that 'there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).'

- It should be noted, however, that data supporting this classification are not definitive. The incidence of neural tube defects and all congenital abnormalities among women exposed to EFV in the first trimester is similar to that of the general population, but insufficient numbers have been studied to state definitively that the drug is safe.[35] Most experts are willing to prescribe EFV for use in the second and third trimester, because the neural tube is formed in the first 4 weeks of pregnancy. If a woman expresses the desire to fall pregnant, we suggest starting an alternative to EFV or switching from EFV to an alternative. However, if a woman falls pregnant on EFV we suggest continuing it (the neural tube forms in the first 4 weeks). In a pregnant woman not yet receiving ART, we suggest starting ART after the first trimester so that EFV can be used, unless the patient has advanced immunosuppression, in which case NVP can be started in the first trimester. Recent guidance from WHO is that EFV can be used throughout pregnancy; their review of current data on EFV safety and risk of teratogenicity was reassuring and, from a public health perspective, the need for simplicity and the toxicity associated with NVP were considered to outweigh concerns regarding unproven risks associated with EFV.[36]
- NVP-based ART is the preferred regimen for women in the first trimester of pregnancy. Initiating NVP at a CD4 count >250 cells/µl is associated with a much higher risk of rash-associated hepatitis. It should be noted that switching to NVP in women who plan to fall pregnant with CD4 counts that have increased to >250 cells/µl on ART is **not** associated with this increased risk. Nevertheless, a background risk of rash and hepatitis remains.
- In women who are wanting to fall pregnant if the CD4 count is >250 cells/µl, or if there is intolerance to NVP, a boosted PI regimen can be used instead of NVP. Studies have shown that LPV concentrations are significantly reduced in pregnancy, but are adequate provided that LPV is the first PI that has been used. Once-daily dosing of LPV/r should not be used in pregnancy. Similarly, concentrations of boosted ATV are reduced in pregnancy, and the dose of ATV should be increased to 400 mg daily with 100 mg ritonavir daily. Unboosted ATV is not recommended in pregnancy.

13.2.2 General points

- Fertility choices in the context of HIV treatment are complex. Clinicians should check these choices at every patient visit to minimise risks. Adequate access to safe and effective contraception should be provided. For further guidance:

  Southern African HIV Clinicians Society. Guideline on safer conception in fertile HIV-infected individuals and couples. *Southern African Journal of HIV Medicine* 2011;12:31-44.
- Clinicians should be aware that women may fall pregnant unintentionally, but that the response may still vary from welcoming the pregnancy to wanting a termination.
- In general, far too few women in the Southern African region receive prophylaxis for PMTCT. Every effort must be made to ensure rapid ascertainment of HIV status and access to appropriate PMTCT and ART.
- South African data suggest that most HIV transmissions to babies occur from HIV-positive mothers with CD4 counts <350 cells/µl. Rapid ART initiation for the mother at this level will have a large effect on both maternal and child health.
- All pregnant women of unknown HIV status or who were previously HIV-negative should be offered an HIV test, irrespective of previous sexual activity, marital status, social group or perceived HIV risk status. Ideally, testing should be repeated in the last trimester, as some studies have suggested a greater HIV acquisition risk during pregnancy.
- Mother-to-child transmission is a rapidly evolving field, and international guidelines should be monitored for major changes.

13.2.3 Recommendations

For women who are pregnant and **not** receiving ART, the following is recommended as best standard of care in situations where resources are available:

- All pregnant women should be initiated on triple-drug ART, if adequately prepared, irrespective of CD4 cell count and viral load.
- HIV testing and staging must be done quickly and ART adherence counselling should be accelerated, with the aim to put women on treatment within 2 weeks of first visit (and more rapidly in the third trimester of pregnancy). Women who are being initiated onto ART for PMTCT should ideally be initiated after the first trimester, but women with a CD4 count <200 cells/µl or with severe HIV morbidity should be started in the first trimester.
- Women with baseline CD4 counts <350 cells/µl should have their ART continued indefinitely.
- Women who elect to breastfeed and have a baseline CD4 count >350 cells/µl should continue ART until weaning has occurred.
- ART should be stopped after delivery in women with baseline CD4 counts >350 cells/µl, provided that they are formula feeding.
- If a woman presents during labour and is not receiving ART, single-dose NVP should be given to mother and baby, with additional AZT and 3TC for 1 week or single-dose TDF/FTC to the mother to reduce the risk of NNRTI resistance developing (NVP has a very long half-life).
- Refer to PMTCT guidelines for recommended regimens for the baby.

13.3 ARV dosages in renal failure (Table 9)

Renal function is estimated either by the modified Cockgraft-Gault equation (see Table 9) or the modification of diet in renal disease (MDRD) method, which most laboratories report as 'e-GFR'. The results of these formulae differ slightly, but either can be used for clinical management.

For peritoneal dialysis, the dose given with a creatinine clearance <10 should be given daily. For haemodialysis, the dose given with a creatinine clearance <10 should be given daily, but must be given **after** dialysis on dialysis days, to prevent the drug from be dialysed out.

13.4 ARV dosages in liver impairment

Unlike in renal impairment, there is no blood test that can accurately quantify liver impairment. Child-Pugh class C may require dose

adjustment for the relevant ARVs listed in Table 10. In general, the combination of TDF with 3TC (or FTC) and EFV (or RAL) is regarded as the least hepatotoxic. If the patient has active hepatitis B, discontinuation of ARVs that have activity against hepatitis B (TDF, 3TC and FTC) can cause severe flares of hepatitis (see section 13.5).

13.5 Hepatitis B co-infection

Hepatitis B is a common co-infection in Southern Africa with HIV, with significant implications for progression to cirrhosis, as well as for treatment options. Clinicians are encouraged to support current efforts in the region to vaccinate all children for hepatitis B, and to extend coverage to eligible adults. Access to vaccination, laboratory resources and treatment options are all limited to some extent in Southern African countries, and the recommendations below should each be considered in the light of the local context.

All HIV-infected patients should be screened for active hepatitis B (limiting screening to those with liver function abnormalities will miss many cases as liver enzymes are often normal in hepatitis B infection). Hepatitis B surface antigen is an appropriate screening test. Hepatitis B DNA viral load correlates with disease progression and may be used to monitor anti-hepatitis B therapy, but it is expensive and availability is limited.

Hepatitis B/HIV co-infection is associated with:

- an increased risk of chronic liver disease
- a higher hepatitis B viral load
- diminished responses to hepatitis B vaccine
- poorer responses to interferon-alpha treatment
- an increased incidence of drug-induced hepatotoxicity (particularly with NVP)

Table 9. ARV dosage adjustments in renal failure

	Creatinine clearance	
Drug	**10 – 50**	**<10**
AZT	Unchanged	300 mg daily
ddI	>60 kg body weight: 200 mg daily <60 kg body weight: 150 mg daily	>60 kg body weight: 100 mg daily <60 kg body weight: 75 mg daily
3TC	150 mg daily	50 mg daily
D4T	15 mg 12-hourly	15 mg daily
ABC	Unchanged	Unchanged
TDF	AVOID	AVOID
PIs	Unchanged	Unchanged
NNRTIs	Unchanged	Unchanged

*Source: Bartlett JG. *Medical care of patients with HIV Infection 2010,* and *The Sanford guide to Antimicrobial Therapy 2010.*

AZT = zidovudine; ddI = didanosine; 3TC = lamivudine; D4T = stavudine; ABC = abacavir; TDF = tenofovir; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.

The modified Cockgraft-Gault equation:

$$\text{creatine clearance}^{*} = \frac{(140 - \text{age}) \times \text{ideal weight}}{\text{serum creatinine}}$$

*For women, multiply the total by 0.85.

- a flare of hepatitis within 3 months of commencing ART (due to hepatitis B-IRIS, which is difficult to differentiate from drug hepatotoxicity).

Drugs directed against hepatitis B that have no or minimal anti-HIV activity (e.g. entecavir and telbivudine) are largely unavailable or extremely expensive in our region. For practical purposes, the only available therapy is to use ARVs that also have anti-hepatitis B activity (TDF, 3TC and FTC). As with HIV, these drugs suppress hepatitis B, but do not eradicate it. Effective treatment prevents or slows progression to cirrhosis.

Indications for specific hepatitis B treatments[37] include any one of the following:

- a positive test for hepatitis B e antigen
- raised ALT (>2x the upper limit of normal (ULN))
- evidence of fibrosis on biopsy or on appropriate imaging
- a hepatitis B viral load >10 000 copies/ml (or 2 000 IU/ml).

If any of the above criteria are met, then ART should be commenced irrespective of the CD4 count. The ART regimen should include TDF and 3TC (or FTC). Using 3TC without including TDF leads to hepatitis B resistance in 80 - 90% of patients after 5 years of treatment. If patients meet criteria for switching to a second-line ART regimen (to treat their HIV), this combination (TDF and 3TC/FTC) should be continued to suppress HBV infection, as interruption of TDF and/or FTC/3TC has been associated with life-threatening hepatitis flares. The second-line ART regimen should be shaped around these 2 drugs in discussion with an experienced treater. NVP should be avoided in patients with hepatitis B co-infection.

In patients with hepatitis B and renal dysfunction, the use of TDF may be considered with dosing frequency adjustment based on creatinine clearance (see package insert) and more frequent creatinine monitoring. If renal dysfunction is severe or renal function deteriorates with TDF, 3TC monotherapy (with or without pegylated interferon-alpha) should be considered. Pegylated interferon-alpha is very costly. For further guidance:

Southern African HIV Clinicians Society. Management of HIV-hepatitis B co-infection. *Southern African Journal of HIV Medicine* 2011;12:27-33.

13.6 Malaria

There are several drug interactions between antimalarials and ARVs:

- Artemether-lumefantrine (Coartem) can be safely administered with NVP. There are no data yet on interactions with EFV, but the combination is likely to be safe. Boosted PIs dramatically increase the plasma concentrations of lumefantrine, but a dose reduction is not recommended, as the toxicity threshold of lumefantrine seems to be high. Close monitoring for toxicity is recommended when co-administering artemether-lumefantrine with ART.
- Quinine concentrations are significantly decreased by LPV/r, probably due to induction of metabolism by ritonavir. It is likely that quinine concentrations will also be reduced by EFV and NVP; therefore, quinine should be avoided in patients receiving PIs or NNRTIs. Patients with severe malaria should receive artesunate and those with milder malaria should be treated with artemether-lumefantrine.
- Among drugs used for chemoprophylaxis, there are no clinically significant pharmacokinetic interactions between ARVs and mefloquine or doxycycline. However, mefloquine and EFV both

Table 10. Prescribing ARVs in liver impairment

Class	Drug	Prescribing notes
NRTIs	ABC	Reduce adult dose to 200 mg bd for significant liver impairment Contra-indicated in severe hepatic impairment
	ddI	Use with caution: recent reports implicate use as a risk factor for the development of hepatic decompensation in patients being treated for cirrhosis due to hepatitis C
	FTC	In patients with chronic hepatitis B, there is a risk of rebound hepatitis when FTC is discontinued or if hepatitis B resistance to FTC develops
	3TC	In patients with chronic hepatitis B, there is a risk of rebound hepatitis when 3TC is discontinued or if hepatitis B resistance to 3TC develops
	D4T	Use with caution and never combine D4T and ddI in patients with liver disease
	TDF	In patients with chronic hepatitis B, there is a risk of rebound hepatitis when TDF is discontinued
	AZT	Decrease dose by 50% or double dosage interval if significant liver disease
NNRTIs	EFV	Caution should be exercised in administering EFV to patients with liver disease Therapeutic drug monitoring should be done if available
	NVP	Avoid if significant hepatic impairment or active hepatitis B or C
PIs	ATV	Avoid in severe hepatic impairment
	IDV	Reduce unboosted adult dose to 600 mg 8-hourly if significant hepatic impairment
	LPV/r	LPV is highly metabolised in the liver and concentrations may be increased in patients with hepatic impairment Therapeutic drug monitoring should be done if available
	DRV	Use with caution or avoid if significant liver disease
	SQV	Avoid: there have been reports of worsening liver disease and development of portal hypertension after starting SQV in patients with severe liver disease

NRTIs = nucleoside reverse transcriptase inhibitors; ABC = abacavir; ddI = didanosine; FTC = emtricitabine; 3TC = lamivudine; D4T = stavudine; TDF = tenofovir; AZT = zidovudine; NNRTIs = non-nucleoside reverse transcriptase inhibitors; EFV = efavirenz; NVP = nevirapine; PIs = protease inhibitors; ATV = atazanavir; IDV = indinavir; LPV/r = lopinavir/ritonavir; DRV = darunavir; SQV = saquinavir.

cause frequent neuropsychiatric side-effects; therefore, doxycycline is the preferred chemoprophylactic agent for patients receiving EFV.

- There are several interactions with atovaquone-proguanil (Malanil). Atovaquone concentrations are reduced by PIs and EFV. It is also likely that NVP decreases atovaquone concentrations. Proguanil concentrations are also reduced by PIs and EFV. Use of atovaquone-proguanil is therefore best avoided in patients receiving PIs or NNRTIs.

14. ARV toxicity monitoring and management

Currently used ART is generally well tolerated. Many adverse drug reactions are mild and occur only in the first few weeks of therapy. If toxicity does not resolve or is severe, then the offending drug should be substituted as indicated below. It is important to ensure that the viral load is suppressed before substituting a single drug, otherwise resistance may develop to the new drug, consequently compromising future regimens. Single drug substitutions can be performed safely in the first 6 months of ART without measuring the viral load.

It is rarely necessary to stop the entire ART regimen due to toxicity. It is advised to switch only the culprit drug and continue the rest of the ART regimen. In certain life-threatening situations (e.g. hepatitis with liver failure, lactic acidosis), it may be necessary to cease use of all ARVs. In patients with severe NNRTI-related toxicity, a PI should be substituted. If this is undesirable (e.g. in a patient receiving TB therapy), use of the NNRTI should be stopped and 2 NRTIs should be continued for 1 week to reduce the risk of resistance developing to NNRTIs, which have a long half-life.

14.1 Haematological toxicity

Cytopaenias occur commonly in HIV infection without exposure to ART. Patients receiving AZT, D4T or cotrimoxazole may experience abnormalities in their FBCs. Significant bone marrow toxicity from cotrimoxazole generally only occurs with high doses used for treating opportunistic infections. Patients receiving prophylactic cotrimoxazole uncommonly develop isolated neutropaenia. FBC monitoring is necessary with AZT; this should be performed monthly for 3 months, then after 6 months of therapy and thereafter if clinically indicated (it is unusual to see haematological toxicity occurring after 6 months). The main problem arising from AZT use is anaemia and neutropaenia; platelet counts generally rise with use of the drug. Management guidelines are provided in Table 11. Macrocytosis is usual with D4T and AZT therapy; there is no need to measure vitamin B_{12} and folate concentrations, unless there are other indications that these may be deficient.

Pure red cell aplasia, which presents with severe anaemia and low reticulocyte index, has rarely been associated with 3TC. A bone marrow examination should be performed to confirm the condition. Parvovirus B19 infection should be excluded (a polymerase chain reaction (PCR) test should be requested on blood sent in an ethylenediaminetetra-acetic acid (EDTA) tube).

14.2 Hepatotoxicity

- Liver function tests (LFTs) should be performed at ART initiation and measurement interval should be tailored thereafter to individual drug regimens. The full panel of LFTs is expensive; therefore, it

Table 11. Guidelines for managing haematological toxicity (mainly AZT-induced)

Hb	>8 g/dl Monitor	7.0 - 7.9 Repeat 4 weeks Reduce AZT 200 mg bd or consider switching AZT	6.5 - 6.9 Repeat 2 weeks Consider switching AZT	<6.5 Switch AZT
Neutrophils	1 - 1.5x10^9/l Repeat 4 weeks	0.75 - 1.0 Repeat 2 weeks	0.50 - 0.75 Repeat 2 weeks Consider switching AZT	<0.5 Switch AZT

Hb = haemoglobin; AZT = zidovudine.

Table 12. Guidelines for managing hepatotoxicity

ULN*	<2.5 x ULN	2.5 - 5 x ULN	>5 x ULN
ALT	Monitor	Repeat at 1 week	Discontinue relevant drug(s)
ALP	Monitor	Repeat at 2 weeks	Ultrasound Consider biopsy
Bilirubin	Repeat at 1 week	Discontinue relevant drug(s)	Discontinue relevant drug(s)

*Any elevations with symptoms of hepatitis (nausea, vomiting, right upper quadrant pain) should be regarded as an indication to stop relevant drugs.
ULN = upper limit of normal; ALT = alanine transaminase; ALP = alkaline phosphatase.

is recommended that only ALT is monitored, as this is the most sensitive indicator of drug-induced liver injury. The full LFT profile should be requested in patients with symptoms suggestive of hepatitis. All ARV classes have been associated with hepatotoxicity – most commonly NNRTIs. The NRTIs very rarely present with acute hepatitis. Mild ALT elevations occur very commonly and usually transiently with many drugs in general. ALT elevations >5xULN are significant.

