



EMAIL: info@tac.org.za WEBSITE: <http://www.tac.org.za>

TAC COMMENTARY ON THE DRAFT 2008 DEPARTMENT OF HEALTH MANAGEMENT OF HIV GUIDELINES¹ -- PRESENTED TO THE SANAC TTT ON TREATMENT, CARE AND SUPPORT (15 MAY 2008)

The Treatment Action Campaign (TAC) welcomes the release of the National Department of Health's revised *Guidelines for the Management of HIV and AIDS in Health Facilities* ("the Guidelines"). We also applaud the Department for its continued support of a World Health Organisation (WHO) - recommended public health approach to HIV/AIDS treatment and care. This approach has seen more than 400,000 people in South Africa initiated onto antiretroviral (ARV) treatment leading to increased lifespan and quality of life for the majority of people living with HIV/AIDS.

There are a number of positive features to the new Guidelines which we feel will lead to further improvements in the standard and quality of care for people with HIV. These include:

- The attention to detail, particularly with regard to drug regimens and treatment protocols, management of adverse events and management of opportunistic infections.
- The introduction of tenofovir (TDF) into the first-line regimen.
- The commitment to improving adherence.
- The raising of the treatment initiation threshold.
- The commitment to down-referring patients to maintenance facilities as espoused by the National Strategic Plan. Down-referral will make treatment more accessible, reducing the costs of travel for patients, likely resulting in improved rates of treatment uptake and adherence. It will also ease the burden on secondary and tertiary-level health facilities.

However, we have critical concerns about the new Guidelines which we call upon the Department to urgently address before the document is finalised. This is the first major revision to the Guidelines since they were originally published in 2004.² We recommend that Guidelines be updated more regularly, perhaps as often as once every two years. We also recommend that in future the Guidelines be more reactive to new scientific findings that should have an impact on clinical practice. There should be a mechanism for introducing urgent revisions to

¹ Drafted by TAC Policy Researcher Andrew Warlick: andrew@tac.org.za. Special thanks to Nathan Geffen, Polly Clayden, Simon Collins, Victor Lackay, Jonathan Berger, Greg Gonsalves, Marc Cotton and Krista Dong for their assistance and input.

² National Department of Health. 2004. National Antiretroviral Guidelines. <http://www.doh.gov.za/docs/factsheets/guidelines/artguidelines04/intro.pdf>

the Guidelines following new important scientific and clinical data from randomised controlled trials, particularly findings on adverse effects. However any such emergency revisions must take into account a public-health approach, cost-effectiveness and cost-benefit analysis. Processes for updating the Guidelines should be formalised and agreed upon by all stakeholders.

We also wish to point out that the antiretroviral tender was published before the Guidelines and the problems with the tender³ have created the unsatisfactory situation in which the tender drives the choice of drugs used in ARV sites instead of the Guidelines. The tender process must be open, flexible and immediately directed to take into account the new Guidelines.

Lastly, we ask that future Guidelines include references and indicators for the level of evidence for its recommendations, as is standard in the World Health Organisation and other guidelines.

Our primary concerns with the Guidelines are:

- The CD4 count threshold for Highly Active Antiretroviral Treatment (HAART) treatment initiation should be raised from 250 to 350 cells/mm³.
- The time period between treatment assessment and treatment commencement is too long and should be kept to an absolute minimum. Patients with critically low CD4 counts or who are diagnosed with advanced AIDS illnesses must be initiated onto HAART immediately, unless contraindicated.
- Pap smears, recommended by the Guidelines for HIV-positive women at the time of treatment commencement, should be offered sooner.
- The paediatric treatment protocol must be revised to recommend HAART for all infants who are diagnosed with HIV.

1. **Revise HAART Selection Criteria:**

1.1 Raise the Treatment Threshold: Commence HAART at 350

The Guidelines raise the CD4 count threshold at which HAART is indicated from 200 to 250 cells/mm³. While TAC supports the Department of Health's decision to raise the threshold for HAART initiation, we argue that the threshold should be raised further to a CD4 count of 350 cells/mm³. Treatment guidelines in most industrialised countries have already been revised to recommend the initiation of HAART when the CD4 count falls below 350 cells/mm³ and we call on the South African National Department of Health to follow suit.

