

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 Boule). 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 μ l 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/ μ l and in Gugulethu, Cape Town, it is less than 100/ μ l after 3 years of the programme. A CD4 count of < 200 cells/ μ l 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/ μ l. Until CD4 count testing is more widely available,

the practical entry into ARV programmes will continue to be based on presence of clinical symptoms. The only way to clinically identify patients before AIDS develops is to encourage programme entry at WHO clinical stage 3. Extension of ARV treatment protocols to include the treatment of WHO stage 3 patients will largely access patients who are already in the health care system and at a time when their mortality is already approximately 2% per month. Lastly, expansion of the clinical criteria for programme access to stage 3 disease will decrease the numbers of patients progressing to AIDS in the population and is therefore a more efficient medium-term strategy.

CONCLUSIONS

Extension of South African Department of Health ARV treatment guidelines to include the treatment of HIV-symptomatic patients (i.e. WHO stage 3 and 4) will bring us into line with all other major national and regional treatment guidelines.

A CD4 count < 200 cells/ μ l will only become a practical entry threshold to ARV programmes when CD4 counts are more widely available; meanwhile clinical criteria will continue to define most programme entry.

The CD4 count of < 200 CD4 cells/ μ l is a very sensitive but not specific threshold for identifying those at high risk of death and therefore greatly increases the potential number of patients qualifying for the ARV programme. CD4 counts will become more relevant over time as testing becomes more widespread.

The present policy of restricting clinical entry to those with AIDS, results in unacceptably high pre and in-programme death rates.

In order to achieve the primary aim of the ARV programme, to minimise deaths of PWA, symptomatic patients (i.e. WHO stage 3 and 4) should be initially targeted for ART.

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MODERATOR'S SUMMARY

Guidelines for the initiation of antiretroviral treatment have seen considerable changes over the years. Initially, we were

persuaded by clinicians in resource-rich settings to 'hit early, hit hard' – in other words, to commence ARV treatment at almost any stage of HIV infection. This was clearly not a sound option as prolonged therapy with potentially toxic drugs leads to treatment failure, resistance, cumulative toxicities and patient treatment fatigue. We were then persuaded that deferring therapy until certain end-points were reached was the desirable option. Deferred therapy had different meanings in the resource-rich and resource-poor settings. In most guidelines in resource-rich settings treatment was recommended when patients had an AIDS-defining condition, CD4 count < 200, stage 3 disease, and in asymptomatic patients whose CD4 count < 350 and viral load count was factored in. In resource-poor settings the 2002 WHO guidelines were generally adopted, and these were embraced by the South African National Programme. These guidelines advised that treatment should commence for WHO Stage 4 disease or a CD4 < 200. As Professor Wood pointed out, waiting for patients to develop stage 4 disease may lead to an alarming mortality as there are inevitable delays in accessing treatment while patients are being assessed and enrolled on programmes. He also argued that patients should enter programmes at WHO clinical stage 3. The majority of these patients are already in the health care system and their mortality rate is considerably lower.

Professor Gary Maartens' argument is not totally dissimilar and he endorses the Southern African HIV Clinicians Society Guidelines which extend the conservative national guidelines to include patients with WHO clinical stage 3 disease and a CD4 count < 350. In asymptomatic patients close monitoring in the CD4 stratum between 200 and 350 is recommended. This recommendation is similar to that of the 2003 revision of the WHO guidelines in which WHO stage 3 disease is added to the initiation criteria together with a CD4 count of < 350 in those countries that can measure CD4 counts.

It is sobering to reflect on the scenario that adding WHO stage 3 to the initiation criteria would approximately treble the number of patients eligible for ARV therapy.

The ARV guidelines of the Southern African HIV Clinicians Society were drawn up taking in mind the constrained resources in our country and do reflect a balance between need and resources. It is interesting to note that they are very similar to the latest version of the WHO clinical guidelines. Both speakers in this debate have endorsed this as a reasonable approach for our country in future.