- Ideally, in patients starting NVP, ALT should be monitored at 2, 4, 8 and 12 weeks after initiation. If monitoring is performed, a system should be in place to obtain the result and contact the patient; routine ALT monitoring makes little sense in settings where the result will only be available when the patient is seen in 2 - 4 weeks, or where the patient cannot be contacted. It is essential to educate all patients starting NVP about the symptoms of hepatitis (nausea, vomiting, anorexia, malaise, jaundice and right upper quadrant pain) and drug rash, which is frequently associated with hepatitis. If such symptoms develop, ALT should be determined urgently.
- Hepatotoxic drugs should be discontinued at high levels of LFT abnormality (Table 12) or at lower levels if any symptoms of hepatitis appear. Rechallenge may be considered in selected cases; a specialist should be consulted. If hepatitis occurs together with a rash or fever, or with other systemic involvement, then rechallenge with NNRTIs, ABC or cotrimoxazole should **not** be attempted.
- Prolonged use of NRTIs, especially D4T and ddI, may cause fatty liver. Typically, ALT concentration is more signficantly elevated than AST, and the concentration of cannalicular enzymes (GGT and alkaline phosphatase (ALP)) is more significantly elevated than the transaminases. Non-tender hepatomegaly may be present. Ultrasound or computed tomography (CT) imaging may show decreased hepatic density. The condition is not benign and fibrosis has been reported with long-term ddI use. Patients should be advised to avoid alcohol. Patients receiving d4T or ddI should be switched to safer NRTIs.
- In patients with severe hepatitis or jaundice, the international normalised ratio (INR) should be assessed, as well as features of hepatic encephalopathy (i.e. features of hepatic failure).
- If the concentration of cannalicular enzymes is more significantly elevated than ALT, or if conjugated bilirubin is elevated, an ultrasound of the liver should be conducted to exclude biliary obstruction.
- Isolated unconjugated hyperbilirubinaemia (drug-induced Gilbert's syndrome) is associated with certain PIs (IDV and especially ATV). Although this is a benign condition, it is often cosmetically unacceptable to patients.
- Patients with underlying hepatitis B or C infection frequently experience a 'flare' of hepatitis when ART is commenced, as a consequence of IRIS. Hepatitis B can also flare when ARVs that have activity against hepatitis B (TDF, 3TC and FTC) are discontinued or when hepatitis B resistance develops.
- Many other drugs can cause hepatotoxicity, notably anti-TB agents (including prophylactic isoniazid) and azoles. Cotrimoxazole is a rare cause of hepatitis, usually with a cholestatic picture.

14.3 Hyperlactataemia

- This side-effect has become less common with fewer patients starting ART with D4T and with the use of lower doses. However, clinicians should remain vigilant in patients receiving D4T and be aware that this side-effect can occur with all other NRTIs, although very rare with ABC, TDF, 3TC and FTC. Mildly elevated lactate is not uncommon in patients treated with NRTIs, but is generally asymptomatic. Asymptomatic elevated lactate does not predict the

The potential of NRTIs to cause elevated lactate varies (from most likely to least likely):
stavudine/didanosine > zidovudine > tenofovir/emtricitabine/lamivudine/abacavir

development of lactic acidosis; it is therefore unnecessary to monitor levels in asymptomatic patients.

- Lactic acidosis is a serious, rare, potentially fatal side-effect of NRTIs, most commonly associated with D4T, particularly when combined with ddI. Symptomatic hyperlactataemia without acidosis is more common, but seldom seen with the safer NRTIs recommended.
- The combination of D4T and ddI is associated with a high risk of symptomatic hyperlactactaemia or lactic acidosis (particularly in pregnancy). This combination should therefore be avoided.
- Symptoms are non-specific and include nausea and vomiting, abdominal pain, dyspnoea, fatigue and weight loss.
- Risk factors for hyperlactataemia include:
  - female gender
  - obesity
  - the use of NRTIs for >6 months
  - the development of NRTI-induced peripheral neuropathy or fatty liver.
- A raised lactate of >5 mmol/l together with metabolic acidosis confirms the diagnosis of lactic acidosis. Low serum bicarbonate (<20 mmol/l) is the most sensitive marker of acidosis. Associated abnormalities include elevated AST and ALT, lactate dehydrogenase and creatinine kinase. Treatment is supportive. High-dose riboflavin (50 mg) and L-carnitine may be used (no evidence for either intervention). Management depends on the lactate and bicarbonate concentrations:
  - **Lactate <5 mmol/l and bicarbonate >20 mmol/l and minor symptoms.** NRTIs should be switched to agents less associated with hyperlactataemia: TDF or ABC (if these are unavailable, then AZT could be used) plus FTC or 3TC. Symptoms and serial lactate should be monitored for several months (lactate levels decrease slowly over weeks).
  - **Lactate >5 mmol/l and bicarbonate >15 mmol/l.** NRTIs should be discontinued and the patient should be admitted. If the patient is on an NNRTI regimen, a boosted PI should be added. If the patient has already failed an NNRTI and is on a boosted PI, RAL and/or etravirine (ETV) should be added, if available, or the patient should be continued on the boosted PI only. When lactate has normalised, the patient should be switched to TDF or ABC with 3TC or FTC, as above.
  - **Lactate >5mmol/l and bicarbonate <15 mmol/l.** NRTIs should be discontinued and the patient should be admitted, preferably to an intensive care unit. If the patient is on an NNRTI regimen, a boosted PI should be added. If the patient has already failed an NNRTI regimen and is receiving a boosted PI, RAL and/or ETV should be added, if available, or the patient should be continued on a boosted PI only. Bicarbonate replacement is controversial, but most experts would use this strategy to partially correct severe acidosis. Broad-spectrum antibiotics are recommended as sepsis can mimic NRTI-induced lactic acidosis (this can be discontinued if procalcitonin is normal). On recovery, all NRTIs should be avoided in future regimens (some experts would be prepared to use safer NRTIs, as above).

For further guidance:

Southern African HIV Clinicians Society. Guidelines for the prevention, diagnosis and management of NRTI-associated symptomatic hyperlactataemia and lactic acidosis. *Southern African Journal of HIV Medicine* 2006;7:8-15.

14.4 Dyslipidaemia

- PIs, with the exception of unboosted ATV, can cause fasting hypertriglyceridaemia and elevated LDL-cholesterol. Boosted ATV is associated with less severe dyslipidaemia. D4T can cause mild hypertriglyceridaemia. PIs are associated with the most marked elevation of triglycerides. EFV can cause elevated total cholesterol and mild hypertriglyceridaemia.
- Diet and lifestyle modification should always be advised. Diet is more effective for controlling hypertriglyceridaemia than hypercholesterolaemia. Other cardiovascular risk factors should be addressed.
- If patients receiving PIs develop dyslipidaemia that warrants lipid-lowering therapy, they should be switched to boosted ATV, if possible, rather than adding therapy for the dyslipidaemia. Switching the PI to RAL is another option, because RAL has a favourable lipid profile. However, RAL should only be used in a regimen with 2 other fully active drugs.
- Marked hypertriglyceridaemia (>10 mmol/l) can cause pancreatitis and requires urgent treatment with diet, fibrates and switching to boosted ATV (fibrates can be stopped after 1 month followed by reassessment). Indications for statin therapy in HIV-infected patients should be the same as in uninfected patients, according to the Framingham heart disease risk score. Many statins have interactions with PIs that can lead to potentially toxic statin concentrations, with the exception of pravastatin and fluvastatin, which can be used without dose adjustment. Atorvastatin concentrations are significantly raised by PIs, but lower doses (e.g. 10 mg daily) can be used. Lovastatin and simvastatin should not be co-administered with PIs, as their concentrations are dramatically increased and severe rhabdomyolysis has been reported.
- We suggest assessing lipids after 3 months on a PI regimen. If normal at this stage, the assessment should be performed annually only in those with other cardiovascular risk factors.

14.5 Lipodystrophy

- Long-term ART use may cause chronic lipodystrophic changes, with a change in body fat distribution. This can present with fat accumulation (visceral obesity, breast enlargement, 'buffalo hump' or lipomata) or fat loss (lipo-atrophy, presenting as facial, limb and buttock wasting) or with both.
- The thymidine analogue NRTIs (AZT and especially D4T) are associated with fat loss.
- Previously, PIs were thought to be the cause of lipohypertrophy. However, more recent studies have shown that all classes of ARVs are associated with fat gain to the same extent. Furthermore, longitudinal studies comparing HIV-uninfected people with HIV-infected people on long-term ART have demonstrated that the extent and distribution of fat gain are similar. These data suggest that fat gain is a consequence of treating HIV. The appearance of the fat gain is particularly unsightly when accompanied by subcutaneous fat loss.
- The re-distribution of body fat may be cosmetically unacceptable to the patient, resulting in discontinuation of ART.
- Lipo-atrophy improves when D4T/AZT is substituted with TDF or ABC, but resolution is very slow and usually incomplete; therefore, it is important to recognise lipo-atrophy early or, better still, to use NRTIs that are not associated with the condition.

- There is no good evidence to support the switching of ARVs in patients with fat accumulation. Exercise is of some assistance in reducing abdominal fat. Surgery should be considered in selected cases with focal fat gain (e.g. those with prominent 'buffalo humps'). Metformin modestly reduces weight and improves insulin resistance in patients with the metabolic syndrome or isolated dysglycaemia.
- Visceral fat accumulation is associated with insulin resistance and dyslipidaemia. Other cardiovascular risk factors should be addressed in all patients.

14.6 Hypersensitivity

- Rash with NNRTIs is common (more severe and frequent with NVP) in the first 6 weeks of therapy. If the rash is accompanied by systemic features (e.g. fever, elevated ALT or hepatitis), mucosal involvement or blistering, the NNRTI should be discontinued immediately and rechallenge must not be performed. If the rash is mild and occurs without these features, the NNRTI can be continued and the rash can be treated symptomatically with antihistamines and, possibly, topical steroids. Systemic steroids should not be used.
- In patients who develop rashes during the low-dose NVP 'lead in' phase (200 mg daily), the dosage must not be increased to 200 mg 12-hourly until the reaction has completely resolved. This 'treat-through' approach is only acceptable if the patient can carefully be observed, otherwise NVP should be substituted.
- There is a possible cross-reaction between NVP and EFV, although most studies report no evidence of this. It is acceptable to substitute EFV for NVP in the event of hypersensitivity, unless the reaction was severe. There are hardly any data on substituting NVP for EFV in the event of hypersensitivity; therefore, this substitution is not recommended.[38]
- ABC hypersensitivity is primarily a systemic reaction occurring within the first 8 weeks of therapy in approximately 3% of cases. Fatalities may occur on rechallenge. Therapy must be discontinued and never re-introduced. The manifestations of hypersensitivity include fever, rash, fatigue and abdominal or respiratory symptoms. If there is any doubt concerning the diagnosis (e.g. if the patient has a cough with fever), then the patient should be admitted for observation. Symptoms progress if hypersensitivity is present. The hypersensitivity reaction has been shown to occur on a genetic basis, being virtually confined to the HLA-B*5701 allele, which is very uncommon in Africans. If affordable and available, this allele should be excluded prior to using ABC in populations where the allele occurs.

14.7 Nephrotoxicity

Analysis for serum creatinine and urine proteinuria must be performed at baseline in all patients to detect sub-clinical renal disease, as there is an increased risk of renal failure in HIV infection due to a variety of causes. The dose of NRTIs needs to be adjusted in renal failure (Table 9).

In a minority of patients, TDF may cause a tubular wasting syndrome (including wasting of phosphate and potassium). If patients receiving TDF develop muscle weakness or other muscle symptoms, then potassium and phosphate levels must be assessed. TDF can also cause acute renal failure, but this is uncommon. TDF should be discontinued immediately in patients with acute renal failure; it can be recommenced when the renal failure has resolved only if an alternative cause of renal failure is established.

It is essential to estimate the creatinine clearance before commencing TDF, which should not be used if the clearance is <50 ml/min. For patients receiving TDF, creatinine should be monitored at 3 months, 6 months and then 6-monthly. In high-risk patients (particularly those with co-existent hypertension or diabetes), creatinine should also be checked at 1 and 2 months. Long-term use of TDF with other nephrotoxic agents (e.g. aminoglycosides or NSAIDs) should be avoided. In patients in whom TDF is avoided because creatinine clearance is <50 ml/min at baseline, it may be possible to switch to TDF at a later point if renal function improves. This is often the case if patients had chronic diarrhoea or other opportunistic infections at the time of ART initiation.

14.8 Neuropsychiatric toxicity

AZT and RAL frequently cause headaches when started, but this usually resolves. EFV frequently causes neuropsychiatric effects in the first few weeks of therapy, typically presenting with insomnia, vivid dreams and dizziness. Both dysphoria and euphoria may occur. Fortunately, these features subside in the majority of patients within the first 4 - 6 weeks. Psychosis may occasionally occur. If the neuropsychiatric effects of EFV are not tolerated, then the patient should be switched to NVP or another alternative.

14.9 Dysglycaemia

The older PIs, notably IDV, may cause diabetes. However, the newer PIs (ATV, DRV and LPV) do not. Visceral fat gain, which occurs to a similar extent with all ARV classes, is associated with insulin resistance. Blood glucose should be assessed serially in these patients as part of a cardiovascular risk assessment.

14.10 Gynaecomastia

Gynaecomastia involves the development of breast tissue in men. This is not related to lipodystrophy. It may be bilateral or unilateral. Serum testosterone should be measured and replacement therapy given if this is low. Gynaecomastia is most consistently associated with EFV, so patients should be switched to NVP or another alternative.

15. Immune reconstitution inflammatory syndrome (IRIS)

Approximately 10 - 20% of patients who start ART with advanced immunosuppression experience clinical deterioration during the first months due to IRIS. Two forms are recognised: unmasking IRIS occurs in patients who have an unrecognised opportunistic infection when ART is started and who then present with an exaggerated inflammatory features of that infection during early ART due to it being 'unmasked' by recovering immunity; paradoxical IRIS occurs in patients who are being treated for an opportunistic infection when they start ART, but who develop an immune-mediated worsening or recurrence of features of that infection after starting ART. IRIS is most frequently described in association with TB and CM. Skin conditions such as molluscum contagiosum and Kaposi's sarcoma may also worsen due to IRIS. The diagnosis of IRIS can be difficult, mainly because there is no confirmatory diagnostic test. Diagnosis relies on recognition of the characteristic clinical presentation, ensuring that opportunistic infection(s) are correctly diagnosed, and excluding alternative causes for deterioration such as drug resistance (e.g. MDR-TB). Case definitions for TB and cryptococcal IRIS have been published.[39,40] It is important to ensure that the underlying opportunistic

infection is treated appropriately. ART should be continued, unless IRIS is life-threatening (e.g. neurological involvement in TB-IRIS with depressed level of consciousness). Corticosteroids have been shown to reduce morbidity and improve symptoms in paradoxical TB-IRIS,[41] and can be used in mycobacterial and fungal forms of IRIS when other causes for deterioration have been excluded, and particularly when IRIS features are severe.[42] Practical guidelines for TB-IRIS management have recently been published.[43]

16. Third-line ART

Third-line ART (also referred to as 'salvage' therapy) is used when a patient has experienced virological failure on drugs from the NRTI, NNRTI and PI classes (with documented PI resistance). Before considering third-line therapy, adherence interventions should be intensified and, if there is still no viral suppression, a resistance test must be performed to confirm the presence of resistance to the PI being used in second-line therapy. This test is very expensive and the patient must be on the failing ART at the time, as 'wild-type' HIV is more fit and outgrows the resistant mutant population which therefore cannot be detected within some weeks/months after cessation of ART. However, third-line regimens are also extremely expensive and are not justified if the patient does not have resistance necessitating such a switch. Data show that currently most patients failing second-line regimens in SA are infected with an HIV virus without PI mutations. In these patients, improved adherence is required rather than third-line regimens. The decisions regarding treatment choices in third-line therapy are complex and need to be guided by resistance patterns found on resistance testing. It is essential that resistance tests are interpreted in conjunction with a full ART history by an expert.