The movement towards earlier treatment initiation has been driven largely by two factors: a) improved understanding of the risk factors associated with adverse effects and drug toxicity related to the use of antiretrovirals, and b) mounting scientific evidence indicating significant health benefits and improved treatment outcomes in patients initiated on HAART programmes with higher CD4 counts.

³ See the AIDS Law Project's Memorandum on the 2008 State ARV Tender available online at: www.tac.org.za/community/files/ALPMemorandumOn2008ARVTender.pdf

The case for delayed treatment (i.e. treatment initiation at CD4 counts less than 200) evolved within a context wherein the risks associated with long-term use of ARVs were deemed to outweigh any perceived short-term health benefits of starting at a slightly higher CD4 count. Many antiretroviral drugs can cause adverse, sometimes even life threatening, side-effects and long term use of ARVs has been linked to mitochondrial toxicity and drug resistance. Concerns over side-effects, drug toxicity and resistance coupled with a concern that the risk of developing AIDS-related illnesses was sufficiently low at CD4 counts above 200 to warrant delayed treatment have long supported a “start later” approach in which HAART initiation is postponed for as long as possible. In addition, the cost of medications for large-scale public health programmes was also a factor considered in determining initiation criteria.

However a wide body of research collected over the last decade indicates that concerns over the perceived risks of early treatment initiation have been mistaken and that earlier commencement of HAART is likely associated with lower mortality, faster immune recovery, and less, rather than more, drug-related toxicity and adverse side-effects. The most serious impact is the reduction or prevention of a range of co-morbidities that impact on the individual and the public health system.

A number of studies have shown that low CD4 counts are in fact one of the preeminent risk factors for drug-related toxicity and that patients who are initiated onto HAART with lower baseline CD4 counts are actually **more**, not less, likely to experience adverse effects than those patients who begin treatment with higher CD4 cell counts. In the HIV Outpatient Study (HOPS) cohort, for example, the factor most strongly associated with the presence of lipodystrophy was baseline CD4 cell count, with abnormal fat loss occurring in 30.8% of patients with baseline CD4 counts of 200 but only 3.3% of patients with a baseline count of 350⁴. Likewise the incidence of peripheral neuropathy has been shown to be heightened in patients with lower baseline CD4 cell counts at the time of their treatment commencement⁵.

Apart from reducing the risks of adverse side effects and drug-related toxicity, earlier treatment initiation has also been shown to reduce morbidity and mortality. Data obtained from the Strategies for the Management of Antiretroviral Therapy (SMART) trials clearly demonstrates that untreated HIV infection in patients with CD4 cell counts below 350 cells/mm³ increases the risk of developing not only HIV/AIDS related illnesses, but a variety of non-AIDS defining health conditions such as heart, kidney and liver disease as well as some forms of cancers.

Several recent studies have confirmed that earlier HAART initiation reduces the likelihood of morbidity and death. A 2003 study demonstrated that the mortality rate among patients who started HAART within a CD4 range of 350-500 was approximately 60% of the rate for those patients who were initiated onto treatment with CD4 counts of less than 350.⁶ Data from this study also found that those patients who began treatment with higher CD4 counts were

⁴ See: Lichtenstein KA, Ward DJ, Moorman AC, et al. *Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. AIDS* 2001, 15:1389–98 and Lichtenstein KA, Delaney KM, Armon C, et al. *Incidence of and risk factors for lipodystrophy in ambulatory HIV-1 infected patients. J Acquir Immune Defic Syndr* 32:48–56, 2003.

