

## ISSUES IN MEDICINE

# The 2010 South African guidelines for the management of HIV and AIDS: A review

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## Background

The South African (SA) National Department of Health (DoH) released new guidelines for the management of HIV/AIDS in April 2010. We discuss here controversial issues and operational challenges in the guidelines; the stimulation of debate and contributing to future guidelines; the timing of initiation of antiretroviral treatment, scope and timing of laboratory monitoring and testing of concomitant conditions, operational challenges such as paediatric HIV treatment and nurse-driven care, and procedures relating to the guidelines such as the need for transparency of the guideline committee and the standard of evidence used to develop the guidelines. We welcome comment and sharing of further insights that will contribute to future guidelines.

Our motivation stems from the facts that South Africa's HIV epidemic is not abating; its Millennium Development Goals are not being met; and child and maternal mortality are worse than they were in 1990.<sup>1</sup> The Department of Virology of the University of Pretoria convened a meeting of private and public health practitioners in June 2010 to debate the DoH's new antiretroviral treatment (ART) guidelines.

## Are the goals realistic? Are these 'national' guidelines and do they address private and public health sector needs equally?

### Feasibility and standardisation

The goals are laudable, their scope daunting. But are they achievable? According to the spokesperson for the SA National AIDS Council, 'The purpose [of the guidelines] is to bring these into line with international recommendations and ensure the use of more efficacious drugs.'<sup>2</sup> How will these goals be implemented and progress and success measured?

### Guidelines for the public or private sector or both?

The guidelines focus on needs of the public health sector, whose huge numbers dwarf private-sector HIV medicine. But both systems must find common ground as health borders are porous. Drugs and

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**Table I. Goals of the 2010 ART guidelines**

- Achieving best possible health outcomes in the most cost-efficient manner
- Implementation of nurse-initiated ARV-treatment
- Decentralisation of service delivery to primary health care (PHC) facilities
- Integration of services for HIV with TB, maternal and child health (including prevention of mother to child transmission), sexual and reproductive health, and wellness programmes
- Earlier diagnosis of HIV
- Prevention of HIV disease progression
- Prevention of AIDS-related deaths
- Retention of patients on lifelong therapy
- Prevention of new infections among children, adolescents and adults
- Mitigation of the impact of HIV/AIDS on society

tests must be identical or similar. Guidelines should inform and aid integration e.g. when the guidelines do not refer to the use of viral genotyping or baseline hepatitis B screening, does this mean that these tests are unavailable or unnecessary? National guidelines must inform health workers broadly and wisely.

### Transparency

International guidelines are referenced throughout and recommendations graded. The panel of experts responsible for drafting the guideline is identified. A guideline must be seen to be objective, truthful, credible and relevant. Since we could not locate information about the panel of experts from the 'guideline' website,<sup>3</sup> we question the adequacy of representation from all stakeholders, including the private sector.

## When should ART be started?

### Starting CD4 level

The guidelines recommend that therapy in adults be started at CD4  $\leq$  200 cells/ $\mu$ l except in pregnancy and active tuberculosis, where therapy can now be started at CD4  $\leq$  350 cells/ $\mu$ l. A stated objective is to 'ensure timely initiation of antiretroviral drugs.' At the 2009 International AIDS Society (IAS) Conference, the president of the society stated that CD4  $\leq$  350 cells/ $\mu$ l should be considered a 'minimum standard of care' for commencing ART, which is supported by the World Health Organization (WHO), European and British AIDS societies. The IAS-USA panel recommend higher levels:  $\leq$  500 CD4 cells/ $\mu$ l.<sup>4</sup>

### Risks of delaying ART

The outcomes of more than 45 000 patients starting ART since 1997, from 18 observational cohorts in Europe and North America, were reviewed. Delaying ART until CD4 251 - 350 cells/ $\mu$ l demonstrated a 28% (HR 1.28, 95% CI 1.04 - 1.57) increased risk of AIDS and death compared with those starting at higher levels i.e. 351 - 450 cells/ $\mu$ l.<sup>5</sup> This finding suggested that CD4 of 350 cells/ $\mu$ l be the

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minimum threshold for starting ART, and initiated the international debate about the benefits of starting even earlier. These results have been reproduced in the developing world: in Haiti, adults with CD4 counts between 200 and 350 cells/ $\mu$ l were randomised to start ART immediately or defer treatment until CD4 had dropped below 200 cells/ $\mu$ l. A fourfold increase in mortality in the deferred arm led to the premature discontinuation of this study on ethical grounds.<sup>6</sup>

Delay in starting ART increases disease- and treatment-related morbidity and costs: the effects of opportunistic disease are more severe, drug toxicity is more frequent, and the immune reconstitution inflammatory syndrome (IRIS) more overwhelming.<sup>7-9</sup> IRIS is a particular problem in southern Africa where concomitant infections such as tuberculosis and cryptococcal meningitis are frequent and initiation is late. The guidelines should specifically address the timing of ART initiation in the face of active opportunistic infections and the management of IRIS, including when steroid use is warranted, but is silent on these issues.