Current international guidelines promote the idea that virological suppression is a realistic goal for third-line therapy. This is certainly true with the availability of several new classes of ARV agents (entry inhibitors and InSTIs) together with newer PIs (DRV and tipranavir) and NNRTIs (ETV).[44] As these drugs become available in the region for patients who require them, they provide the possibility of effective suppression with third-line therapy. DRV, ETV and the InSTI RAL are now registered in South Africa. No firm recommendations for a generic third-line regimen can be made and regimen choice should be individualised. An expert treater should always be consulted. A few guidelines regarding third-line ART regimens are further discussed:

- There is a need for specific adherence counselling in patients preparing to start third-line ART, with a frank discussion that this regimen is likely to be their last option for the foreseeable future.
- First-generation NNRTIs (NVP and EFV) have no place in third-line therapy as they do not impair viral fitness.
- A boosted PI with the broadest resistance profile should be selected (this is currently DRV).[45] DRV must be used twice daily in this context (600 mg 12-hourly with 100 mg ritonavir 12-hourly). LPV may be used if the drug is still active based on a resistance test (e.g. if the patient failed second-line ATV therapy).
- The addition of 3TC (or FTC) is recommended as the M184V mutation that it selects for impairs viral replication. Other NRTIs (the most active based on resistance testing) should also be added.
- Consideration of the addition of other salvage drugs (e.g. RAL[46] and/or ETV[47,48]) will depend on genotype resistance test result and cost issues. RAL is preferred because it belongs to an entirely new class with no risk of cross-resistance from prior ART exposure in first- and second-line therapy. Because most patients are not receiving an NNRTI at the time of failing second-line therapy when a genotype resistance test is typically performed, prior NNRTI mutations related to first-line NNRTI failure may be archived at this time. Therefore, it is difficult to be certain from this genotype as to whether ETV is compromised; however, data from South Africa suggest that the majority of patients who have failed NVP or EFV are still susceptible to ETV.[49]
- We advise against double ritonavir-boosted PIs.[1]
- If viral suppression is not achieved on salvage therapy, there is still benefit in continuing failing ART because of the residual partial activity and 'crippling' effect of such ART. 'Crippling' describes the fact that mutant viruses often have less replicative capacity. Provided that the viral load can be maintained below 10 000 copies/ml, the CD4 count will usually be maintained or even increase.[30]

For further guidance, the Southern African HIV Clinicians Society will be publishing ART resistance guidelines in late 2012.

17. Support and counselling

17.1 ART-related counselling

Many patients are afraid of starting ART. The patient should be reassured that the drugs work and that side-effects are usually minor and transient, or manageable. The patient should be given a treatment plan, specifying the reasons for commencing therapy and the drugs to be used (with names and details including the appearance of each drug, when and how they are to be taken, and a brief indication of anticipated side-effects and toxicity).

Adherence in the order of 95 - 100% is required for virological suppression. Poor adherence results in the development of drug resistance. The desire to stop therapy or alter the number or timing of the drugs must be avoided. The patient must be encouraged to discuss drug-related issues with his/her clinician before any changes are made.

17.2 Lifestyle, nutrition, traditional medication and supplements

A healthy lifestyle is recommended, including a balanced diet, plenty of exercise, giving up smoking, moderating alcohol and having a positive outlook on the future. Various adjuncts to therapy are widely used in the community. These include specific diets, food/nutritional supplements, vitamins and so-called immune 'boosters'. Scientific evidence to support the use of these is largely absent. Some herbs and high doses of trace elements and fat-soluble vitamins may cause harm and ought to be discouraged. There are also potentially important drug interactions between some herbal remedies and ARVs. For further guidance:

Southern African HIV Clinicians Society. Nutrition and HIV/AIDS: Nutritional guidelines for HIV-infected adults and children in Southern Africa: Meeting the needs. *Southern African Journal of HIV Medicine* 2007;8:22-32.

Southern African HIV Clinicians Society. Nutrition and HIV/AIDS: Nutritional guidelines for HIV-infected adults and children in Southern Africa: Meeting the needs. *Southern African Journal of HIV Medicine* 2008;9:34-59.

17.3 Immunisations

HIV infection is associated with a suppression of both humoral and cell-mediated immune response, which may impair the response to vaccinations reducing their efficacy, especially if the CD4 count is <200 cells/µl. The safety of live attenuated vaccination is also modified by HIV-infection and live vaccines are contra-indicated in symptomatic HIV disease or if the CD4 count is <200 cells/µl. The decision to use a vaccine must be based on best assessment of risks and benefits.

Travellers to areas endemic for malaria and yellow fever need to be cautioned. The forested regions where contact with the mosquito vector and the virus is possible must be avoided. Yellow fever vaccination poses a risk to HIV-positive travellers whose CD4 count is <200 cells/μl. Such persons should be encouraged to make alternative arrangements or to travel with documentation that permits travel without prior vaccination.

17.4 Opportunistic infections

The use of appropriate prophylaxis (primary or secondary) is essential in patients initiating ART. In general, prophylaxis can be discontinued once the CD4 count has increased to 200 cells/μl (but certain minimal durations of prophylaxis apply for secondary prophylaxis – local and international guidelines should be consulted).

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Appendix: WHO stage 3 and 4 conditions (2006 revision)

WHO stage 3 conditions

- unexplained severe weight loss (over 10% of presumed or measured body weight)
- unexplained chronic diarrhoea persisting for longer than 1 month
- unexplained persistent fever (intermittent or constant for longer than 1 month)
- persistent oral candidiasis
- oral hairy leukoplakia
- pulmonary TB (current)
- severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, severe pelvic inflammatory disease)
- acute necrotising ulcerative stomatitis, gingivitis or periodontitis
- unexplained anaemia (<8 g/dl), neutropaenia (<0.5x10^9/l) and/or chronic thrombocytopenia (<50x10^9/l).

WHO stage 4 conditions

- HIV wasting syndrome
- pneumocystis pneumonia
- recurrent severe bacterial pneumonia
- chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)
- oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- extrapulmonary TB
- Kaposi's sarcoma
- cytomegalovirus infection (retinitis or infection of other organs)
- central nervous system toxoplasmosis
- HIV encephalopathy
- extrapulmonary cryptococcosis including meningitis
- disseminated non-tuberculous mycobacteria infection
- progressive multifocal leukoencephalopathy
- chronic cryptosporidiosis
- chronic isosporiasis
- disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- recurrent septicaemia (including non-typhoidal salmonella)
- lymphoma (cerebral or B cell non-Hodgkin)
- invasive cervical carcinoma
- atypical disseminated leishmaniasis
- symptomatic HIV-associated nephropathy
- symptomatic HIV-associated cardiomyopathy.

Supplementary material

1. Starting ART in hospital

Starting ART in eligible patients in an inpatient setting can be considered in certain circumstances, and should be strongly considered during prolonged hospitalisation, where adherence, toxicity management and other support can be directly provided. However, limited data have shown what many experienced clinicians predicted – that patients who are initiated on ART within the hospital have high default rates. This may be due to several factors – patients who wait to become severely ill and enter hospital may still have high levels of denial; they may be too ill to take in adherence counselling; and discharge may not be managed well. The clinician must carefully weigh up the high risk of deferring ART in terms of mortality and morbidity, and the risk for the individual patient of default which cannot easily be predicted.

If a patient is considered for initiation in hospital, the following should be attended to:

In hospital

- Before discharge, the patient must understand the reasons for initiation of ART
- If the patient is too ill/not mentally competent, a caregiver and/or family member who will act as a directly observed therapy supporter should be involved
- Care should be exercised regarding ART drug interactions with concomitant medication.

On discharge

- Give very clear ART clinic directions, with a referral letter and details of documentation needed by the clinic
- Patients should be encouraged to attend the ART clinic as soon as possible for an appointment and should be informed of reasonable clinic appointment waiting times
- Sufficient medication must be provided to last to the ART clinic visit
- These patients are often discharged on newly initiated TB treatment; few programmes as yet offer integrated TB/ART clinical services, and the need for separate clinical visits should be carefully explained
- Discharging patients directly into the care of adequately counselled family members can be invaluable.

2. High-risk patients

Patients who are at high risk for early mortality, IRIS and ART side-effects include:

- patients with a low BMI, anaemia and low albumin levels
- patients with newly diagnosed opportunistic illness, especially TB and CM
- patients with low CD4 counts.

These patients should be initiated on ART as quickly as possible after any underlying opportunistic illnesses have been addressed (note the specific guidelines regarding ART timing in TB and CM in the guidelines), and should be counselled about the risk of IRIS, which may be misinterpreted as ART side-effects. Ideally, patients should have access to rapid referral systems, in the events of experiencing complicated IRIS or side-effects.

In addition, patients with any of the following are at high risk of default or inadequate adherence:

- uncontrolled depression
- poverty
- ambivalence about their HIV status
- distrust of the formal health sector
- lack of home support or high levels of community stigma
- alcohol or other substance abuse
- post-partum women.

Adherence issues are addressed in the Southern African Antiretroviral Resistance Treatment Guidelines, and include attention to treating mental illness and substance use, giving access to support groups, addressing potential workplace related issues including drug toxicity issues, additional counselling if denial is an issue, honest discussions about alternative health providers and churches that may undermine adherence, better post-partum integration of women/child HIV services, and actively linking poorer patients to poverty alleviation programmes.

3. Common ART misconceptions

- *You cannot take ART if you do not have food available.* None of the commonly used first- and second-line options have meaningful food restrictions. Patients should be warned that their appetite may return and that this may even be uncomfortable. However, food insecurity should be managed actively through rapid referral, and this should never be a reason to delay ART initiation.
- *Doses need to be taken at precisely the same time each day.* This myth was especially prevalent in the earlier days of ART, with anecdotes of patients returning to clinic in despair, after having interrupted their therapy for several weeks after missing a dose due to oversleeping by an hour. Encouraging patients to establish a routine helps with adherence, but delayed dosing is rarely a problem, even if out by many hours. Most of the drugs have long half-lives, and patients should be told simply to take their dose once they remember to do so.
- *You must never drink alcohol again.* Heavy alcohol use may affect adherence, and may potentiate the hepatic toxicity of ART and other hepatic pathology. However, data do not support the commonly held notion that alcohol speeds up the progression to AIDS, nor is there any evidence that moderate alcohol use has any negative effect on the health of HIV-positive individuals. Local guidelines for the general population around responsible alcohol use should be followed; prohibition is not advocated.
- *Disclosure is a prerequisite for ART.* This myth probably followed early experiences with highly rationed ART, where all possible adherence strategies were aggressively pursued to optimise outcomes, and bringing in a 'treatment buddy' was required to access ART. However, it became a form of punishment by some unsophisticated counsellors and clinicians, often under the pretext of preventing transmission, through making HIV status public. This tactic is almost certainly illegal and certainly unethical, and while disclosure may assist patients with support and adherence, this should be suggested and based on the patient's individual circumstances. Forced disclosure can result in violence at the hands of a partner or community, and undermines confidence in confidentiality within the entire health system. Patients should be counselled about the pro's and cons of disclosure, and assisted through the process as needed.
- *Unprotected sex causes virological failure.* This myth probably emerges from a convoluted understanding of the transmission of resistant virus. Theoretically, unprotected sex with someone who is failing ART may allow for the passage of resistant virus, but this is unusual.

Patients should be counselled about safe sex, however, unprotected sex itself will not result in virological failure.

4. Adherence interventions

Causes of poor adherence are often complex and linked to social issues. Common causes include:

- *Inadequate treatment literacy.* Most HIV programmes have extraordinary adherence rates when compared with other chronic diseases; this is largely due to effort being made to ensure patients understand HIV. If a patient fails therapy, some examination of the pre-ART counselling may be merited.
- *Side-effects.* Side-effects are a very common reason for patients to default therapy. A careful history of often subtle but distressing side-effects (bad dreams, sleepiness, poor concentration, nausea, loss of appetite, change of body shape), in conjunction with a work history (shift work in particular) may allow for drug substitutions. Subtle lipo-atrophy changes from D4T and AZT are often not taken seriously by healthcare providers, until disfiguring. Regular enquiry and immediate drug substitutions where possible should form part of every healthcare worker encounter.
- *Depression and other mental illnesses.* Undiagnosed or under-treated depression and other mental illness (the frequency of major depression is 2 times higher in HIV-positive subjects than in matched HIV-negative subjects) may undermine adherence. Patients with depression usually respond well to an anti-depressant medication in combination with non-pharmaceutical interventions. If they do respond it should be given for at least 6 months.
- *Poverty and food insecurity.* Both of these have been related to poor adherence and increased missed clinic visits. Patients often lose their jobs due to ill health during the period leading up to ART initiation, and should be encouraged to return to the job market as soon as feasible or to seek support. This may lead to moving away from the ART clinic, and referral must be facilitated. Access to available grants, social support and employment non-governmental organisations (NGOs) may provide additional support.
- *Work-related issues.* These include shift work and ability to attend clinic visits on weekdays. They are a major cause of poor adherence. Long clinic waiting times, including monthly pick-ups, may make holding down a job untenable, especially with an unsympathetic employer. Clinicians should try to encourage clinics to be flexible, run smoothly for healthy patients, and provide 3 - 6-monthly pharmacy refills.
- *Substance use.* Excessive alcohol use may cause significant problems with adherence. In addition, other recreational drugs may cause problems in certain parts of the country, and use fluctuates according to availability and fad.
- *Social problems.* Stigma and poor social support networks. Perceived stigma is correlated with poor adherence; this may manifest in a fear of tablets being found, an inability to solicit family or partner support, or anxiety regarding an employer, neighbours or a community. Social support groups may assist.
- *Denial.* Initiation of ambivalent, conflicted patients on ART is unlikely to have a successful outcome. Involvement of family members and partners may be an effective mechanism for addressing denial.
- *Pill burden.* This is less of an issue than previously, but must be considered in patients who are failing treatment. Dosing simplification should be a major part of advocacy within public sector programmes.
- *Altered fertility intentions.* HIV-discordant or -concordant couples may spontaneously decide to cease their ART regimen as they intend to begin a family; sympathetic and facilitatory fertility counselling during ART initiation counselling, should prevent this.
- *Conflict of opinions.* Conflict of opinions on the use of ARVs occurs frequently between healthcare providers, certain alternative health providers and churches. This is best addressed with an honest and non-judgmental conversation

Practical adherence tools

Tools such as pillboxes, diaries and setting alarms may help patients to remember to take their medication. Having an emergency supply of a single dose on hand (e.g. in the handbag or workbag) may be useful for situations when patients have unexpected delays in getting home. Medicine formulations and trade names may change, and patients should be educated to recognise the generic name of their current regimen to avoid confusion.

Estimated use of abacavir among adults and children enrolled in public sector antiretroviral therapy programmes in Gauteng Province, South Africa

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In South Africa, abacavir (ABC) is currently recommended as part of first- and second-line antiretroviral therapy (ART) for HIV-positive paediatric patients. Concerns about overprescribing of the drug, particularly to adults, led to an analysis of ABC use in public sector ART programmes. We investigated current prescription of the drug to adults and children accessing ART in 4 public sector programmes across Gauteng Province, South Africa. ABC was almost exclusively prescribed to children initiating ART and adults requiring regimen changes due to drug toxicities. Patterns of ABC use among HIV-positive paediatric patients followed national ART treatment guidelines on the application of the drug. Although ABC is commonly used in the private sector for adults, the current national ART treatment guidelines for adults and adolescents should include ABC as an alternative to standard first- or second-line ART.

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Abacavir (ABC), a nucleoside reverse transcriptase inhibitor (NRTI), has been shown to be an effective component of combination antiretroviral therapy (ART) regimens for both paediatric and adult patients.[1-3] South African (SA) national ART treatment guidelines recommend ABC for first- and second-line regimens in paediatric patients aged ≥3 months.[4] Despite demonstrating a durable antiretroviral response, ABC is not a preferred option for first- or second-line adult regimens in SA, primarily due to its relatively high cost, but also due to concerns about toxicity, particularly hypersensitive reactions, although these are only experienced in 4% of individuals receiving ABC.[5-7] Such reactions commonly present as a rash and fever, but may manifest as fatigue, flu-like symptoms or gastrointestinal upset. Common adverse effects include headache, loss of appetite, nausea and diarrhoea.[7] Of all nucleoside reverse transcriptase inhibitors (NRTIs), ABC is associated with the lowest rate of mitochondrial dysfunction, including lactic acidosis, peripheral neuropathy and lipoatrophy.[5] Substitution of stavudine (d4T) with ABC improves mitochondrial indices, reduces adipocyte apoptosis,[8] and has been shown to be superior to substitution with zidovudine (ZDV) in adults. In older children, once-daily use of ABC has also been shown to be effective, facilitating adherence and improving patient satisfaction.[9-11] ABC-containing regimens are used in adult cases where standard first- and second-line treatments have either failed or cannot be tolerated.

Given current national guidelines for limited inclusion of ABC in highly active ART (HAART) regimens, use of the drug among HIV-positive adults eligible for treatment is generally expected to be low. In 2011, however, a higher than anticipated use of ABC was observed across all provinces of SA. Actual use outpaced the projected need for the drug, placing strains on supplies and programme budgets. In response to concerns about the unnecessary use of ABC (300 mg), we investigated current prescribing of the drug to adults and children accessing ART in public sector programmes across Gauteng Province.