⁵ See: Kelleher T, Cross A, Dunkle L. *Relation of peripheral neuropathy to HIV treatment in four randomized clinical trials involving didanosine. Clin Ther* 21:1182–92, 1999; Simpson DM, Haidich A-B, Schifitto G, et al. *Severity of HIV-associated neuropathy is associated with plasma HIVG-1 RNA levels. AIDS* 16:407–12, 2002 and Lichtenstein KA, Armon C, Baron A, Moorman AC, Wood KC, Holmberg SD. *Modification of incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV Outpatient Study (HOPS) cohort. Clin Infect Dis* (in press).

⁶ Palella FJ Jr, Knoll MD, Chmiel JS, et al. *Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. Ann Intern Med* 138:620–6, 2003.

statistically significantly more likely to achieve lower viral loads. Similarly, a later study revealed that the incidence of new opportunistic infections was significantly lower for patients who started therapy at CD4 cell counts of 351–500 compared with those who started at counts of 201–350⁷. More recently, a 2007 randomised study in Cote D'Ivoire also found significantly improved treatment outcomes and much reduced mortality and morbidity in patients who started HAART before their CD4 counts fell below 350 cells compared to those patients who started treatment later.⁸ There is also compelling scientific evidence of significant health advantages for pregnant women who initiate ARV therapy treatment at CD4 cell counts of 350 cells/mm³ rather than 200 cells/mm³. A recent study published in the *Lancet* (February 2008) also confirms the benefits of this approach for children who are negative at birth. In accordance with this evidence, early treatment initiation for pregnant women was the recently recommended by the Department's Expert Task Team on PMTCT.

Finally, earlier treatment initiation has also been shown to reduce the sexual transmission HIV⁹; commencing treatment at higher CD4 counts could therefore possibly prove to be an efficient and cost effective intervention for preventing new HIV infections¹⁰.

Based on the evidence noted above we are strongly in favour of raising the treatment initiation threshold to a CD4 count of 350. Nevertheless we recognise that in a context where many public health facilities in South Africa have lengthy waiting-lists for treatment, earlier universal treatment initiation could possibly overwhelm existing capacity. We recommend a more cautious, tempered approach to the matter. Our final recommendation to the Department is threefold:

1. While we accept that in the absence of health-systems capacity strengthening earlier initiation could not be effectively implemented, we call on the Department to actively take steps to progressively realise the goal of universal HAART initiation at CD4 counts of 350 over the next three years.
2. We ask that the Department recommends the immediate implementation of earlier treatment commencement at those health facilities where capacity does currently exist.
3. We request that the Department immediately implements a national policy of early treatment initiation for all pregnant women with CD4 counts of 350 or less. Given the fact that the suggested initiation regimen for pregnant women in the Guidelines (regimen 1b: stavudine (d4T)+lamivudine (3TC)+nevirapine

⁷ Sterling TR, Chaisson RE, Keruly J, Moore RD. *Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study.* *J Infect Dis*, 188:1659–65, 2003.

⁸ Moh R et al. *Incidence and determinants of mortality and morbidity following early antiretroviral therapy initiation in HIV-infected adults in West Africa.* *AIDS* 21: 2483–2491, 2007.

⁹ Quinn TC, Wawer MJ, Sewankambo N, et al. *Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group.* *N Engl J Med* 342:921–9, 2000.

¹⁰ For further research on the benefits of earlier treatment initiation see: Badri M, Ehrlich R, Wood R, Pulerwitz T, Maartens G. *Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area.* *Int J Tuberc Lung Dis* 5:225-232, 2001; Post FA, Wood R, Maartens G. *Acquired immunodeficiency syndrome in Africa: survival according to AIDS defining illness.* *S Afr Med J* 91(7):583-586, 2001; Badri M, Bekker L-G, Orrell C, Pitt J, Cilliers F, Wood R. *Initiating highly active antiretroviral therapy in sub-Saharan Africa: an assessment of the WHO revised scaling up treatment guidelines.* *AIDS* 18(8):1159-1168, 2004; Badri M, Maartens G, Bekker L-G, Wood R. *The spectrum and prognosis of severe HIV-related diseases in Cape Town.* *S African Journal of HIV Medicine*:19:11-16, 2005.

