WE SHOULD NOT CHANGE GUIDELINES FOR INITIATION OF HAART IN ADULTS IN THE SOUTH AFRICAN PUBLIC SECTOR

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The current South African Department of Health guideline on when to initiate highly active antiretroviral therapy (HAART) in adults is based on the 2002 WHO guidelines. It is a very conservative guideline, with HAART being initiated with AIDS, diagnosed either clinically (World Health Organization (WHO) stage 4) or immunologically (CD4+ lymphocyte count < 200 cells/µl). The current Southern African HIV Clinicians Society guidelines extend these conservative guidelines to include patients with other evidence of clinical immune suppression (WHO clinical stage 3) and patients with CD4 counts 200 - 350 cells/µl. In common with international guidelines, it is recommended that patients in the CD4 stratum 200 - 350 cells/µl be followed up until their CD4 count is close to 200 cells/µl, unless their viral load is high. I shall centre my argument on the proposal to use the SA HIV Clinicians Society guidelines to initiate HAART in the public sector.

The evidence that starting HAART at CD4 counts 200 - 350 cells/µl leads to a better outcome than at counts < 200 cells/µl is persuasive rather than definitive as it comes from observational cohort studies, not randomised controlled trials. These cohort studies show worse short-term (generally 3 years) survival in patients commencing HAART at counts < 200 cells/µl. The magnitude of this benefit is less impressive when controlled for lead time,[1] which is a source of bias in cohort studies. Nevertheless, the survival benefit remains even after correcting for lead time. The key issue though is that the survival benefit is over the short term.

As argued by Philips *et al.*,[2] HAART is a long-term intervention. We do not yet know how long HAART will prolong survival, but it is unlikely that the average patient will have normal survival. We know that there is a steady failure rate on HAART, and that achieving virological success (an undetectable viral load) is progressively more difficult with successive regimens, largely owing to resistance. Although there is clinical benefit in continuing HAART despite resistance, ultimately HIV disease progression does occur.[3] Taking a longer time view of HAART, Philips *et al.* concluded that it is 'likely that those deferring ART [until CD4 counts < 200 cells/µl] ... eventually will experience somewhat lower long-term risk of AIDS and death than if they had started ART immediately', because most patients will eventually fail therapy. Therefore I do not believe there is a compelling case to be made for moving the CD4 count criterion for starting HAART in the public sector.

Starting at WHO stage 3 is attractive for resource-poor countries, particularly for those without access to flow cytometry for CD4+ lymphocyte count monitoring. Clinical staging is simple to learn for nurse-driven services. Furthermore, it is known that WHO stage 3 confers a relatively poor survival independently of the CD4 count. However, when facilities to monitor CD4 counts exist, these should be used in conjunction with WHO staging. Tuberculosis occurs across a wide spectrum of immunity in HIV infection. In our study of incident cases of tuberculosis, about a third of cases presented with CD4 counts > 500 cells/µl.[4] I do not believe that these patients need HAART. A further problem is that oral thrush, a common stage 3 condition, can occur with seroconversion or following a course of antibiotics. The 2003 revision of the WHO guidelines of when to initiate HAART in resource-poor settings has added WHO 3 together with CD4 count < 350 cells/µl for those countries, like South Africa, which can measure CD4 counts. Although I do believe we should consider

adding this to our public sector guideline in the future, I do not believe we should add it soon.

South Africa has a massive burden of HIV infection. Adding WHO stage 3 to the criteria of when to start HAART will approximately treble the number of eligible patients. Even if we only targeted stage 4 patients (without using CD4 criteria) and only managed to treat 50% of these, we would still need to treat approximately 1 400 000 by 2008 (extrapolated from ASSA 2002 model by Andrew Boulle). Until it is clear that we can achieve this daunting target we should not talk about easing the criteria for initiation. We have an obligation to first deal with those who are suffering most.

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SHOULD WE BE INITIATING ANTIRETROVIRAL THERAPY EARLIER?