Methods

In 2011 we performed a cross-sectional study of 4 urban public sector antiretroviral clinics in Gauteng Province supported by Right to Care – a non-governmental organisation supporting ART rollout in SA with funding from the United States Agency for International Development (USAID)/

President's Emergency Plan for AIDS Relief (PEPFAR).[12] The clinics operate according to SA national ART guidelines and are run by the national Department of Health, as part of its development of accredited Comprehensive Care, Management and Treatment (CCMT) sites with doctor-managed initiation and follow-up.[13,14] Age categories were defined according to the World Health Organization (WHO) for paediatrics (<10 years of age), adolescents (aged 10 - 18 years) and adults (aged >18 years).[15] Medical records were reviewed for all patients actively receiving HAART at the Themba Lethu Clinic (TLC) in central Johannesburg (JHB) and at 3 other adjacent sites to the north, east and west of TLC. Data on current drug regimens, patient demographics and clinical characteristics were extracted from TherapyEdge-HIV™ (TE), an electronic patient management system used at the clinics. Use of TE data was approved by the Human Research Ethics Committee of the University of the Witwatersrand (HREC-Medical M060626/M110140).

Results

Of 23 084 patients, 76% (22 089) were adults and 5% (995) were children and adolescents (aged ≤18 years), reflecting that the HIV clinics were mainly adult-orientated. The majority of patients attending the central-JHB (12 120/12 185; 99.5%), west-JHB (1 875/2 267; 82.7%) and east-JHB (2 705/2 773; 97.5%) clinics were adults aged >18 years. TLC had a small cohort of paediatric (<10 years) and adolescent (10 - 18 years) patients (65/12 185; 0.5%), compared with north-JHB, where paediatric/adolescent (470/5 859; 8.0%) and adult HIV-positive patients (5 389/5 859; 92%) were seen separately (Table 1).

The total number of patients receiving ABC was 619/23 084 (2.7%). An estimated 0.9% (206/22 089) of adults attending the 4 sites were prescribed ABC-containing regimens at the time of the study, compared with 42% (413/995) of paediatric/adolescent patients (≤18 years). Among patients aged ≤18 years, 11% (7/65), 54% (254/470), 33% (128/392) and 35% (24/68) were receiving ABC-containing regimens at the central-, north-, west- and east-JHB clinics, respectively. At the west- and east-JHB clinics, nearly all patients receiving ABC (98%; 128/131 and 96%; 24/25, respectively) were aged ≤18 years. The number of adults receiving ABC varied from 2.3% (3/131) in west-JHB, to 4% (1/25) in east-JHB, 27% (95/349) in north-JHB and 94% (107/114) in central-JHB. Despite the small size of some cohorts, the results demonstrated a variation in the number of adults prescribed ABC at these 4 clinics.

Among paediatric and adolescent patients (aged ≤18 years), median time receiving ART and ABC varied by clinic. The TLC paediatric/adolescent population had a median duration on ART of 91 months (IQR 40 - 94 months) compared with 37 months (IQR 24 - 51) at the north-JHB clinic and 6 months at both the west-JHB (IQR 3 - 27 months) and east-JHB (IQR 2 - 8 months) clinics. A longer median duration of ART was associated with longer time receiving ABC, with paediatric/adolescent patients at TLC prescribed the drug for a median 40 months (IQR 20 - 94 months). The median time on ABC was shorter at the north-JHB (13 months; IQR 6 - 24 months), west-JHB (5 months; IQR 2 - 8 months) and east-JHB clinics (5 months; IQR 2 - 6 months). More than half of the paediatric/adolescent patients at TLC (4/7; 57%) and the north-JHB clinic (129/254; 51%) had been receiving ABC for longer than 12 months. Among adult patients receiving ABC at the clinics at the time of the study, 35% (TLC; 37/107) and 73% (north-JHB; 69/95) had been receiving the drug for longer than 1 year. Only 6% (8/128) of patients attending the west-JHB clinic were prescribed ABC for longer than 12 months.

The majority of adult patients prescribed ABC at the time of the study were switched onto the drug from other regimens, with only 18% (19/107) of adult patients at TLC and 28% (27/95) of adult patients at north-JHB clinic initiated on an ART regimen containing ABC. Among adult patients reporting a reason for switching to ABC from another regimen (52%; 81/156), the most common reasons were peripheral neuropathy (17%, 14/81), abnormal fat distribution (28%, 23/81) and toxicity (35%, 28/81). Few specific reasons for switching to an ABC-containing regimen were given for paediatric/adolescent patients (25%, 62/247), but among those cases where a reason was reported, abnormal fat distribution was the leading cause of regimen change (76%, 47/62).

Discussion

When considering sites where both adults and children are routinely treated with ART, ABC is primarily prescribed to children. At the east- and west-JHB clinics, the drug was almost exclusively provided to patients aged ≤18 years. We demonstrated a high variation in the prescription of ABC to adult and paediatric/adolescent patients at the 4 sites across Gauteng Province. While we did not demonstrate dramatic over-use of the drug, 67% of patients receiving ABC were children, consistent with guidelines, while 33% were adults, as a likely result of being switched to ABC from another ART regimen due to adverse effects or toxicity.

However, approximately 23% (46/202) of adults at central- and north-JHB were initiated on an ABC-containing regimen. A large proportion of ABC users at the north-JHB clinic (73%; 254/349) were paediatric/adolescent patients compared with a smaller proportion (27%; 95/349) of adults, yet still less than 2% (95/5 859) of patients aged ≥18 years were on an ABC-containing regimen. A large proportion of these adult patients receiving ABC reported long-term use of the drug (73% for 1 year or longer). The large number of adult patients receiving ABC at the north-JHB clinic was likely related to being switched onto ABC from another ART regimen due to an adverse effect (i.e. peripheral neuropathy, lactic acidosis or lipoatrophy/lipodystrophy) – less than 30% of patients aged ≥18 years were initiated on an ABC-containing regimen.

The majority of paediatric/adolescent patients (<80%) at the north-JHB clinic were switched onto an ABC-containing regimen, with 19% (39/201) being due to abnormal fat redistribution. Once-daily use of ABC has been shown to be effective in older children, thereby facilitating adherence and improving patient satisfaction; and it is therefore possible that specialist paediatricians at north-JHB might have prescribed/switched adolescents to ABC for adherence issues.[10,11] Twenty-one per cent of paediatric/adolescent patients were initiated on an ABC-containing regimen. A large proportion of these patients reported long-term use of the drug, with 51% (129/254) receiving ABC for longer than 1 year. This is likely due to the ageing paediatric population receiving care which has maintained paediatric regimens even after moving into adolescence (age 10 - 18 years).

Conversely, <1% (107/12 120) of adults at TLC were receiving ABC, only 35% (37/107) of whom had received the drug for longer than 1 year. Adults were unlikely (17.8%; 19/107) to be initiated on an ABC-containing regimen but rather switched to such a regimen due to toxicity (82.2%; 88/107). The CD4 count (267 cells/mm^3; IQR 160 - 392) and proportion with a detectable viral load (13%; 10/80) at the initiation of ABC confirmed that adults patients were most likely switched to ABC rather than initiated on the drug. TLC treats few patients aged <18 years (0.5% of total patients); however, 71% (5/7) of paediatric/

Table 1. Current use of abacavir (300 mg) at 4 Right to Care-supported sites across Johannesburg, Gauteng Province, South Africa

	Themba Lethu Clinic – central JHB (*N*=12 185) 114 (0.9%)		North JHB (*N*=5 859) 349 (6.0%)		West JHB (*N*=2 267) 131 (6.0%)	East JHB (*N*=2 773) 25 (0.9%)
Total proportion of patients currently receiving ABC†	**>18 years (*N*=12 120) 107 (0.9%)**	**≤18 years (*N*=65) 7 (11%)**	**>18 years (*N*=5 389) 95 (1.8%)**	**≤18 years (*N*=470) 254 (54%)**	**≤18 years (*N*=392) 128 (33%)**	**≤18 years (*N*=68) 24 (35%)**
Patient demographics and clinical characteristics						
Gender						
Male, *n* (%)	47 (44)	5 (71)	31 (34)	136 (54)	49 (38)	11 (46)
Female, *n* (%)	60 (56)	2 (29)	63 (66)	118 (46)	79 (62)	13 (54)
Age at initiation (years), median (IQR)	42.2 (34.9 - 51.0)	14.0 (10.9 - 16.2)	39.5 (33.1 - 44.8)	6.1 (2.4 - 9.1)	4.5 (1.8 - 7.7)	2.8 (1.0 - 5.7)
Baseline CD4 (cells/mm^3), median (IQR)	78 (31 - 171)	3.5 (3.0 - 4.0)	117 (37 - 186)	351 (149 - 665)	380 (162 - 604)	440 (232 - 746)
Baseline CD4, %	7.2 (3.5 - 13.6)	0.9 (0.6 - 1.2)	9.2 (4.5 - 14.2)	14.7 (8.9 - 21.1)	14.5 (9.0 - 19.3)	16.4 (7.3 - 24.7)
Baseline BMI (kg/m^2), median (IQR)	21.0 (18.8 - 24.8)	17.1 (16.7 - 17.6)	22.2 (19.2 - 25.6)	14.5 (12.8 - 16.1)	14.7 (12.6 - 16.4)	15.6 (14.7 - 17.0)
Baseline haemoglobin (g/dl), median (IQR)	10.7 (8.8 - 12.5)	10.7 (2.7 - 16.9)	11.0 (9.9 - 12.7)	10.9 (9.9 - 11.7)	10.4 (9.5 - 11.3)	9.8 (8.4 - 10.9)
Time receiving ART (months), median (IQR)	31.3 (14.3 - 59.5)	90.9 (39.8 - 94.3)	25.7 (16.9 - 41.3)	36.6 (24.3 - 51.3)	6.4 (3.0 - 26.9)	5.7 (1.9 - 8.0)
ABC use						
Age at start of ABC (years), median (IQR)	43.4 (36.5 - 52.4)	14.3 (11.1 - 16.2)	39.8 (33.8 - 46.2)	7.9 (4.5 - 10.9)	5.7 (2.4 - 8.9)	3.7 (1.5 - 5.8)
CD4 at start of ABC (cells/mm3),* median (IQR)	267 (160 - 392)	4.0 (3.0 - 945)	239 (136 - 425)	846 (526 - 1208)	404 (201 - 743)	480 (243 - 919)
CD4 percentage at start of ABC,* median (IQR)	14.7 (8.8 - 22.1)	1.2 (0.6 - 26.7)	16.0 (9.2 - 21.3)	28.3 (21.3 - 33.7)	15.8 (10.2 - 23.6)	17.5 (7.3 - 27.9)
Detectable viral load (>400 copies/ml) at start of ABC,* *n*/*N* (%)	10/80 (13)	1/7 (14)	20/75 (27)	19/209 (9)	13/32 (41)	12/13 (92)
Weight at start of ABC (kg),* median (IQR)	56 (50 - 66)	30 (15 - 41)	61 (52 - 69)	22 (16 - 28)	18 (11 - 24)	13 (9 - 18)
Time receiving ABC (months), median (IQR)	8.5 (4.4 - 16.3)	39.8 (20.0 - 94.3)	16.2 (11.9 - 19.1)	12.5 (6.0 - 24.2)	4.9 (2.3 - 8.3)	4.5 (1.8 - 6.4)
Receiving ABC for >12 months, *n* (%)	37 (35)	4 (57)	69 (73)	129 (51)	8 (6)	0/24 (0)
Initiated on ABC, *n* (%)	19/107(17.8)	5/7 (71.4)	27/95 (28)	53/254 (20.9)	88/128 (68.8)	20/24 (83.3)
Switched onto ABC, *n* (%)	88/107(82.2)	2/7 (28.6)	68/95 (72)	201/254 (79.1)	40/128 (31.2)	4/24 (16.7)
Reason for switching, *n*						
Virological failure	2	-	-	-	-	-
Clinical progression	1	-	1	1	1	-
Abnormal fat redistribution	5	1	18	39	7	-
Peripheral neuropathy	2	-	12	2	-	-
Toxicity (predominantly kidneys)	10	-	3	-	-	-
Anaemia	4	-	-	-	-	-
Hyperlactataemia/lactic acidosis	1	-	3	1	-	-
Toxicity	12	-	3	6	-	-
More effective drug/interaction	2	-	1	2	2	-
Pregnancy	1	-	-	-	-	-
Other/not specified	48	1	27	150	30	4

ABC = abacavir; JHB = Johannesburg. *Within 90 days of ABC initiation. †ABC initiated between April 2004 and August 2011.

adolescent patients on an ABC-containing regimen were initiated on such a regimen.

Differences in ABC use across clinics possibly also partially reflect differences in clinical practice. More than 50% of children from the north-JHB clinic were receiving ABC for longer than 1 year, compared with 16% and 0% at west- and east-JHB, respectively. This could be a reflection of advice and recommendations concerning treating ART side-effects, from specialist paediatric HIV physician services available at north-JHB clinic (not available at the other sites). This advice might have included switching from stavudine- to ABC-containing regimens before implementation of the new national ART treatment guidelines. The switching of many children to ABC at north-JHB (79.1%; 201/254) before implementation of the national guideline could explain the perception of high consumption of this drug in JHB.

The majority (79%) of children from the north-JHB clinic were switched onto ABC from another regimen, while 69% and 83% of children from west- and east-JHB, respectively, were initiated onto ABC. This likely reflects the implementation of the 2010 SA national ART treatment guidelines at these 2 sites, which recommend that infants and children be initiated on a regimen of ABC and lamivudine (3TC) plus lopinavir/ritonavir (LPV/r) or efavirenz (EFV).[16] Among paediatric and adolescent patients, the most frequent reason for switching onto an ABC-containing regimen was ART toxicity and side-effects, most commonly abnormal fat redistribution. This highlights the toxicity of NRTIs, particularly d4T, didanosine (ddI) and zidovudine (AZT), even in children.[7]

The majority of adults prescribed ABC at the time of the study had been switched onto the drug from other regimens. Specified reasons for prescribing ABC to these adults were largely related to ART toxicity and side-effects, including renal toxicity, anaemia, peripheral neuropathy, abnormal fat distribution, and hyperlactataemia or lactic acidosis. This highlights the need to make ABC available to adults and include the drug in the national guidelines for adults as an alternative to standard first- and second-line ART.

Study strengths and limitations

The biggest strengths of this study include the size of the cohort and the depth of the data (using a standardised, electronic data-capturing system, data on ART regimens, visit dates, outcomes, laboratory investigations and demographic data is of high quality).[12] Since these are clinical cohorts, the findings should be considered in light of the study limitations which include missing data (laboratory investigations and reasons for switching) or under-reported conditions or adverse drug effects and the generalisability of the results. This study was done in RTC-supported sites in Johannesburg, thus with a higher level of clinical support and progressive prescription than other sites (i.e. rural sites without any supporting NGO). It is likely that ABC use, especially in adults, would be lower in rural, unsupported sites.

Conclusion

After reviewing the data, there did not appear to be a dramatic over-use of ABC (300 mg) in the 4 Gauteng sites. At the time of the study, there were 619 patients on ABC-containing regimens, accounting for only 2.7% of all the patients currently receiving ART at these clinics. Further, patterns of use at the 4 sites appeared in line with national ART treatment guidelines; most patients prescribed ABC were paediatric patients or adults experiencing drug toxicities on non-ABC-containing regimens.

Conflict of interest. The authors declare that no competing interests exist. Right to Care (RTC) funded part of the research and supported the provision of treatment for the study's patients.

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TB/HIV integration at primary care level: A quantitative assessment at 3 clinics in Johannesburg, South Africa

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Background. In 2004 the World Health Organization (WHO) released the Interim Policy on Collaborative TB/HIV activities. According to the policy, for people living with HIV (PLWH), activities include intensified case finding, isoniazid preventive therapy (IPT) and infection control. For TB patients, activities included HIV counselling and testing (HCT), prevention messages, and cotrimoxazole preventive therapy (CPT), care and support, and antiretroviral therapy (ART) for those with HIV-associated TB. While important progress has been made in implementation, targets of the WHO Global Plan to Stop TB have not been reached.

Objective. To quantify TB/HIV integration at 3 primary healthcare clinics in Johannesburg, South Africa.

Methods. Routinely collected TB and HIV data from the HCT register, TB 'suspect' register, TB treatment register, clinic files and HIV electronic database, collected over a 3-month period, were reviewed.

Results. Of 1 104 people receiving HCT: 306 (28%) were HIV-positive; a CD4 count was documented for 57%; and few received TB screening or IPT. In clinic encounters among PLWH, 921 (15%) had documented TB symptoms; only 10% were assessed by smear microscopy, and few asymptomatic PLWH were offered IPT. Infection control was poorly documented and implemented. HIV status was documented for 155 (75%) of the 208 TB patients; 90% were HIV-positive and 88% had a documented CD4 count. Provision of CPT and ART was poorly documented.