(NVP)) contains nevirapine which is contraindicated for women with CD4 counts above 250 and the fact that all other standard first line regimens contain efavirenz (EFV) which is contraindicated for the early stages of pregnancy, we suggest a regimen of zidovudine (AZT) + lamivudine + lopinavir/ritonavir (LPV/r, branded as Kaletra) as the optimal initiation regimen for pregnant women with CD4 counts between 250 and 350. We are, however, aware of the potential cost-implications of the inclusion of Kaletra and would therefore be willing to accept the initiation (or switch) of pregnant women onto efavirenz at a safe point in pregnancy or thereafter. The obvious health and prevention benefits to the woman, the child and the family make this an imperative.

Furthermore, we wish to point out that there is a contradiction between the Guidelines and the new prevention of mother-to-child transmission (PMTCT) protocol, which we ask the Department to resolve. The new PMTCT protocol keeps the CD4 count threshold for HAART initiation at 200 while the Guidelines recommend 250. Again, we recommend that the threshold for pregnant women should be 350. The PMTCT programme is an excellent opportunity to begin treating women before they have advanced to AIDS and thereby reduce the unnecessarily high levels of morbidity and mortality currently being experienced in the public sector due to patients seeking treatment too late.

1.2 Alcohol and Substance Abusers Should Not Be Excluded From HAART

It is unclear from the wording on page 10 of the Guidelines as to whether or not active alcohol and substance abuse constitute exclusionary criteria for HAART referral. We therefore ask for this section to be amended so that its meaning is clearer. We strongly object to any attempt to exclude access to HAART for active substance abusers. Substance users, especially injecting drug users (IDUs), and people who abuse alcohol are at high-risk for HIV infection and it is ethically and legally untenable to deny them fair and proper access to any HIV-related health services including antiretroviral therapy.

We share the Guidelines' concern that substance use is a risk factor for poor adherence. The response to this risk should not be to deny treatment but to implement treatment support and harm reduction programmes that improve adherence amongst substance abusers.

2. Modify Treatment Readiness Assessment And Preparation Protocol

2.1 HAART Programme Induction Period Should Be Reduced, Particularly For Critically Ill Patients

Once patients have been indicated for HAART the Guidelines set out a 2-4 week induction programme for all candidates "except patients with CD4 counts of <50" who "should be considered for a shorter induction period"¹¹. A four week induction period is far too lengthy. Research indicates that most patients enrolled on HAART programmes who die, do so

¹¹ *Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three*, p. 12.

before commencing treatment¹². Furthermore, the longer the gap between patient treatment literacy training and ARV initiation, the greater the risk of low literacy rates when assessed by the doctor, as well as loss to follow-up and further delay in treatment initiation.

Therefore, every effort should be made to keep the time period between assessment and treatment initiation to an absolute minimum; the Guidelines should be more explicit in this regard. While we accept that “except for post-exposure prophylaxis, HAART is not an emergency treatment”¹³ insofar as section 27 of the Constitution understands emergency medical treatment AIDS-related mortality is an individual and public emergency. We urge the Department to recognise that, due to late presentation for testing and care, antiretroviral therapy in South Africa is often an urgent treatment; this fact must be acknowledged within the Guidelines. It is not enough that patients with CD4 counts less than 50 be ‘considered’ for shorter induction periods: in cases where it means a choice between life and death, urgent initiation is the only reasonable and lawful approach. Patients with severe immunosuppression or AIDS-defining illnesses should be actively fast-tracked for immediate treatment initiation following stabilisation of acute infections, unless there is a valid clinical reason for not doing so.

We therefore recommend that the guidelines include a protocol for triaging critically ill patients for HAART both from outpatient and inpatient settings and requiring sustained treatment education when the patient is stabilised..