Late ART initiation is linked to the risk of AIDS- and non-AIDS-defining malignancy,<sup>10</sup> drug resistance<sup>9</sup> and increased risk of failure to reconstitute the immune system.<sup>11</sup> Patients starting ART at CD4  $\geq$ 350 cells/ $\mu$ l are more likely to achieve normal CD4 counts within 4 years of starting treatment.

### Economics of starting ART at earlier CD4 levels

Why would the DoH want to delay the start of ART? Costs and a limited capacity are probable constraints. Nevertheless, there are compelling data from cost-effectiveness studies and mathematical modelling that the early start of ART in South Africa can be cost-effective in adults and children, even at levels  $>$ 350 cells/ $\mu$ l.<sup>12</sup> There are caveats: poor adherence, adverse events and loss to follow-up can increase costs and undermine the investment. Increased caseloads would demand more from a tired and demoralised health sector. But few South Africans currently present with CD4 counts  $>$ 200 cells/ $\mu$ l. Raising the CD4 bar to 350 cells/ $\mu$ l is unlikely to swamp our HIV clinics. Innovative and supportive handling of this challenge could catalyse improvement of the delivery of care to all South Africans.

Statistical modelling shows that earlier treatment would not have had a major impact on the number of patients receiving ART. If patients initiate treatment at a threshold of  $\leq$ 200 cells/ $\mu$ l, the number of patients on ART would increase by approximately 233% from roughly 950 000 in 2009 to approximately 3.16 million by 2016. Adoption of the new South African guidelines would result in a further increase of 14%, and the WHO guidelines in only an additional 10% by 2016.<sup>13</sup> Some of our poorer neighbours, such as Botswana and Zambia, have already adopted these guidelines, and a few others, such as Malawi, Tanzania and Nigeria, have conducted WHO-supported feasibility studies and announced plans to roll out the new WHO guidelines by mid-2011.

### Laboratory monitoring: Which tests? How often, if at all? Utilitarian concerns, limited resources

Laboratory monitoring is concerned with the virus, the immune response and toxicity. Insights gained from such monitoring have led to enormous achievements. However, tests are expensive and difficult to regulate, and results frequently ignored. Would money be spent more efficiently on scaling up access to ART? Perhaps with this in mind, can the guidelines significantly reduce baseline and follow-up tests? Will fewer viral loads lead to the impaired management of adherence and resistance? Will less monitoring mean greater delay in diagnosing adverse events? Will this compromise patients' health?

### Laboratory tests in Africa: are these necessary?

The Development of AntiRetroviral Therapy in Africa (DART) study addressed the difference between clinically driven monitoring (CDM) and laboratory and clinical monitoring (LCM). No 'real-time' viral load (VL) results were provided in either, but CD4 results were reported to each group and haematology and chemistry data could be accessed in the CDM arm if 'clinically indicated'. Grade 3 and 4 events were provided immediately irrespective of the group. This important aspect of the study has been overlooked by policymakers, who reduced laboratory monitoring based on the DART study. Even though overall survival was excellent after 5 years, 28% CDM v. 21% LCM participants had a new WHO stage 4 event or died (6.94; 95% CI 6.33 - 7.60 and 5.24; 4.72 - 5.81 per 100 person-years, respectively). The absolute difference of 1.70 per 100 person-years (95% CI 0.87 - 2.54) translated into a significant relative HR of 1.31 (95% CI 1.14 - 1.51;  $p=0.0001$ ).<sup>14</sup> Worryingly, the proportion of patients with HIV RNA  $>$ 1000 copies/ml increased from 15% at 24 weeks to 24% at 48 weeks; 18 (58%) of 31 genotyped samples at 24 weeks had  $\geq$ 1 major nucleoside reverse transcriptase inhibitor (NRTI)-associated mutation, compared with 41 of 47 (87%) at 48 weeks. A mean of 2.0 (95% CI 1.3 - 2.8) thymidine analogue mutations (TAMs) developed between weeks 24 and 48.<sup>15</sup>

### VL monitoring

The guideline discarded baseline VL monitoring. The first VL is drawn at 6 months on therapy, repeated at 12 months, and thereafter annually. Baseline VL is related to risk of drug resistance and death, progression of disease, occurrence of opportunistic diseases (particularly cancers), and response to therapy.<sup>10</sup> When the starting-point of a journey is unknown, progress is difficult to map. After taking ART for 6 months, the VL will be either detectable or undetectable. If undetectable, either the virus is well suppressed, or undetectable from the start i.e. an elite controller, an unusual recombinant form, or a false-positive HIV ELISA. How would one know?