Conclusion. The coverage of most TB/HIV collaborative activities was below Global Plan targets. The lack of standardised recording tools and incomplete documentation impeded assessment at facility level and limited the accuracy of compiled data.

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HIV-associated tuberculosis (TB) continues to pose a considerable global public health threat. In 2010, 1.1 million (13%) of the 8.8 million new TB cases globally were among people living with HIV (PLWH) and HIV accounted for 25% of the 1.4 million TB deaths. South Africa ranked third in the number of incident TB cases in 2010 with an estimated 61% of TB patients infected with HIV. Despite important efforts to curb the TB epidemic, South Africa (SA) was the only high-burden country where the TB burden continued to rise in 2010.[1]

To address the HIV-associated TB epidemic, in 2004 the World Health Organization (WHO) published the Interim Policy on Collaborative TB/HIV activities.[2] To decrease the burden

of TB in PLWH, the guidelines recommend intensified TB case-finding (ICF), isoniazid preventive therapy (IPT) and infection control in healthcare and congregate settings. In 2008, these activities were packaged as the '3Is'. To decrease the burden of HIV in TB patients, the guidelines promote HIV counselling and testing (HCT) and HIV prevention methods for all TB patients, and cotrimoxazole preventive therapy (CPT) and HIV/AIDS care and support including antiretroviral therapy (ART) for those co-infected.

In 2006, the Stop TB Partnership launched the 'Global Plan to Stop TB 2011 - 2015', providing a roadmap for scaling up prevention and treatment and research and development.[3] The plan outlined specific TB/HIV collaboration targets, providing a framework for measuring WHO TB/HIV collaborative activities.

Despite an increasing body of evidence on the effectiveness and feasibility of collaborative TB/HIV activities and recent improvements in TB/HIV integration, implementation remains below targets.[1,3] In 2010, key global indicators included merely 12% of eligible patients initiating IPT, and only 34% of TB patients were reported to know their HIV status.[1]

We reviewed routine TB and HIV data to quantify TB/HIV integration, measured against WHO and Global Plan targets,[1,3] at 3 primary healthcare clinics in Johannesburg, SA.

Methods

Study setting and population

Three primary healthcare clinics in the Johannesburg metropolitan area were purposefully selected to represent different geographical catchment areas and non-governmental and Department of Health (DoH) clinics. All clinics provided TB diagnosis and treatment services, HCT, pre-ART care, and continuation of ART for stable patients. Two sites also served to initiate ART. TB and HIV services were performed vertically in different areas of the clinic by different staff who self-identified as either 'TB' or 'HIV' staff.

HIV counselling and testing was performed in those who requested this service, and provider-initiated HCT was offered to pregnant women and clients with AIDS symptoms, including TB and sexually transmitted diseases. CPT was indicated in PLWH with a CD4 count <200 cells/mm^3, as well as in symptomatic HIV disease and in all TB patients.[4] PLWH were eligible for ART if their CD4 count was <200 cells/mm^3 and/or they met the WHO criteria of stage 4 disease.[5] PLWH were eligible for IPT if they were asymptomatic for TB and had a positive tuberculin skin test (TST), or they were a TB contact.[4] Clinic clients with cough persisting for longer than 2 weeks were considered TB suspects, independent of HIV status. The first-line diagnostic for TB was smear microscopy. Smear-negative TB suspects were assessed further by culture (sputum analysis performed by the centralised National Health Laboratory Service) and chest X-ray (performed at nearest hospital).[4]

All clients who presented to 1 of the 3 selected clinics between 19 August and 19 October 2009 and who received TB and/or HIV services were included for analysis. Eligible clients were identified by review of relevant data sources, including the paper SA National DoH HCT register, TB case identification and follow-up register, TB treatment register, and an electronic HIV database (TherapyEdge) (Table 1). Records of all eligible individuals were reviewed 2 months after their clinic visit to allow sufficient time for activities to be performed and results to be captured. Infection control was assessed using a standardised risk assessment tool based on National TB Infection Control guidelines.[6]

Individuals were categorised as: 'HCT clients' if they received HCT during the study period; 'TB suspect' if they had a diagnostic sputum investigation recorded; and 'TB patient' if they were started on TB treatment during the study period. As the WHO guidelines recommend symptom screening at every clinic visit, we included all PLWH encounters, including multiple encounters by individual PLWH that occurred during the specified time period.

Clinic records of clients who were newly tested HIV-positive were reviewed for documentation of TB symptom screening. Names were cross-checked with the 'TB Detection and Follow up Sputum Register' to assess if a sputum specimen was obtained. Data on PLWH were extracted from the TherapyEdge database. For every encounter registered, recorded symptoms and signs were reviewed. For every PLWH with recorded cough, night sweats, weight loss, axillary nodules or fever, the 'TB Detection and Follow up Sputum Register' was cross-checked to assess if a sputum specimen had been obtained. Files of clients entered into the TB Case Identification and Follow up Register

Table 1. Definition of study participants, data sources and activities reviewed

	Definition	Source	TB and HIV activities performed	Reviewed (*N*)
HCT clients	Clinic clients with record of HIV test	HCT register Medical file	Intensified TB screening Staging by CD4 count	1 104
PLWH encounters	Clinic visits by PLWH	Electronic HIV database TB case identification register	Intensified TB screening Referral for TB investigation (if symptomatic)	6 157
TB suspects	Clinic client with record of diagnostic sputum investigation	TB case identification register HCT register Medical file	Diagnostic assessment of TB suspect HCT CPT and ART (if eligible)	602
TB patients starting TB treatment	Clinic client with TB start date during the study period	TB treatment register TB clinic file	HCT CPT Staging by CD4 count ART if eligible	208

HCT = HIV counselling and testing; PLWH = people living with HIV; CPT = cotrimoxazole preventive therapy; ART = antiretroviral therapy; TB = tuberculosis.

and/or the TB register were reviewed for HIV testing, CD4 count, CPT status and ART status.

All data from standardised National DoH registers and TherapyEdge were entered for analysis in an electronic TB/HIV clinic and patient management program (eMuM®). Descriptive statistics were used to characterise the study population. Statistical analyses were performed with SAS software (version 9.2).

The Global Plan targets[3] were used as the standards against which the implementation of these activities was measured. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, the Institutional Review Board of the University of North Carolina, the City of Johannesburg Health Department, and facility managers.

Table 2. Intensified TB case finding during 6 157 clinic encounters among 4 079 individual PLWH at 3 primary care clinics in Johannesburg

	All *n* (%)	Pre-ART *n* (%)	ART *n* (%)	*p*-value
Total, *N* (%)	6 157 (100)	1 274 (21)	4 883 (79)	
Any TB symptom recorded,* *n* (%)	921 (15)	214 (17)	707 (14)	0.04
Cough	678 (74)	181 (85)	497 (70)	
Weight loss	138 (15)	38 (18)	100 (14)	
Night sweats	169 (18)	27 (13)	142 (20)	
Lymphadenopathy	79 (9)	14 (7)	65 (9)	
Fever	58 (6)	14 (7)	44 (6)	
Investigated for TB (if symptomatic), *n* (%)	91 (10)	26 (12)	65 (9)	0.20
Smear-positive	8 (9)	2 (8)	6 (9)	
Smear-negative, culture-negative	52 (57)	17 (65)	35 (54)	
Smear-negative, culture-positive	9 (10)	1 (4)	8 (12)	
Smear-negative, culture missing/ contaminated	22 (27)	6 (23)	16 (25)	

*Patients may have reported more than one symptom.

Results

Activities to reduce the burden of TB among PLWH

HCT clients were young (median age of 27 years) and the majority were female (75%). Of the 1 104 clients tested, 306 (28%) were HIV-positive. Only 57% of HIV-positive patients had a CD4 count result recorded, with a median count of 336 cells/mm^3 (IQR 152 - 502). The proportion of clients newly diagnosed with HIV who were screened for TB symptoms could not be determined, as this activity was not systematically recorded. Based on review of the TB case identification register, only 2/306 (0.6%) HIV-positive HCT clients were assessed by smear microscopy at the time of their HCT visit.

There were 6 157 clinic encounters for 4 079 individual PLWH. The majority (79%) were for patients receiving ART (Table 2). The proportion of individuals with any recorded TB symptom of any duration was slightly higher for pre-ART than ART visits (17% v. 14%; p=0.04). In both populations, coughing was the most frequently recorded symptom (85% and 70%, respectively). Of the 921 clinic encounters with documented TB symptoms, only 91 (10%) resulted in sputum collection, with similar proportions of pre-ART and ART suspects being investigated (12% and 9%, respectively, p=0.20). Among the 91 TB suspects investigated, 8 smear-positive pulmonary TB cases and 9 smear-negative culture-positive TB cases were diagnosed. A culture result was missing or contaminated in 27% (22/83) of smear-negative TB suspects.

The clinics did not collect information on IPT in an IPT register, pre-ART register or in the electronic HIV system, making an accurate estimate of the number of people receiving IPT difficult. According to the clinic directors, a small number of PLWH received IPT in 1 clinic; the other 2 clinics did not provide IPT.

An infection control plan existed in 2 sites, and posters on cough hygiene were displayed in all 3 facilities. Staff training was *ad hoc*; management reported that an effort was made to educate staff on TB and encourage them to know their HIV status and seek appropriate care. There was no triage system or fast-tracking of patients with coughing. Environmental controls were inconsistently used, 30% of windows remained closed. One site had ultraviolet germicidal irradiation in

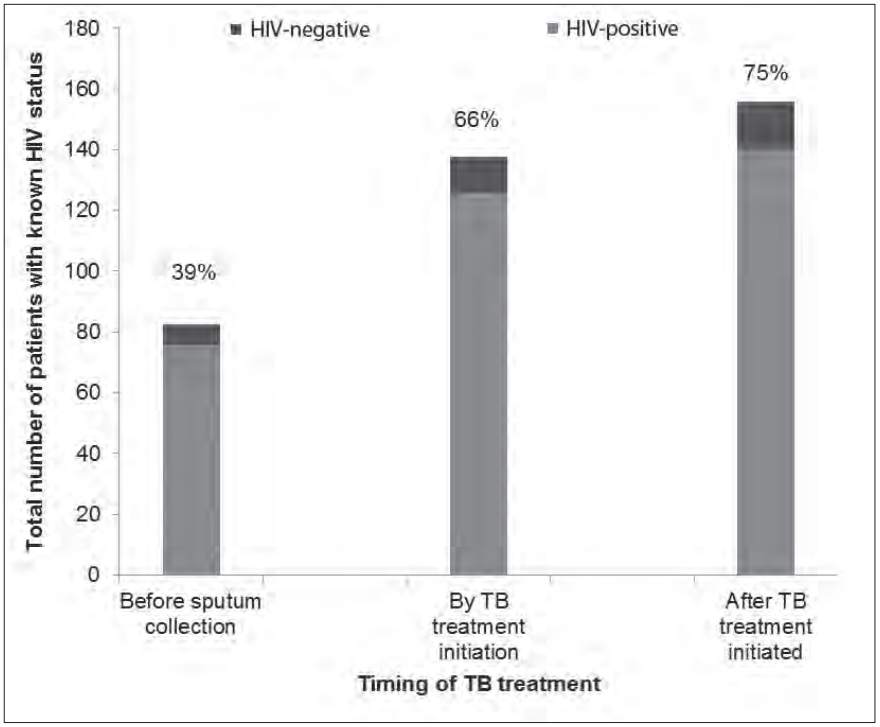

Fig 1. HIV counselling and testing among 208 TB patients registered at 3 primary care clinics in Johannesburg, South Africa.

Table 3. HIV activities recorded among 602 TB suspects at 3 primary care clinics in Johannesburg, South Africa

HIV counselling and testing, *n* (%)	
Known HIV-positive before TB suspect visit	173 (29)
Referred from pre-ART care	26 (15)
Referred from ART clinic	65 (38)
No documentation of HIV care	80 (46)
HCT at time of TB suspect visit (if unknown HIV status), *n* (%)	
Record of HIV counselling and/or testing	217 (51)
HIV-positive	110 (51)
HIV-negative	43 (20)
HIV testing offered but refused	64 (29)
No record of HIV counselling or testing	212 (49)
TB suspects with documented HIV status at end of TB suspect visit	326 (54)
HIV prevalence rate among TB suspects with recorded HIV status, % (95% CI)	73 (0.83 - 0.90)
Staging by CD4 count	
Recorded CD4 count, *n* (%)	
Known HIV-positive before TB suspect visit	132 (76)
Newly diagnosed HIV infection at time of TB suspect visit	90 (82)
Median CD4 count, cells/mm^3 (IQR)	
Known HIV-positive before TB suspect visit	190 (90 - 351)
Newly diagnosed HIV infection at time of TB suspect visit	183 (61 - 289)

the TB clinic area. Personal protection for staff interacting with patients in the form of N95 respirator or surgical masks was available at one clinic, but use was not enforced. TB disease in healthcare workers was not documented.

Activities to reduce the burden of HIV among TB patients

Among the 602 TB suspects, 173 (29%) were known HIV-positive before their suspect visit but only half were documented as receiving HIV care (Table 3). Among the 429 TB suspects with unknown HIV status, 217 (51%) had a record of HCT offer. Of these, 110 (51%) were HIV-positive, 43 (20%) were HIV-negative, and 64 (29%) refused HIV testing. Overall, HIV status was recorded in 54% of TB suspects; 73% (95% CI 0.83 - 0.90) were HIV-infected.

A CD4 cell count was documented in 78% (222/283) of HIV-positive TB suspects. The proportion of suspects staged by CD4 count and the median CD4 count did not differ significantly between those with known status at time of presentation and those tested on the day of the TB suspect visit (76% v. 82%, respectively; p=0.27; and 190 (IQR 90 - 351) v. 183 (IQR 61 - 289) cells/mm^3, respectively).

Among the 602 TB suspects, 143 (24%) were diagnosed with active TB: 80 (56%) with smear-positive TB, 25 (17%) with smear-negative culture-positive TB, 27 (19%) based on clinical and/or radiological criteria and 11 (8%) with extrapulmonary TB. Among the 494 smear-negative TB suspects, a culture was requested in 345 (70%). The culture was positive for *Mycobacterium tuberculosis* in 5%, negative in 48%, and had missing results in 17%. TB treatment was initiated in only 81% (65/80) of TB suspects who were positive on smear microscopy and 26% (7/27) of smear-negative suspects with a positive culture.

During the 3-month study period, 208 patients received TB treatment – the majority (81%) for pulmonary TB. The proportion of TB patients aware of their HIV status increased from 39% before TB diagnosis to 66% at time of TB treatment initiation, and to 75% during TB treatment (Fig. 1). Among the 155 TB patients with known HIV status, 90% were HIV-positive. A CD4 count was documented for almost all HIV-positive TB patients (88%). The median CD4 count was 131 cells/mm^3 (interquartile range (IQR) 60 - 235), and the vast majority (107/123; 87%) had a CD4 count <350 cells/mm^3. There was no documentation of HIV prevention and counselling for HIV-positive or -negative patients, but condoms were freely available at all 3 clinics. According to the staff, most HIV-positive TB patients received CPT, but the proportion receiving such therapy could not be quantified as it was not documented in the TB register, nor consistently recorded in patient files. ART status was not consistently recorded, and patients receiving TB treatment at a clinic not accredited for ART initiation might have initiated ART in another facility, making accurate reporting of the proportion receiving ART impossible.

Discussion

In this quantitative evaluation of collaborative TB/HIV activities at 3 primary healthcare clinics, we confirmed the magnitude of the TB/HIV epidemic and observed strengths and gaps in the fight against TB/HIV at primary care level. However, our analysis was challenged by weaknesses in the routine data required to report on WHO core indicators developed to monitor TB/HIV activities.