2.2 Pap Smears Should Be Performed at the Earliest Possible Opportunity

Given the high incidence rate of cervical cancer in South Africa due to the HIV epidemic, we are pleased that the new Guidelines recommend pap smears for women commencing HAART who have not received one within the previous 12 months¹⁴. Nevertheless we firmly believe that rather than deferring cervical cancer screening until the HAART commencement visit as suggested in the Guidelines, pap smear tests should be offered to all HIV-positive women at the earliest possible opportunity preferably at the point of first contact.

We therefore propose that women who have not received a pap smear within the past year should be referred for one at the time of their HIV-positive diagnosis and that a follow-up test should be performed at the time of HAART commencement if 12 months or more have lapsed since the initial test.

3. Amend Clinical Criteria for Paediatric Treatment: Universal HAART For All Infants Diagnosed With HIV

The clinical criteria for paediatric treatment laid out in the Guidelines should be revised to recommend immediate treatment for all infants diagnosed with HIV. The CHER study (conducted by South Africa’s leading HIV paediatricians) demonstrated unequivocally that infants diagnosed with HIV should commence HAART immediately¹⁵. Mortality in the

¹² Lawn SD, Meyer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS* Dec 2 19(18):2141-8, 2005.

¹³ *Ibid*

¹⁴ *Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three*, p. 13.

¹⁵ See the National Institutes of Health fact sheet on CHER, available online at www3.niaid.nih.gov/news/QA/cher_qa.htm

immediate treatment arm of the study was 4% versus 16% in the deferred treatment arm; a reduction in mortality of 75%. We have been informed that the Department is reluctant to introduce this policy until the study has been published in a peer-reviewed journal. This is an unnecessarily inflexible position which will result in avoidable infant deaths. The study has been submitted for peer review to a leading medical journal and it was funded by the National Institutes of Health, the world's leading medical research institute, which has endorsed its findings. Furthermore, the US paediatric guidelines have been modified to incorporate the CHER findings¹⁶.

4. Review Indications For Changing ARV Regimens

Under indications for second line HAART regimens the Guidelines read: "Second line regimens should only be considered for patients who have experienced virological failure *in spite of a good drug adherence record*" [our emphasis]¹⁷. TAC opposes the automatic exclusion of patients with 'poor' adherence records from accessing second line HAART, to do would most likely be unconstitutional. Virological failure, whatever its cause, warrants initiation onto second line regimens; patients' past adherence should not seek to disqualify them. Besides, proving, with any degree of certainty, that a patient had in fact not been adherent or that non-adherence was the patient's fault is virtually impossible. We therefore insist that above proviso be removed from the Guidelines.

For patients who have failed second line therapy the Guidelines are clear that, "salvage therapy is currently not an available and affordable option in the public health sector" and that "there may be some benefit in continuing on Regimen 2 if an informed patient so wishes. The ethical principle of "first-do-no-harm" should be upheld in such cases"¹⁸. In the absence of salvage therapy we strongly encourage the continued use of second line drugs as current research has shown that HAART continues to provide protective benefit in the central nervous systems of HIV-positive people even after they have failed therapy¹⁹. Continuing second-line HAART after treatment failure is possibly also beneficial because there is evidence that resistant virus has lower fitness than wild-type virus which might become dominant again should treatment be discontinued²⁰.

The next time the Guidelines are reviewed, we will ask the Department to give serious consideration to the introduction of salvage therapy. It should not be considered *a priori* to be unaffordable.

¹⁶ Available online at <http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf>

¹⁷ *Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three*, p. 18

¹⁸ *Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three*, p. 25

¹⁹ Sinclair E et al. *Antiretroviral treatment effect on immune activation reduces cerebrospinal fluid HIV-1 infection*. *J Acquir Immune Syndr* 47:544–552, 2008 and Spudich et al. *Treatment Benefit on Cerebrospinal Fluid HIV-1 Levels in the Setting of Systemic Virological Suppression and Failure*. *JID* 194: 1686-1696, 2006.