If the VL is detectable at 6 months, adherence counselling may be too late. Non-adherence can lead to resistance to the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and 3TC within 4 - 8 weeks. All that is needed is a single-point mutation. Longer time spent on a failing regimen leads to greater numbers of mutations and more complex resistance.<sup>16</sup> Early VL monitoring, 6 - 12 weeks after starting ART, provides the trigger to early intervention and prevention of resistance. Frequent VL monitoring is particularly useful in the first months after starting ART, and the IAS-USA 2010 guidelines recommend repeating VL 2 - 8 weeks after initiation, every 4 - 8 weeks until suppressed, and then every 3 - 4 months for at least the first year.<sup>4</sup>

### Monitoring of liver, renal and hepatitis B status

Given the inherent risks of ART - particularly when initiating treatment at advanced stages of infection - the guidelines make little provision for toxicity monitoring. Tenofovir (TDF) has been introduced into first-line therapy. Reliable suppression of both hepatitis B and HIV in those with dual infection, and the maintenance of normal renal function, need mentioning. The prevalence of HIV-HBV co-infection in South Africa is estimated to be 6 - 17%.<sup>17</sup> TDF, FTC and 3TC share activity against HBV, and monotherapy with these, will lead to HBV drug-resistance. Stopping HBV-suppressive therapy i.e. discontinuing TDF/3TC or TDF/FTC, has been associated with severe 'flare-ups' of the underlying hepatitis B.<sup>18</sup> ART active against HBV therefore must be continued even if HIV virological failure has

occurred. The recommendation that HBV testing is advised before TDF is discontinued lacks emphasis. The guidelines recommend limiting baseline HBV testing to patients with significantly elevated liver transaminases, but a substantial proportion of co-infected patients (84.2% in a South African study) have normal levels at baseline.<sup>17</sup> Baseline HBV testing for all may be more prudent.

TDF causes renal toxicity as early as 5 weeks<sup>19</sup> in 1.5 - 2.3% of patients. The 'guidelines' recommend that creatinine clearance is checked at months 3 and 6 and then annually, but earlier monitoring is needed. TDF has also been linked to the development of Fanconi syndrome, yet no electrolyte monitoring is advised. Glucosuria and proteinuria may direct the caregiver to a renal problem, and routine urine dipstick monitoring should be encouraged.

The second concern is the lack of liver enzyme monitoring on NVP. ALT testing is only recommended if a rash develops on NVP and, since this is an early occurrence, it will not warn of mid-term or late-onset hepatotoxicity. Liver toxicity rates vary between 0 and 27% and are higher in women. There is significant concern about NVP toxicity since the guidelines recommend the use of NVP in pregnant women with CD4 counts  $\leq 350$  cells/ $\mu$ l. NVP has been avoided in women with nadir CD4 counts  $>250$  cells/ $\mu$ l because of the risk of fatal hepatotoxicity.<sup>20</sup> Despite recent studies not confirming this risk,<sup>21</sup> we advise caution and more frequent ALT monitoring since deaths have been reported, mostly in the higher CD4 category ( $>250$  cells/ $\mu$ l) and mostly among women.

### Genotyping, ART regimen sequencing and third-line options

Survival data suggest that 22.5 years, perhaps more, can be added to the life of someone on ART.<sup>22</sup> Will current treatments last that long? The weakness of first-line treatment is the low genetic barrier to resistance. Only 1 or 2 key resistance mutations may confer drug resistance to that regimen and to other agents, thereby limiting subsequent treatment options. Early drug failure is a risk, and delay in switching to second-line treatment will also increase the degree of resistance. Therefore, much second-line therapy may effectively be boosted protease inhibitor monotherapy. It will be difficult to know without genotyping, which is expensive, yet is an essential guide in the planning of 'next' therapies. While first- and second-line regimens can remain largely generic for now, third-line and salvage therapies must be tailored to the recipient unless new classes of ARV are made available.

The guidelines advise that those failing second-line treatment be referred to a specialist. But there are too few specialists and an alternative plan is needed. Patients and their caregivers will soon demand third-line treatments. Via application to the Medicines Control Council, private-sector patients can access new drugs, which are expensive, and local pricing can only be reviewed (and hopefully reduced) upon registration in this country. Placing these drugs into a planned schedule will start to regulate their use wisely and focus on answers to third-line options. In this regard, the guidelines require closer approximation to international counterparts.