The most important strength observed was the high rate of HIV and CD4 testing achieved among TB patients (75% and 88%, respectively). Important gaps included the lack of full TB/HIV integration despite availability of all services at one facility. Firstly, ART coverage among patients with TB could not be ascertained as ART was not documented in the TB register or on the TB treatment card. Secondly, integration of TB services into pre-ART care was poor. Patients newly diagnosed with HIV were not routinely screened for TB, even though a simple TB symptom screen could successfully have been integrated.[7] People newly diagnosed with HIV were not offered IPT, even though most might have been eligible considering that the median CD4 count was 336 cells/mm^3 (higher than the median CD4 count of 111 cells/mm^3 recorded in large ART cohorts in sub-Saharan Africa).[8] Thirdly, TB screening for people enrolled in HIV care was suboptimal. A formalised TB symptom screen was not performed and the TB screening outcome was not recorded as 'no signs', 'suspect', 'on treatment' or 'not assessed', as per WHO recommendations.[9] Consequently, healthcare workers rarely acted upon the information. Only 10% of those presenting with symptoms of TB were assessed by microscopy, and IPT was initiated in only a few asymptomatic PLWH. The 'Proportion of symptomatic PLWH assessed for TB' may be a useful additional indicator. Finally, while

Table 4. Coverage of TB/HIV activities compared with 2010 estimates for SA[1] and The Global Plan to Stop TB targets[3]

Indicator[9]	Global Plan target (2011 - 2015)	SA	Three primary care clinics in Johannesburg
Percentage of HIV-positive patients screened for TB in HIV care and treatment settings (indicator B.1.1)	100%	758 837	• Not recorded at HCT • 100% of PLWH in care screened for TB symptoms • 10% of TB suspects assessed by smear microscopy
Percentage of new HIV-positive patients starting IPT (indicator B.2.1)	100%	124 059 (12%)	• 0% at 2 clinics • Small proportion at 1 clinic
Proportion of healthcare facilities providing services for PLWH that have infection-control practices including TB control (indicator B.3.1)	Target not set but 100% implied	NR	None satisfied the requirements of indicator B.3.1
Proportion of healthcare workers employed in facilities providing care for PLWH who developed TB (indicator B.3.2)	Equal to background rate	NR	NR
Proportion of TB patients with known HIV status (indicator C.1.1)	100%	54%	75%
Proportion of all registered TB patients with documented HIV status who are HIV-positive (indicator C.1.2.1)	NA	60%	90%
Availability of free condoms at TB services (indicator C.2.1)	100%	NR	100%
Proportion of HIV-positive TB patients who receive CPT (indicator C.3.1)	100%	74%	High according to healthcare worked, but poorly documented
Proportion of HIV-positive TB patients enrolled in HIV care services during TB treatment (indicator C.4.1)	100%	NR	Poorly documented
Proportion of HIV-positive registered TB patients given ART during TB treatment (indicator C.5.1)	100%	54%	Poorly documented

NA = not available; NR = not recorded.

some steps were taken towards TB infection control, this was not formally documented. The use of a standardised TB infection control risk assessment tool on a quarterly basis could facilitate monitoring. Given the lack of monitoring at facility level, it is not surprising that global data are lacking on the proportion of healthcare facilities providing services for PLWH that have TB infection control practices (indicator B.3.1) and the proportion of healthcare workers who develop TB (indicator B.3.2).[9]

We also observed shortcomings in non-integrated services. With regard to TB services, only 67% of patients with a microbiological diagnosis of TB initiated treatment, indicating important initial default of patients. Culture results were missing for 17% of specimens sent, resulting in poor service quality and a waste of resources. This could be improved by the introduction of more sensitive TB diagnostic tools with potential for use at point-of-care – such as the Xpert MTB/RIF[10] test and the lipo-arabinomanna (LAM)[11] assay. With regard to HIV services, a CD4 count was recorded for only 56% of people newly diagnosed with HIV, again suggesting a failure to engage and retain patients in care.

The scarcity of data hampered a comparison of our findings with those observed in other settings. Many have discussed the challenges of TB/HIV integration;[7,12-14] however, most data are aggregated at country level and accurate reporting is complicated by the existence of 2 vertical programmes.[15] Coverage of the different components at facility level is not well described. Only 2 other quantitative assessments at facility level have been published: in 2000 - 2002, Coetzee *et al.*[16] observed many missed opportunities for TB and HIV prevention, diagnosis and management at primary care clinics in Khayelitsha; and in 2006, Scott *et al.*[17] audited TB/HIV integration at 16 clinics in Cape Town, using a rapid (2 hours per clinic) audit tool and found poor capacity and weaknesses in quality and continuity of care.[17]

Despite our comprehensive review of data on a large number of clinic clients, our study suffered limitations. To assess routine care, data collection was retrospective; consequently, activities that were performed but not recorded could not be assessed. Furthermore, clients may have received care at other clinics, but we were unable to verify this due to the high number of clinics in the City of Johannesburg (n=90). Data were only reviewed on adult clinic clients; an assessment of TB/HIV activities in children would have been complementary. Finally, SA underwent significant policy changes regarding collaborative TB/HIV since the review was undertaken. ART eligibility criteria changed to a CD4 count <350 cells/mm^3 for TB patients and pregnant women, and ART is currently indicated for all multi-drug resistant

TB patients, regardless of CD4 count. The revised IPT guidelines removed the need for TST and included patients with previous TB and those on ART.

Conclusion

Despite the existence of effective interventions, clear policies and guidelines, the TB/HIV epidemic continues to rage. It is encouraging that most TB/HIV activities were implemented at the primary care clinics, but unfortunately, at coverage levels well below the Global Plan targets (Table 4).[1] This highlights the vast number of opportunities to improve TB control and HIV care as we move towards meaningful TB/HIV integration. The poor quality of routine data was of concern, especially given that primary care clinics are expected to compile data from these sources to report to district and national levels for aggregation, analysis, dissemination and management of the TB and HIV programmes. Collection of TB/HIV collaborative data can be complicated by privacy concerns,[18] the need to share data between 2 vertical programmes, and the lack of investment in monitoring and evaluation tools.[15] Accurate monitoring of TB/HIV activities at all levels (facility, district, national and global) requires rationalisation and standardisation,[18-19] with appropriate treatment cards, registers, cohort reporting forms, and supportive supervision.[9,19] The implementation of integrated TB/HIV electronic data collection and clinic management tools has the potential to galvanise TB/HIV integration at primary care level. We need to ensure that every action is properly recorded and that every loop is closed from diagnosis to treatment of TB and HIV, to result in fully integrated patient care.

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Treating depression in HIV-positive patients affects adherence

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Aim. To determine changes in adherence to antiretroviral therapy (ART) in HIV-positive patients with depression, following treatment with an antidepressant or psychotherapy.

Methods. The study was prospective, randomised and controlled. Consenting volunteers aged ≥18 years and stable on ART for ≥6 months were included in the study. Sociodemographic data were obtained, and a clinical diagnostic evaluation and the Hamilton Depression rating scale (HAMD) were performed on all subjects at entry to and at the end of the study. Participants found to be depressed were randomly assigned antidepressant treatment (20 mg citalopram) or interpersonal psychotherapy (IPT) (5 sessions). Medication was dispensed at each visit and patients were asked to return all unused medication to determine ART adherence. The study was approved by the University of the Witwatersrand.

Results. Sixty-two HIV-positive persons receiving ART participated; 30 were not depressed (control group) and 32 were depressed (patient group). No significant differences in demographic characteristics existed between the control and patient groups. Mean ART adherence at the start of the study was 99.5% (standard error (SE) ±0.46) and 92.1% (SE ±1.69) in the control and patients groups, respectively. Mean ART adherence at the end of the study changed marginally in the control group (99.7%; SE ±0.46) and increased significantly in the patient group (99.5%; SE± 0.13) (p>0.05). The mean ART adherence rate of patients who received pharmacotherapy increased from 92.8% to 99.5%, and of those who received psychotherapy increased from 91.1% to 99.6% (p>0.05). There was no significant association between the increased adherence in the patient group and baseline demographic and clinical characteristics, irrespective of antidepressant therapy or IPT (p>0.05).

Conclusion. Successful treatment of depression with an antidepressant or psychotherapy was associated with improved ART adherence, independent of the type of treatment and sociodemographic factors. It is necessary to identify HIV-positive patients at risk of depression, to initiate antidepressant treatment which may prevent ART non-adherence, and subsequent disease progression and increased morbidity.

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The Joint United Nations Programme on HIV and AIDS recently reported that the number of people newly infected with HIV and the number of AIDS-related deaths are decreasing globally.[1] The programme reported that an estimated 2.6 million people were newly infected with HIV in 2009, representing a 20% drop from the 3.1 million people infected in 1999. In South Africa (SA), the estimated HIV prevalence among all age groups was 10.6% (5.2 million people) in 2008.[2] Although the prevalence in SA has stabilised in recent years, it is still significantly higher than in most countries in sub-Saharan Africa and the rest of the world. Studies have also reported a high prevalence of co-morbid depression among HIV-positive individuals (5 - 48%).[3-9] These variable rates of depression may be explained by variations in the actual populations studied (age, sex, education and ethnicity), different study designs, and differences in the stages of HIV/AIDS.

Adherence refers to the willingness and ability of patients to follow health-related advice, take medication as prescribed, attend scheduled appointments, and complete recommended investigations. Actual adherence to treatment in most chronic diseases varies between 33% and 80%;[10,11] however, the unique characteristics of HIV necessitate near-perfect adherence to antiretroviral therapy (ART).[12-18] Reportedly, ART adherence rates of 90 - 100% are required to: ensure suppression of viral replication;[12,19,20-22] maintain CD4 cell counts; prevent clinical progression to AIDS; and prevent the development of ART drug resistance and resistant HIV strains,[10,23-28] which could leave drug-naive patients with few effective treatment options.

Although debatable, other reports suggest that complete (100%) adherence is required to achieve optimal benefits and to prevent virus mutation to treatment-resistant strains.[29-31]

Depression is reported to be one of the major risk factors affecting ART adherence in HIV-positive patients,[32-35] attributed to a passive[36] or fatalistic-resigned coping style and hopelessness.[37,38] ART adherence is lower in depressed HIV-positive individuals compared with non-depressed individuals. There are published data indicating that treatment for depression is associated with improved adherence.[39,40] However, there is not yet sufficient prospective evidence to support this.

This study, conducted in 2008 at the Perinatal HIV Research Unit (PHRU) of the University of the Witwatersrand, examined ART adherence in a group of HIV-positive patients with depression at Chris Hani Baragwanath Academic Hospital.

The PHRU receives referrals from antenatal clinics for patients who test HIV-positive, and their partners, for initiation of ART. The primary objective was to determine whether any changes in ART adherence resulted following treatment with an antidepressant or interpersonal psychotherapy (IPT).

Methods

The study was prospective, randomised and controlled, and sampling was convenience sampling (as it included patients attending the HIV clinic). Volunteers aged ≥18 years were included in the study. All patients were stable on ART for at least 6 months to reduce any confounding effects of the ART on mood and immunity. Subjects were excluded if they: met the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (DSM-IV) criteria for any other psychotic, mood or substance abuse disorder; were pregnant or nursing; or were medically ill (HIV wasting syndrome, or onset of new opportunistic infections within the preceding 6 weeks). Sociodemographic data were obtained at entry to the study. A clinical diagnostic evaluation and the Hamilton Depression rating scale (HAMD) were performed on all subjects at entry to and end of the study. The depressed patients were randomly assigned to receive either an antidepressant (10 - 20 mg/day citalopram) or IPT. Five IPT sessions were administered during the study period according to the *Comprehensive Guide to Interpersonal Psychotherapy*.[41] These guidelines are clear, easily digested, highly informative, and illustrate the application of a conceptual model in the treatment of depression. While we were not trained or experienced in conducting IPT, it is our opinion that the therapy was correctly administered according to the aforementioned guidelines; there were, however, no objective measures to ensure this, signalling a limitation of our study. Adherence was determined by using the patient self-report (number of doses missed in the preceding 3 days) and the pill count (medication was dispensed at each visit and patients were asked to return all unused medication, which was counted by the investigator).

All participants gave written informed consent to participate. The study was approved by the Committee for Research on Human Subjects, University of the Witwatersrand. In addition to their regular follow-up visits, patients were required to make 2 other visits for which they received financial assistance for travel costs. ART and antidepressant drugs were supplied by the district mental-health clinics.

Descriptive statistics were computed as means and frequencies. The 2-sample *t*-test was used to compare continuous characteristics (age) between the groups. Comparisons of change in adherence as a response to treatment were made between these 2 groups (antidepressant v. psychotherapy). Associations with sociodemographic variables were examined with the use of contingency tables (chi-square test with Yates correction, Fischer's exact test, and odds ratios). All analyses were performed with Statistical Package for Social Sciences (SPSS) software (version 10.0). A p-value <0.05 was considered significant.

Results

Sixty-two HIV-positive persons receiving ART participated in the study; 30 were not depressed (control group) and 32 were depressed (patient group).

Sociodemographic characteristics

In the control group, mean age was 37.7 years (standard error (SE) ±1.2; range 27 - 51); 88% were female; 70% were single (not married, divorced or widowed); 70% were unemployed despite being able and willing to work; and 83.3% had achieved a level of education between grade 8 and 12 (Table 1). All control patients disclosed their HIV status to a partner or family member. The majority (63.3%) were receiving ART from regimen 1a; 23% were receiving triomune.

In the patient group, mean age was 36.8 years (SE ±1.38; range 24 - 53); 90.6% were female; 67.8% were single (not married, divorced or widowed); 81.3% were unemployed despite being able and willing to work; and 71.9% had achieved a level of education between grade 8 and 12 (Table 1). All patients disclosed their status to a partner or family member. Half of the patients were receiving ART from regimen 1a; 15.6% were receiving triomune.

There were no significant differences between the control and patient groups (receiving pharmacotherapy or psychotherapy) with respect to demographic characteristics, namely: gender (chi^2=2.045; p=0.359); marital status; (chi^2=0.547; p=0.761); employment status (chi^2=5.707; p=0.058); highest level of education (chi^2=2.391; p=0.664); number of children (chi^2=5.022; p=0.285); past history of depression (chi^2=4.124; p=0.127); family history of depression (chi^2=2.301; p=0.316); or other concurrent medication (chi^2=0.779; p=0.677) (Table 1).

ART adherence

At entry to the study, the mean ART adherence was 99.5% (SE ±0.46) in the control group, and 92.1% (SE ±1.69) (95% confidence interval (CI) 88.65 - 95.53) in the patient group (Fig. 1). At the end of the study, the mean ART adherence in the control group changed marginally to 99.7% (SE ±0.46) (Fig. 1), while in the patient group, the mean adherence increased significantly to 99.5% (SE ±0.13; CI 99.25 - 99.78; p>0.05). The mean ART adherence rate of the patients receiving pharmacotherapy increased from 92.8% to 99.5%, and those receiving psychotherapy increased from 91.1% to 99.6% (p>0.05) (Fig 2). There was no significant association between this increased adherence rates in the patient group (in those receiving antidepressant medication or IPT) and baseline demographic and clinical characteristics (p>0.05). There was no correlation between the increased adherence rates and changes in HAMD scores.

Discussion

First-line treatment recommended by the 2010 South African Antiretroviral Treatment Guidelines[42] for all new adult and adolescent HIV-positive patients is tenofovir, lamivudine and efavirenz/nevirapine (efavirenz is preferred for TB co-infection, and nevirapine is preferred for women of child-bearing age who are not on reliable contraception). Patients who fail on tenofovir-based first-line therapy may be changed to the second-line treatment of zidovudine, lamivudine and ritonavir. The majority of patients in this study were receiving ART in accordance with these treatment guidelines. Approximately 25% of patients were receiving triomune (a single-tablet fixed-dose combination of stavudine, lamivudine and nevirapine) which enhances compliance. No significant differences existed between the control and test groups with respect to the administering of ART or other baseline characteristics. Hence, it is unlikely that any of these factors may have influenced the study's outcomes.

All participants in the patient group had HAMD scores >15, indicative of depression. Depression was confirmed clinically by eliciting cognitive and affective symptoms that solely reflect mood state (i.e. anhedonia, depressed feelings, and feelings of worthlessness). Fifty-three per cent of the patients had moderate depression (HAMD score 18 - 24) and 44% had severe depression (HAMD scores ≥25).[43] All patients responded to treatment – either pharmacotherapy (citalopram) or

psychotherapy (IPT) – as evidenced by a significant reduction in the mean HAMD scores to <7 in both groups. There was no difference between the type of treatment received and changes in mean HAMD scores. These findings are similar to those of other studies utilising pharmacotherapy[39,40] and psychotherapy,[43,44] which also report that IPT was more successful than supportive psychotherapy in lessening depression in depressed HIV-positive patients who were not acutely ill.

At entry to this study, mean ART adherence of the non-depressed control group was 99.5% – much higher than the 50 - 70% rate reported in other studies in different social and cultural settings.[45-50] The higher adherence rate in our study may be attributed to patient attendance at a rollout clinic that enabled regular monitoring and had the staff and resources to support patients as adherence problems emerged.