²⁰ Troyer R, Collins K, Abraha A, Fraundorf E, Moore D et al *Changes in Human Immunodeficiency Virus Type 1 Fitness and Genetic Diversity during Disease Progression*. *Journal of Virology*, Vol. 79, No. 14: p. 9006-9018, 2005

5. Other Concerns

- While we welcome the Department's commitment to improving Treatment Literacy through patient education we would like to see a national standardisation of patient training materials as currently the quality of such initiatives varies greatly across sites.
- The Guidelines make scant mention of mental health issues despite substantial evidence of linkages between mental health and HIV²¹. We call on the Department to finalise specific clinical guidelines, begun by the Western Cape Department of Health, for the management of mental health disorders in people living with HIV.
- While we are pleased at the inclusion of tenofovir in the first line regimen, we recognise that there is a need for joint urgent action by Government and civil society to bring down the price of the drug in order to increase its affordability and availability. We therefore appeal to Government to utilise the relevant legislation and other tools at its disposal to actively take step to reduce the drug's price in both the public and private sectors. We refer the Department to a recent complaint launched by the AIDS Law Project on behalf of TAC at the Competition Commission against MSD/Merck as an example of the kind of advocacy in which government and civil society should be jointly engaging²².
- We suggest that in regions where lab services are unavailable, lack of viral load and CD4 testing should not be a barrier to treatment access. This is line with the World Health Organisation guidelines.
- The Guidelines advise extreme caution in prescribing tenofovir to patients with renal impairment²³. However given the importance of tenofovir, for efficacy and tolerability it would be more appropriate to follow guidelines from other countries that detail how to dose reduce tenofovir based on creatinine clearance levels.
- The Guidelines recommend switching to regimen 1d for patients who have experienced 'severe' stavudine toxicity (i.e. peripheral neuropathy and lipoatrophy)²⁴. We contend however that there is no reason why a patient should have to wait until their symptoms are "severe" before they can switch regimens. Indeed, they should do so as soon as symptoms of adverse effects appear as these effects become more difficult to reverse the longer they are allowed to develop. Likewise with regards to the Guidelines' recommendation for the management of peripheral neuropathy²⁵: any symptoms should

²¹ Green G, Smith R. The *psychosocial and healthcare needs of HIV positive people in the United Kingdom: a review*. *HIV Med* 5: 5–46, 2004. Vitiello B, Burman MA, Bing EG, Beckman R, Shapiro MF. *Use of psychotropic medications among HIV-infected patients in the United States*. *Am J Psychiatry* 160:547–554, 2003; Williams P, Narciso L, Browne G, Roberts J, Weir R, Gafni A. *The prevalence, correlates, and costs of depression in people living with HIV/AIDS in Ontario: Implications for service directions*. *AIDS Educ Prev* 17:119–130, 2005; Bing E, Burnam A, Longshore D, Fleishman JA, Sherbourne CD, London AS, et al. *Psychiatric disorders and drug use among Human Immunodeficiency Virus–Infected adults in the United States*. *Arch Gen Psychiatry* 58:721–728, 2001 and Ciesla JA, Roberts JE. *Meta-analysis of the relationship between HIV infection and risk for depressive disorders*. *Am J Psychiatry* 158:725–730, 2001.

²² For more information on the complaint please see: www.tac.org.za/community/node/2127

²³ *Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three, p. 53*

²⁴ *Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three, p. 14*

²⁵ *Guidelines for the Management of HIV and AIDS in Health Facilities, Draft Three, p. 49*

prompt a switch of stavudine to an alternative as first option. Alternative management should be deferred to when no other treatment options are available. Again, this shouldn't be dependent on 'severe' neuropathy - by then it is often too late.

- Lastly a number of potential ARV side-effects have been overlooked in the Guidelines these include:
 - Efavirenz can cause paranoia as well as increases in triglycerides
 - Lamivudine may cause hair loss
 - AZT can cause glucose intolerance
 - Stavudine and AZT can cause lipoatrophy
 - NNRTIs can also cause lipohypertrophy

CONCLUSION

We once again thank the clinicians, departmental officials and all health professionals who have made the ARV roll-out programme as success. With all its weaknesses, the programme represents a significant step forward in public health delivery and the saving of lives.