### Managing the epidemic: Decentralising care, empowering nurses

With 5.7 million or more HIV-infected individuals in South Africa, doctors alone cannot provide sufficient care. It makes sense for nurses and 'clinical associates' to broaden this base, as in Malawi and Botswana. In a randomised trial ( $N=812$ ) in South Africa, doctor-managed ART-related care was compared with nurse-managed care.<sup>23</sup> Nurses were as good as doctors in providing care. The actively

sick were excluded from recruitment, and this study therefore lends support to nurses in the caring of well HIV patients. Doctors would be better used caring for the sick. Of concern was the alarmingly high level of cumulative failure at week 120 - 48% (nurse group) and 44% (doctor group) - which suggests that neither doctors nor nurses intervene adequately to prevent treatment failure, and lends further support to more frequent VL monitoring. Based on VL results, a nurse can give step-up adherence counselling and retest after 1 month. If re-suppression of the virus has not taken place, referral to a doctor is recommended.

The role of nurses as caregivers in the HIV epidemic requires clear defining. Health professions councils must provide registration, legal protection and ensure adequate skills. Sick patients will need referral for assessment and care by doctors and, once well, be referred to nurse-level care. Perhaps some nurses will be trained to manage various non-life-threatening medical conditions in the community. But nursing care will only be as good as the next tier of support. At present, the South African public health system shows little evidence of the resilience and goodwill that this venture will demand. The guidelines give no detail in this regard and are also silent on the role of, and guidelines for, clinical mentoring programmes for caregivers.

### Paediatric care

Changes in the paediatric guidelines have brought the private and public sector management of HIV-infected children closer together. Although the Prevention of Mother to Child and Paediatric Treatment guidelines are steps in the right direction, concerns exist about their implementation. Children often present with end-stage disease. The focus should be shifted to active case finding at primary health care level. Clinic staff are often reluctant to initiate children on ARVs, most probably because of inadequate training and the large number of adults requiring care. Support for clinics in this regard should be urgently addressed.

### Prevention strategies

The guidelines should be augmented by greater emphasis on prevention strategies. Prevention of infections (such as pneumonia, tuberculosis, HBV and HPV) through treatment or vaccination should be addressed along with discussion of screening protocols for cervical carcinoma. Specific prevention of HIV transmission deserves attention i.e. condoms, circumcision, microbicides and ART. Prevention of drug toxicity and drug interactions and contra-indications also require more space.

**Table II. Key recommendations from the group**

- More transparency of the guideline process in the future
- Inclusion of all stakeholders
- Earlier commencement of ART
- Advice specifically on the timing of ART initiation in the face of active opportunistic infections
- More comprehensive laboratory monitoring at baseline and on therapy for toxicity and treatment response, specifically more VL monitoring
- Recognition of the special case of hepatitis B in our population
- Recognition of requirements for 3rd-line therapy and the rational use of specialised tests e.g. genotyping
- Empowerment of nurse practitioners and development of task shifting and mentoring protocols
- Integration of paediatric needs into the new guidelines.
- More emphasis on preventive aspects - immunisations, INH preventive therapy, treatment as prevention

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## HEALTH POLICY

# Parenteral artesunate access programme aims at reducing malaria fatality rates in South Africa

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Parenteral artesunate should be used in preference to quinine for the treatment of severe malaria, given its significant mortality and safety benefits. As the product has not yet been registered for use in South Africa, the Parenteral Artesunate Access Programme has been launched to reduce malaria-related mortality. Severe malaria is a medical emergency that requires prompt treatment to prevent death, which occurs in 10 - 50% of patients.<sup>1</sup> Based on high-quality evidence, the World Health Organization (WHO) now strongly recommends intravenous (IV) artesunate in preference to IV quinine for the treatment of severe malaria in adults.<sup>2</sup>

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## Mortality and safety benefit

Artesunate, an artemisinin derivative, is highly effective in the treatment of malaria owing to its rapid parasite clearance, broad stage specificity and easy, safe administration compared with quinine.

The South-East Asian Quinine Artesunate Malaria Multicentre Randomised Controlled Trial (SEAQUAMAT) compared parenteral artesunate and quinine in 1 461 patients with severe *Plasmodium falciparum* malaria with death as the primary endpoint. The mortality rate was 15% in the artesunate arm compared with 22% in the quinine arm, with an absolute mortality risk reduction between study sites ranging from 5 - 9%. Therefore, the numbers needed to treat to save one life ranged from 11 - 20 patients. Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk (RR) 3.2, 1.3 - 7.8;  $p=0.009$ ).<sup>3</sup> A Cochrane systematic review that informed the WHO treatment guidelines favoured the use of IV artesunate over quinine, with a 38% decrease in the risk of death (RR 0.62, 95% confidence interval (CI) 0.51 - 0.75; 1 938 participants, 6 trials).<sup>4</sup>

## The challenge

The Global Health Malaria Elimination Group has set the ambitious goal of eradicating malaria from the planet by 2050.<sup>5</sup> Together with Namibia, Botswana and Swaziland, South Africa supports the WHO Roll Back Malaria (RBM) initiative in Africa and aims to eliminate

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