The study also found that the mean adherence rate, at entry to the study, among the depressed patient group was significantly

Table 1. Sociodemographic characteristics of the control v. depressed patient groups

Characteristics	Study population (*n*=62)	Controls (*n*=30)	Patients (*n*=32)		Significance
			Pharmacotherapy (*n*=19)	Psychotherapy (*n*=13)	
Gender, *n* (%)					chi²=2.045; *p*=0.359
Male	9 (14.5)	6 (20)	1 (5.3)	2 (15.4)	
Female	53 (85.5)	24 (80)	18 (94.7)	11 (84.6)	
Marital status, *n* (%)					chi²=0.547; *p*=0.761
Single	43 (69.4)	21 (70)	14 (73.7)	8 (61.5)	
Married	19 (30.6)	9 (30)	5 (26.3)	5 (38.5)	
Employment status, *n* (%)					chi²=5.707; *p*=0.058
Employed	15 (24.2)	9 (30)	1 (5.3)	5 (38.5)	
Unemployed	47 (75.8)	21 (70)	17 (94.7)	12 (61.5)	
Level of education, *n* (%)					chi²=2.391; *p*=0.664
Grade 0 - 7	5 (8.1)	2 (6.7)	1 (5.2)	2 (15.4)	
Grade 8 - 12	48 (77.4)	25 (83.3)	14 (73.7)	9 (69.2)	
Tertiary	9 (14.5)	3 (10)	4 (21.1)	2 (15.4)	
Number of children, *n* (%)					chi²=5.022; *p*=0.285
0 - 1	23 (37.1)	13 (43.3)	7 (36.8)	3 (23.1)	
>1	39 (62.9)	17 (56.7)	12 (63.2)	10 (76.9)	
PH of depression, *n* (%)					chi²=4.124; *p*=0.127
Yes	4 (6.5)	1 (3.3)	3 (9.4)	0 (0)	
No	58 (93.5)	29 (96.7)	16 (84.2)	13 (100)	
FH of depression, *n* (%)					chi²=2.301; *p*=0.316
Yes	1 (1.6)	0 (0)	1 (5.3)	0 (0)	
No	61 (98.4)	30 (100)	18 (94.7)	13 (100)	
ART					chi²=15.68; *p*=0.047
Regimen 1°	35 (56.5)	19 (63.3)	7 (36.8)	9 (69.2)	
Regimen 1b	8 (12.9)	1 (3.3)	5 (26.3)	2 (15.4)	
Triomune	12 (17.9)	7 (23.3)	4 (21.1)	1 (7.7)	
Other regimens	7 (12.7)	3 (10)	3 (15.8)	1 (7.7)	
On other medication					chi²=0.779; *p*=0.677
Yes	54 (87.1)	26 (86.7)	17 (89.5)	11 (84.6)	
No	8 (12.9)	4 (113.3)	2 (10.5)	2 (15.4)	

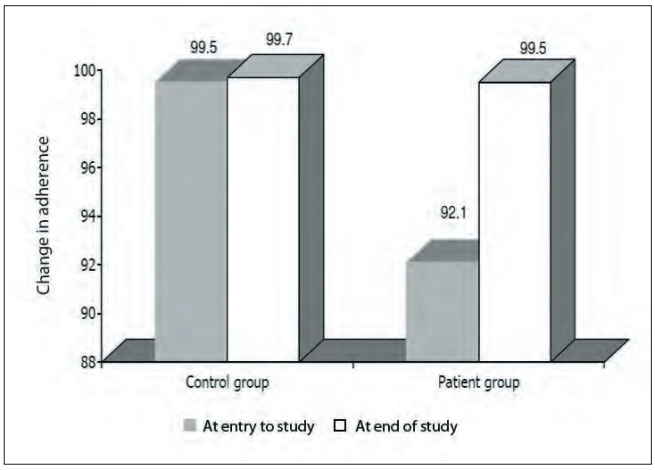

Fig. 1. Changes in ART adherence in the control and patient groups.

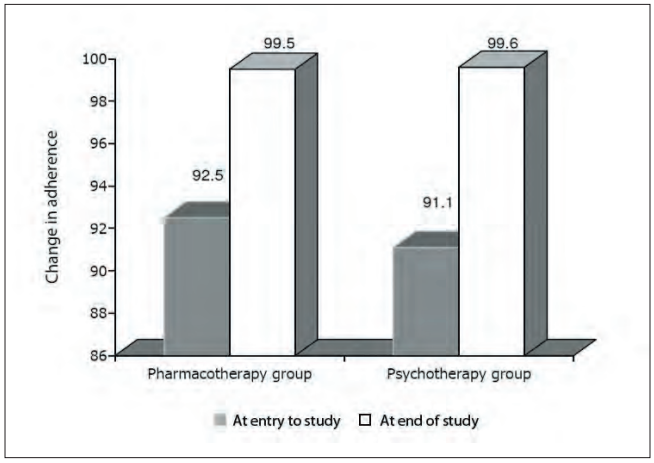

Fig. 2. Changes in ART adherence in the antidepressant v. IPT groups.

lower (92.1%) than that of non-depressed control group. As previously discussed, studies have reported that depression is a risk factor for non-adherence to highly active ART.[32-35] Depression is associated with a passive[36] or fatalistic-resigned coping style and hopelessness[37] with resultant poor treatment adherence. This study adds support to the findings of the above studies. Furthermore, following 2 months of treatment, the mean adherence rate of the depressed patients increased significantly to >99%, independent of the type of treatment received (pharmacotherapy or psychotherapy). Other published studies have reported similar improved ART adherence in depressed HIV-positive patients following treatment with an antidepressant or IPT.[5,51] When medication is used to treat depression, it is important for clinicians to evaluate tolerability and potential adverse effects which may paradoxically decrease adherence.[52] Selective serotonin reuptake inhibitors (SSRIs) have become widely used in HIV-infected depressed patients because of good tolerability and lack of negative effect on adherence. If, however, adherence is negatively impacted by pharmacotherapy, IPT may be the preferred treatment choice, as it results in increased physical and emotional functioning without tolerability issues. Finally, a combination of both forms of therapy may result in further improved outcomes.

Some researchers question the feasibility of the rapid scaling-up and sustainability of ART programmes in depressed people,[25,53] citing concerns about the low and suboptimal adherence in depressed patients leading to the development of resistant HIV strains.[54-56] Resistant strains may leave subsequently infected patients without effective treatment options[24] or require a change to second-line treatment regimens, which are ten times more expensive than first-line regimens.[57] On the contrary, the results of our study and others have shown that the onset of depression in HIV-positive patients is negatively associated with ART adherence, and can be significantly improved with treatment. Screening for depression in all ART rollout clinics is essential and HIV-positive patients found to be depressed must be offered ART and treatment for their depression.

Although not considered or evident in our study, many other factors have been reported to negatively affect ART adherence. These factors are commonly divided into 5 intersecting categories: patient variables; treatment regimens; disease characteristics; patient-provider relationships; and clinical setting.[59] Patient variables include sociodemographic factors (age, gender, race, income, education, literacy and housing status) and psychosocial factors (mental health, substance abuse, family support, religious beliefs about illness and medication, and knowledge and attitude about HIV and its treatment).[58-67] Studies investigating the role of patient variables as predictors of adherence have largely produced inconsistent results. The tendency to ascribe low adherence to often-deprived social groups is a well-established trend;[68] however, as experience with antibiotics has demonstrated, low adherence is widespread and unpredictable rather than restricted to certain social classes.[69] Moreover, adherence rates have been shown to vary between individuals and within the same individual over time.[59]

Adherence is therefore best thought of as a variable behaviour rather than a stable characteristic of an individual, and most people will exhibit low adherence some of the time.[68] Treatment regimen factors include the number of pills prescribed, the complexity of the regimen (dosing frequency and food instruction), the specific type of ART and treatment side-effects. The latter two are associated with sub-optimal adherence,[58] although experience of symptoms and views about medications may vary according to the type of regimen used.[70-72] Patient-provider relationship factors include: overall satisfaction and trust in the provider and clinic staff (opinion of the provider's competency, provider's willingness to include the patient in the decision-making process, and compatibility of race/ethnicity between patient and provider); affective tone of the relationship (warmth, openness and co-operation); and satisfaction with the health service (adequacy of referral, availability of transport, general environment and flexibility of appointments).[73]

Methods used to asses adherence fall into 3 categories: subjective measures (self-report, others' report of adherence, and medical chart review); objective measures (pill counts, pharmacy refill records, and use of mechanical or electronic monitors of pill or drug use); and physiological methods or indicators (plasma assay and laboratory reports).[15] The hierarchy of adherence measures ranks physician and self-assessment reporting as the least accurate, pill count as intermediate and electronic drug monitoring as the most accurate adherence markers.[25] Each of these measures is associated with certain inaccuracies and implementation difficulties. Pharmacy refill records require that patients always use the same pharmacy. Pill counts require patient co-operation to bring their pills to the requested health visits, and not to share pills. The medication event-monitoring system (MEMS) allows recording of when a drug container is opened via a micro-processor in the cap of the container. However, this requires that patients only remove one dose at a time. Moreover, caps only measure bottle opening and not medication ingestion. The pill count method

may overestimate adherence compared with MEMS by about 10%,[48,74] but still has a higher accuracy compared with structured questionnaires.[75]

The subjective measure of patient self-report is the most commonly used measure of adherence. In this measure the patient is asked how many doses were missed in the past day, 2 days and 2 weeks or, alternatively, the percentage of prescribed doses taken in the past 4 days.[47] The format of the questions varies from study to study. Using this measure, inaccuracies may result from use of a longer recall time, in patient forgetfulness and when questioning is imprecise or inconsistent. Further, responses may be influenced by patients' desire to provide a socially acceptable answer, particularly when the interviewer is a health worker whose role has been to exhort the patient to adhere. Nevertheless, self-reported adherence questionnaires are simple and inexpensive and the most widely used method in clinical settings.[29,30] No single measure of adherence is appropriate for all settings or outcomes; therefore, the use of more than one measure is recommended, as performed in this study, to allow the strength of one method to compensate for the weakness of the other and to determine adherence levels more accurately.[76]

Study limitations

The relatively small sample size might have hampered statistical comparisons between treatment groups, while the short duration of follow-up might have masked a greater degree of outcomes in both groups. The study was open-labelled, which could have influenced the response to treatment. This was not a population-based study (patients were recruited from the HIV Research Unit); therefore, the results may be biased by the methods of recruitment and enrolment and are not generalisable. Further, an overwhelming majority of the subjects were female; the treatment of HIV-positive men, who face different psychosocial and socio-economic pressures, may have produced different outcomes.

Strengths of the study include the use of more than one adherence measure to reduce inaccuracies. Moreover, comparison of the sociodemographic characteristics did not reveal any substantive differences between the groups.

Conclusion

The onset of depression in HIV-positive patients is negatively associated with ART adherence. Treatment of this depression with an antidepressant or psychotherapy is associated with significant improvement in ART adherence. Poor adherence leads to ART resistance, which may require a change to a second-line treatment regimen (ten times more expensive than first-line drugs). It is therefore important that healthcare providers identify depression in at-risk patients, to enable closer monitoring and treatment.

Note. This report was part of a large study on HIV and depression. The sociodemographic features of the study population described have previously been reported:

Moosa MYH, Jeenah FY. Antidepressants versus interpersonal psychotherapy in treating depression in HIV-positive patients. South African Journal of Psychiatry 2012;18(2) 47-52.

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Persistent dizziness and recurrent syncope due to HIV-associated Addison's disease: Case report from a resource-limited setting

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Addison's disease or primary adrenal insufficiency is a well-recognised fatal endocrine condition among HIV-infected patients. HIV infection is associated with adrenal gland destruction and profound disruption of the hypothalamic-pituitary adrenal axis. We describe a case of HIV-associated Addison's disease in a 58-year-old newly diagnosed HIV-seropositive male patient, highlighting its occurrence in this era of the HIV/AIDS pandemic.

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Addison's disease, or primary adrenal insufficiency, is a chronic disorder of the adrenal cortex resulting in inadequate production of glucocorticoids and mineralocorticoids. It is an often-missed and potentially lethal condition associated with increased mortality if untreated.[1] Addison's disease typically presents with nonspecific vague symptoms of an insidious onset, such as fatigue, malaise, abdominal pain, weight loss, nausea and vomiting. Physical signs include orthostatic hypotension or shock, and hyperpigmentation, while biochemical indicators include hyponatraemia, hyperkalaemia and hypoglycaemia.[1,2] Causes of Addison's disease include: autoimmune adrenalitis; chronic infections such as tuberculosis (TB), cytomegalovirus (CMV) infection; adrenal haemorrhage or infiltration; and genetic and idiopathic causes.[1]

Addison's disease has also been documented among HIV-infected patients.[3] The potential pathophysiological mechanisms of adrenal dysfunction include direct destruction of the adrenal glands caused by HIV or opportunistic infections such as CMV or TB, neoplastic infiltration, and the effects of pro-inflammatory cytokines. The disease may also be drug-induced, e.g. by ketoconazole and rifampicin.[3,4]

Case description

A 58-year-old newly diagnosed HIV-seropositive antiretroviral therapy (ART)-naive male patient presented with a 3-month history of progressive darkening of the palms of his hands, persistent postural dizziness, fatigability, profound general body weakness, syncope and recurrent episodes of fasting hypoglycaemia. He did not report a history suggestive of TB, fever, headaches, convulsions or chronic glucocorticoid use.

Physical examination revealed mild pallor of the mucous membranes, generalised hyperpigmentation involving the face, oral mucosa and the palmar creases, and absence of peripheral lymphadenopathy. Small volume tachycardia (110 beats/min) with postural hypotension (supine blood pressure 90/50 mmHg, sitting blood pressure 70/40 mmHg) was noted on cardiovascular examination. There were no signs of CMV retinitis or papilloedema on fundoscopy. An extensive clinical evaluation did not reveal any underlying neoplasm.

Laboratory tests revealed a mild normocytic normochromic anaemia (10.6 g/dl; range 12.0 - 16.0), a CD4 count of 17 cells/mm^3, random blood sugar of 2.6 mmol/l (3.5 - 7.0), hyponatraemia (128 mmol/l; 135 - 150), mild hyperkalaemia (5.8 mmol/l; 3.5 - 5.5), raised creatinine (137 μmol/l; 0 - 106) and a low 8 am cortisol level (151.2 nmol/l). Results were normal for serum cryptococcal antigen (CRAG), liver function, serum albumin and corrected calcium level tests.

An electrocardiogram and echocardiography, performed to rule out any structural heart lesion, were normal. Results of a chest X-ray and abdominal ultrasound were also normal. Due to financial constraints, an 8 am serum adrenocorticotrophic hormone (ACTH) test, specific adrenal auto-antibody test and computed tomography (CT) scan of the adrenal gland were not performed.

A diagnosis of probable HIV-associated Addison's disease and severe immunosuppression was made. The patient received a slow bolus of intravenous 50% dextrose, intravenous fluids and hydrocortisone. He was later maintained on oral prednisolone (5 mg in the morning and 2.5 mg in the evening) and ART was initiated (emcitrabine, tenofovir and efavirenz). Oral fludrocortisone and hydrocortisone were not used as they are not readily available in the country. The patient was discharged following remarkable improvement, and was fully counselled about his condition. No opportunistic infection has been discovered at subsequent follow-up visits.

Discussion

This case demonstrates that HIV-associated Addison's disease occurs especially with severe immunosuppression. An 8 am cortisol level <165 nmol/l (6 µg/dl) is highly suggestive of Addison's disease,[1] as demonstrated in our patient. However, most patients require further assessment with a synthetic ACTH test (250 µg Synacthen) for confirmation of the disease. Notably, this test is not readily available in most resource-limited settings. An increase in the serum cortisol level 1 hour after the Synacthen injection to >500 nmol/l (18 µg/dl) confirms the absence of the disease.[1,2]

HIV has a direct independent destructive effect on the adrenal glands and disrupts the hypothalamic-pituitary-adrenal axis, producing subclinical to overt features of Addison's disease. Co-existing opportunistic infections, such as TB and CMV, among HIV-infected patients increase the risk of developing Addison's disease.[3,4] Biochemical evidence of primary adrenal insufficiency is more common in the late stages of HIV infection and with severe immunosuppression, as in this case.[5,6]

European studies of hospitalised patients with advanced HIV infection reported a 17 - 22% prevalence of Addison's disease.[6,7] However, a varying prevalence has been documented in Africa. Meya *et al.*[8] reported a prevalence of 19% among 113 critically ill HIV-infected Ugandan patients. The majority of these patients had TB, Kaposi sarcoma and cryptococcal meningitis as the main underlying co-morbidities.[8] None of the patients had advanced HIV infection as the sole clinical diagnosis. In contrast, studies by Soule[9] and Ross *et al.*[10] among South African patients reported no HIV/AIDS-related Addison's disease.

