ISSUES IN MEDICAL PRACTICE

Should we be initiating antiretroviral therapy earlier?

An argument in favour

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Antiretroviral programme rationales

Antiretroviral (ARV) 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 in the age group 20 - 40 years, a period 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. The WHO called for 'unprecedented action' to ensure that by the end of 2005 at least 3 million people in need of ARV treatment will have access to it. To date the national evaluations of the status of ARV 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 recognise in the 2003 guidelines preface that the guidelines will need to be updated on a regular basis in order to reflect 'best current clinical practice'.[1] The South African national rollout programme currently uses the older WHO 2002 guidelines, which are no longer internationally recognised as '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 South African guidelines recommend both clinical and CD4 criteria for allowing access to the ART programme.

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Appraisal of current 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 a CD4 count below 200/µl have an approximately 1% monthly mortality. Clinical AIDS is therefore very specific for identifying patients at high risk of death, while a CD4 count of < 200 is a very sensitive measure. Secondly, the majority of patients access health care and ARV programmes because they have clinical symptoms rather than because they have just passed the threshold of 200 CD4 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 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 ARVs 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.[2] Waiting time to access ARV programmes elsewhere 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 manage and investigate clinically, thereby consuming a disproportionate amount of programme resources. AIDS is therefore too late a threshold for entry into an ARV programme.[3]

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 shown that the death rate of patients with WHO stage 3 disease is 2 - 2.5 times higher than that of asymptomatic patients with a CD4 cell count below 200. 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 identify patients clinically 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/µl 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 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 current 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 programme, to minimise deaths of PWA, symptomatic patients (i.e. WHO stages 3 and 4) should be initially targeted for ARV therapy.

1. World Health Organization. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. 2003 revision. Geneva: WHO, 2004.
2. Coetzee D, Hildebrand K, Boulle A, *et al*. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004; **18:** 887-895.
3. 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* 2004; **18**(8): 1159-1168.