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ANTIRETROVIRAL PROGRAMME RATIONALES

Antiretroviral therapy (ART) programmes are a part of the response to the massive mortality occurring in the countries most affected by the HIV epidemic. UNAIDS estimated that 2.3 million deaths from AIDS occurred in sub-Saharan Africa during 2004. South Africa faces the prospect of an accumulated 6 - 7 million AIDS deaths by 2010, with the majority affecting the age group 20 - 40 years, a stage of life when adults are productive and caring for the next generation. In September 2003 the World Health Organization (WHO) declared the lack of access to HIV treatment a global health emergency. WHO called for '*unprecedented action*' to ensure that by the end of 2005 at least 3 million people in need of ART will have access to it. To date the national evaluations of the status of ART programmes have revolved around reporting on numbers on treatment rather than impact on AIDS mortality. The primary purpose of the South African and other national ARV programmes is to minimise HIV-associated mortality.

DEBATE FOCUS

The key to the present debate revolves around the thresholds of ART initiation as set out in various treatment guidelines and how different programme entry criteria impact on population HIV-related deaths. The WHO Treatment Guidelines Committee recognises in the 2003 guidelines preface that they will need to be updated on a regular basis in order to reflect 'best current clinical practice'. The SA national rollout programme currently uses the older WHO 2000 guidelines, which are not internationally recognised as the 'best current clinical practice' and have ceased to be used by many other countries in our region such as Botswana, Namibia and Uganda.

The current SA guidelines recommend both clinical and CD4 criteria for allowing access to the ART programme.

APPRAISAL OF PRESENT SA GUIDELINES

Firstly the clinical and CD4 count criteria are very mismatched. Patients with AIDS die at a rate of 6% per month while asymptomatic patients with CD4 counts < 200 µl have approximately a 1% monthly mortality. Clinical AIDS is therefore very specific for identifying patients at high risk of death while a CD4 of < 200 is very sensitive measure. Secondly, the majority of patients access health care and antiretroviral (ARV) programmes because they have clinical symptoms rather than because they have just passed the CD4 threshold of < 200 cells. The median CD4 cell count of patients accessing ARVs in Kampala, Uganda, is still 65/µl and in Gugulethu, Cape Town, it is less than 100/µl after 3 years of the programme. A CD4 count of < 200 cells/µl will gain utility when a large proportion of people living with AIDS (PWAs) have access to sequential CD4 count monitoring. This CD4 count threshold would then be a very sensitive but not specific measure for identifying patients at high risk of death. However, widespread CD4 count testing is not widely available in South Africa or elsewhere in sub-Saharan Africa. Thirdly, the clinical threshold of AIDS as an entry criterion for ART results in high mortality, as there are inevitable delays in accessing treatment. In Gugulethu the time between referral and commencing ARVs is short at 28 days. However, 66% of programme deaths are recorded during this period, occurring almost exclusively in those patients with AIDS before they could start ARVs. The reported delay in the Médecins Sans Frontières, Khayelitsha, ARV project was 4 months. Waiting time to access ARVs in other programmes is frequently much longer. Waiting lists in Cape Town hospitals have been up to 8 months and are in excess of 8 months in Malawi, which results in an unrecorded 50% of AIDS patients dying before access to ARV programmes. Currently this pre-treatment mortality is not recorded as part of the treatment programme, although reduction of HIV mortality is the primary aim of ARV treatment. AIDS patients not only have a high in-programme death rate, they are also difficult to clinically manage and investigate, thereby consuming a disproportionate amount of programme resources. AIDS is therefore too late a threshold for entry into an ARV programme.

If the guidelines do not represent 'best current clinical practice' but are being used as a means of rationing access to care, they should identify those who will benefit most from therapy. Clinical stage is more predictive of HIV mortality than CD4 count. South African published data have reported that the death rate of patients with WHO stage 3 disease is 2 - 2.5 times higher than that of asymptomatic patients with < 200 CD4 cells/µl. Until CD4 count testing is more widely available,