The management of Addison's disease is focused mainly on the correction of hypovolaemia and electrolyte imbalances with adequate amounts of intravenous fluids, the correction of hypoglycaemia, long-term glucocorticoid and mineralocorticoid replacement and the management of underlying causes.[1,2] A CT scan of the adrenal glands is significant in cases secondary to infections such as TB, as well as in post-sepsis adrenal haemorrhage and neoplastic infiltration. In particular, TB of the adrenal glands revealed by CT imaging presents initially with bilateral adrenal enlargement; calcifications develop later in the disease.[1] CT imaging is costly, however, and not readily available in most resource-limited settings. In cases of HIV-associated Addison's disease, extensive screening for occult opportunistic infections prior to ART initiation and timely initiation of ART are highly recommended.

Conclusion

As demonstrated by this case, clinicians should have a high index of suspicion of Addison's disease in HIV-infected patients presenting with typical electrolyte abnormalities or unexplained hypotension. The disease should be managed instantly and appropriately to reduce the risk of mortality.

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CASE REPORT

Control and non-progression of HIV-1 infection in sub-Saharan Africa: A case and review

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Elite and viraemic controllers represent unique subsets of HIV-infected patients who may also be long-term non-progressors (LTNPs). LNTPs constitute an estimated 1 - 15% of the total HIV-positive population in the USA and Europe, but less is known about their epidemiology in sub-Saharan Africa. Though the exact mechanisms for long-term non-progression appear to be numerous and are still under investigation, research on elite controllers may hold the key to new therapeutics and vaccine development. The clinical management of such patients can be challenging, as there are no standard guidelines for treatment, particularly in resource-limited settings. We describe the case of an HIV-infected Botswanan man who is likely an elite or viraemic controller.

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In 2005, a 54-year-old Motswana male with no known history of medical problems, travel outside Botswana, or HIV risk exposure to persons beyond Botswana, was diagnosed with HIV (rapid test). He was asymptomatic upon presentation, his baseline CD4 was 989 cells/mm^3 (35%) and baseline HIV viral load was <400 copies/ml (assay limit of detection: 400 copies/ml). In 2006, a subsequent rapid HIV-test was also positive, as was qualitative HIV-PCR, although quantitative viral load remained <400 copies/ml. From diagnosis to date of this report, the patient remained asymptomatic with a robust CD4 cell count (Fig. 1) and undetectable viral load, without antiretroviral therapy (ART).

The patient's wife was diagnosed with HIV in 2003 at the age of 37 years. She was severely immunosuppressed at presentation (CD4 count of 40 cells/mm^3). She was initiated on ART and remained virologically suppressed (unclear baseline viral load). The couple's daughter was diagnosed with HIV in 2005 at the age of 9 years (CD4 count – 254 cells/mm^3; baseline viral load – 144 000 copies/ml). At the time of the report, she was virologically suppressed with robust immune response on ART.

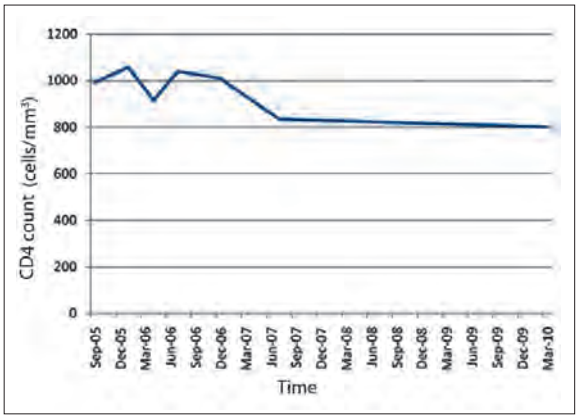

Fig. 1. CD4 cell count of the patient over time.

Discussion

HIV-infected individuals who take longer than 10 years to progress to AIDS have historically been called long-term non-progressors (LTNPs). The study of LTNPs has revealed much about the natural history of HIV infection. Most infected individuals who are not treated with ART advance to AIDS over approximately a decade.[1] Since first investigated

in the late 1990s, it has been shown that not all elite controllers follow the same natural history; some control the virus but eventually progress and others control the virus without progression.[1,2] Whether HIV elite controllers are 'ultra-slow progressors' or totally non-progressive remains to be determined. Little is known about the epidemiology of LTNPs in sub-Saharan Africa (SSA). A Ugandan study found rates of long-term non-progression and elite control among 9% and 1%, of the total HIV-seropositive population, respectively.[3] In the few studies demonstrating the existence thereof in SSA, the cohorts have been very small, the viral and host genetics have not been explored and, in some cases, the cohorts have used significantly different definitions of long-term non-progression.[3-5] Therefore, the mean progression of elite controllers or LTNPs without ART in SSA is largely undefined, especially with regard to HIV subtype C.

Multiple attempts have been made to define and classify HIV disease by clinical progression. The HIV controller consortium has defined 2 groups of HIV-infected patients: elite controllers with viral loads off ART <50 HIV RNA copies/ml for at least 1 year, and viraemic controllers who maintain viral loads of 50 - 2 000 copies/ml without treatment for at least 1 year.[1,6] Casado and colleagues further differentiated groups into elite controllers, 'classic' LNTPs (viraemic controllers v. viraemic non-controllers depending on the viral load), chronic progressors and rapid progressors (who progress to AIDS within 3 years of diagnosis).[7] They defined elite controllers as patients with a positive HIV test, who have viral loads consistently lower than the assay detection level for longer than 10 years.

Features unique to Botswana and Southern Africa

In resource-limited settings, the differentiation of elite controllers from viraemic controllers may be complicated. Though modern assays can detect viraemia >50 copies/ml, older assays – widely used in Botswana's national HIV programme – have a minimum detection level of 400 copies/ml. Even though 95% of all HIV patients do eventually show signs of progression, without highly specialised testing for protective and progressive factors, it is difficult to practically categorise and predict disease progression.[8] Viral suppression is correlated with certain practical clinical outcomes, including partner and mother-to-child transmissibility, and AIDS-free survival.[9]

In Botswana's national ART programme, where patients qualify for ART at a CD4 count <350 cells/mm^3, baseline viral loads are not performed, without which the practitioner cannot differentiate between an LTNP, who has a higher probability of progression of AIDS, and an elite controller. There are case reports of elite controllers progressing after super-infection with 2 different HIV subtypes,[10,11] heightening the importance of secondary prevention strategies in counselling patients.

Some limitations of our case merit further discussion. The lack of subtype analysis is notable; this was neither available nor cost-effective for the patient, given the constraints of Botswana's HIV programme, and the lack of value that this would add to clinical management under current national HIV guidelines. The patient's viral load was repeated at 3-monthly intervals and remained <400 copies/ml. However, viral loads were performed with the Standard Roche Amplicor HIV-1 Monitor test, which is not designed to detect non-M-group HIV (such as group O) or HIV-2.[12,13]

Though HIV-2 and group O HIV-1 could not be ruled out, the patient was presumed to have HIV-1 subtype C. HIV epigenetics of southern Africa, and Botswana in particular, show that the majority of HIV-infected patients are infected with HIV-1 subtype C.[12-14] A 2005 study found a 98.6% prevalence of HIV-1 subtype C among randomly selected samples of HIV-infected patients from 22 health districts in Botswana.[15] Cases of subtype A, B, F1, G, U and CH recombinant have been confirmed in South Africa,[13] while isolated cases of group O have been noted in Zambia.[12] Regional prevalence of HIV-2 is very low in southern Africa, with most cases reported in Angola and Mozambique.[12] The prevalence of HIV-2 is highest in West Africa, with HIV-1 group O being more prevalent in west and central Africa, particularly Cameroon, Guinea and Gabon.[12] While the possibility that our patient acquired HIV from a different source cannot be excluded, the patient denied travel outside of Botswana or to any of the aforementioned regions, as well as sexual relations with commercial sex workers and intravenous drug use. The HIV status of the wife and child also served to support the patient's diagnosis of HIV-1 subtype C; the child was perinatally infected and all members were presumed to have the same strain of HIV. The child had a detectable baseline viral load and both the wife and child experienced immune decline to AIDS, necessitating highly active ART (HAART). This case is particularly interesting because little is known about the rate of the clinical progression of subtype C, compared with other subtypes. Moreover, the epigenetics of subtype C in southern Africa may not be conducive to LTNPs. One study of HIV-1 subtype C in Botswana showed a potentially higher median viral load for extended periods of time.[14] Prior to that in a Senegalese study, HIV-1-infected patients with subtype C, D or G were at higher risk of developing AIDS than their subtype A counterparts.[16]

This case of a likely elite or viraemic controller LTNP in Botswana illuminates gaps in our knowledge of the molecular mechanisms and clinical management of such patients. Most research on elite controllers and LTNPs has been confined to the basic sciences to elucidate the immune mechanisms involved, in hope of providing the basis for new therapeutics and vaccine development.[17-30] Complex host factors appear to be implicated in the control of HIV viral replication as well as viral dynamics.

Our case highlights the importance of the host immune response. The patient's daughter was unable to halt HIV progression and the wife had progressive immune decline, despite questionable viral suppression at baseline. Both were presumed to be infected with the same strain of HIV-1 as our patient.

Important knowledge gaps

Elite controllers are an area of ongoing research and discovery. Numerous viral factors have been posited as the aetiology of elite control. Some studies have confirmed infection with an attenuated replication-incompetent HIV virus in some patients.[8] In particular, mutations in specific HIV genes such as *nef*, *rev*, *tat*, *vif*, *vpr* and *vpu* have been implicated.[18,19,31] However, the majority of elite controllers have been found to be infected with replication-competent HIV,[7,32,33] leaving the interaction with complex host immune mechanisms as the predominant explanation for the existence of most elite controllers. The transmission of HIV from a patient with AIDS to an elite controller has been described[34] as well as a case of continued viral suppression in the face of super-infection with a pathogenic HIV-1 strain.[35] However, the exact viral factors and associated roles in the development of elite controllers is still unknown.

Proposed host immune mechanisms are numerous and have been reviewed elsewhere.[6,8,31-33] Briefly, roles for both adaptive and innate immune mechanisms have been elucidated.[31] HLA class alleles have been implicated: one study showed the expression of allele HLA B*57 in half of their elite controller cohort;[6] however, other studies did not detect this in the majority of their cohort.[9,29]

Natural killer responses and high HIV-specific CD4 and CD8 activation may also be involved.[32,33] Studies evaluating the presence and titres of anti-HIV antibodies have yielded conflicting data, but may have uncovered a potential mechanism in some elite controllers.[21,26,27,32] With continued basic science research, perhaps a greater understanding of the interactions between host and viral factors will become clearer.

Approach to management

As elite controllers appear to comprise less than 1% of the total population of HIV-infected individuals,[31] there is a paucity of data on the mortality, natural progression and optimal management of these individuals.[1] Historically, studies have enrolled a relatively small number of elite controllers, lacked the further differentiation and unified definitions of LTNP and/or elite controllers, evaluated data from subsets from larger studies, and focused on immune mechanisms instead of clinical progression.[1,8,9,36]

Though the majority of elite controllers maintain high and stable CD4 cell counts for longer than 10 years with low rates of clinical progression,[37,38] a minority of patients eventually require treatment as a result of a loss of viral control or progressive immune decline despite continued viral suppression.[1,11] The exact mechanisms, though unknown, may involve low levels of viral replication or factors independent to viral load, such as immune and T-cell activation and pro-inflammatory markers.[1,37,39] In a trial of HIV-1 seroconverters with spontaneous viral suppression, 6.7% of patients progressed to an AIDS-defining illness with 3 patients developing progressive disease in the face of continued viral suppression.[38,40] However, given that the dynamics and clinical progression of elite controllers may differ from other LTNPs (such as viraemic controllers), the lack of differentiation of these groups limits the utility of many older studies.[1,36] Though a system based on clinically distinct classifications is advocated by Graber *et al.*, Casado and colleagues support clinical definitions based on viral and host factors.[7,36] Though there is no standard consensus, more recent studies have capitalised on our evolving knowledge of the different classifications of LTNPs. Okulicz and colleagues have recently shown a decreased risk of AIDS-defining illnesses,[1] stable CD4 and longer duration of CD4>350 cells/mm^3 in elite controllers than in viraemic controllers.[1] There is also conflicting evidence regarding the rate of recovery after the initiation of antiretroviral therapy (ART) in LTNPs. Okulicz *et al.* showed that the LTNP elite controllers appear to reconstitute T-cells more slowly than other patients, while McKinnon and colleagues found that only CD4 nadir, and not elite controller status, was associated with slower rates of immune reconstitution.[1,5,41]

The clinical management of elite controllers is not discussed in the World Health Organization (WHO) HIV/AIDS guidelines, but is briefly touched upon in the United States Department of Health and Human Services (DHHS) and International AIDS Society (IAS) guidelines. The DHHS guidelines mention LTNPs with high viral loads and elite controllers with immune or clinical failure and state that: 'although therapy may be theoretically beneficial for patients in either group, clinical data supporting therapy for non-progressors and elite controllers are lacking.'[42] The IAS HIV guidelines state that ART should be considered for patients with CD4<500 cells/mm^3, 'unless the patient is an elite controller or has stable CD4 with low level viraemia.'[43] Though most expert consultants commence ART in elite controllers based on the same criteria as for HIV progressors, optimal management is unknown. There has been some suggestion that elite controllers may benefit from ART, in decreasing immune activation, which appears to play a central role in immune decline over time[40] and in non-AIDS complications such as cardiovascular and neurological disease.

Conclusion

This case of an elite or viraemic controller illustrates the limitations of national health guidelines, such as those in Botswana, which do not specifically address treatment strategies for elite controllers and/or LTNPs. The case also emphasises how further classification of LTNP types may guide strategies in the future, particularly in the developing world where assays are generally not as sensitive. The omission of LNTP subsets, such as elite or viraemic controllers, from the national guidelines of most African countries is not surprising given that they comprise a very small minority of patients, and emphasis has historically been on preventing and treating opportunistic infections and AIDS. Further research should be devoted to assessing the prevalence, natural history, morbidity and mortality of elite controllers and LTNPs in sub-Saharan African, to create consensus on rational and optimal management.

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CPD QUESTIONNAIRE
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Two CPD points are awarded for the correct completion and submission of the questions below.

CPD questionnaires must be completed online via www.cpdjournals.co.za. After submission, you can check the answers and print your certificate.

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TRUE (A) or FALSE (B) – click on the correct answer:

Regarding Addison's disease in HIV-infected individuals:

1. HIV has a direct effect on the adrenal glands and may also disrupt the hypothalamic-pituitary-adrenal axis.

2. CT scanning is not a valuable investigative modality in suspected Addison's disease in an HIV-infected individual.

Regarding non-progression of HIV disease:

3. Long-term non-progressors (LNTPs) are defined as individuals who take longer than 10 years to progress to AIDS, while elite controllers are individuals who maintain relatively low levels of viraemia without antiretroviral therapy (ART).

4. LNTPs and elite controllers are determined by host genetics and HIV subtype; viral diversity has little role in determining which individuals will be LTNPs.

5. There is strong evidence that all LNTPs and elite controllers will benefit from immediate initiation of ART.

Regarding management of depression in individuals receiving ART:

6. Treating depression can improve ART adherence, and antidepressive medication is superior to psychotherapeutic interventions for this purpose.

Regarding choice of antiretroviral drugs for adult therapy:

7. Abacavir (ABC) hypersensitivity occurs in 10% of African patients, and this increased frequency is the principal reason why this agent is not widely recommended in South African guidelines.

8. In adults, ABC is commonly used in single-drug substitutions required due to toxicity to specific agents (e.g. peripheral neuropathy attributed to D4T).

9. Protease inhibitors (PIs) can cause dyslipidaemia; as a result, a statin should be routinely considered in all HIV-infected patients starting lopinavir/ritonavir.

10. Among NRTIs, zidovudine is more likely to cause hyperlactataemia than lamivudine.

11. In the event of mild ART toxicity, it is advisable to stop all antiretroviral agents, and re-introduce one agent at a time to identify (and then avoid) the responsible agent.

12. The combination of TDF and ddI should be avoided due to poor virological outcomes.

13. There is evidence to suggest that ABC may not be as effective as tenofovir in achieving and sustaining viral suppression in adults.

14. ART failure is best defined as two viral load measures >400 copies/ml on specimens approximately 2 weeks apart.

15. In HIV-infected patients who also have hepatitis B, TDF and 3TC play an important role in managing both infections.

16. Saquinavir, if affordable, is the PI of choice in individuals with no prior PI exposure.

17. The use of two NRTIs should be avoided in second-line therapy, if at all possible.

18. Emtricitabine and lamivudine are essentially interchangeable in terms of their efficacy.

19. Gynaecomastia is a notable side-effect of efavirenz.

Regarding integration of tuberculosis (TB) services into HIV care and treatment:

20. Evidence from HIV clinics in Gauteng suggests that isoniazid preventive therapy and TB screening are being implemented for the vast majority of patients, thereby helping to reduce the burden of TB in HIV-infected individuals.

INSTRUCTIONS

1. Read the journal. All the answers will be found there.
2. Go to www.cpdjournals.co.za to answer the questions.

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