Raising the CD4+ initiation threshold with our eyes wide open

The World Health Organization (WHO) recently advocated raising the CD4+ count threshold for initiating antiretroviral therapy (ART) for HIV-infected adults to 500 cells/μl, from the current 350 cells/μl.[1] Following previous WHO guidance, the current South African (SA) strategy of treating everyone with a CD4+ count <350 cells/μl, and all pregnant women and TB patients, has led to remarkable achievements, cutting mother-to-infant transmission dramatically and increasing life expectancy.[2,3] The question is: should SA follow the latest WHO recommendation?

There are uncontested reasons for using antiretrovirals (ARVs) – treatment of significant HIV-related immunodeficiency, and prevention of transmission of HIV from mother to child and between discordant couples.[1] In addition, there is good reason to believe that treating more people will result in an overall decrease in HIV transmission in the general population. Tantalising evidence from KwaZulu-Natal suggests that a decrease in the incidence of HIV is seen even with relatively modest levels of ART coverage.[4] Possible benefits of the provision of early ART include improved protection against activation of tuberculosis and protection from possible long-term consequences of HIV-induced inflammation, although there is controversy over how significant this protection is.[5,6] There are further concerns that the observational studies driving decisions to raise the CD4+ bar did not factor in widespread interruptions in ARVs, which are being experienced across the country, or the necessity to revert to more toxic regimens that include stavudine when newer and safer drugs run out.[7] Drug toxicity, resistance and burdens placed on the health system need to be weighed carefully against the relatively modest potential benefits.[8]

What are the implications of implementing the new WHO guidelines for the SA health system? The main issue is how to find and treat the huge pool (over 2 million) of HIV-positive people with a CD4+ count <500 cells/μl who would be eligible for ART. SA has taken 10 years to put just over 2 million people on treatment.[3] Between 300 000 and 500 000 people have become infected each year for the past decade. Projecting forward, each of these new annual cohorts would need to start treatment some years into the future when their CD4+ counts fall below the recommended threshold: after 7 years if the threshold is 200 cells/μl, after 5 years if the threshold is 350 cells/μl, and after just 2.5 years if the suggested threshold of 500 cells/μl is accepted.[9,10] The number of people newly infected with HIV each year has fallen steadily over the last decade, and this decline will be registered as a slow decrease in the annual requirement for ART initiation over the following decade.

When the CD4+ threshold changes, it is not just the predictable annual cohort of symptomatic patients that comes on stream for ART. Each time the threshold is raised, large numbers of asymptomatic HIV-positive individuals enter the eligible treatment pool: two annual cohorts (of 600 000 - 1 million individuals) when the threshold is raised from 200 to 350 cells/μl, and another two and a half annual cohorts (of about 800 000 individuals) when the threshold is 500 cells/μl. In all, the last two WHO guideline increases will add over 2 million patients (CD4+ count 200 - 500 cells/μl) to the treatment pool – in addition to the 300 000 - 500 000 mostly symptomatic (CD4+ count <200 cells/μl) ART-eligible patients who need treatment each year. This number includes about 400 000 HIV-positive pregnant women who will need to start ART each year, according to new Department of Health guidelines.

To put this in perspective, the SA health system started a *total* of about 400 000 people on ART last year – while each year, for the past 5 years, the annual capacity of the system to start people on ART has expanded by only about 20%.[2,3,10]

As pressure mounts for the country's health system to fall in line with the global movement to provide ever-earlier access to ART, planners should consider designing a response for SA's globally unique burden of disease, its populations with compelling needs (i.e. those who are already receiving treatment, and newly symptomatic, immunocompromised, pregnant and paediatric patients), and its available resources. Rather than adding yet another 1.5 million individuals (with CD4+ counts of 350 - 500 cells/μl) into the ART pool, a strong case can be made for SA to keep 350 cells/μl as the threshold for now. This would allow time to build a system to take care of the 1 million largely asymptomatic individuals who were added to the ART pool when the threshold increased to 350 cells/μl, and the priority populations who need all available ART resources. In addition, it would give time to resolve the operational issues to ensure uninterrupted ART, strengthen the decentralised treatment sites, and ensure better retention in care of those already receiving ART.

Using the imaginative systems improvement and decentralised approaches that revolutionised the delivery of prevention of mother-to-child transmission of HIV in this country, SA can then rapidly phase in the expanded service to test and treat a much larger population.[11] Looking to the future, the SA health system will need to prepare for the inevitable move towards provision of chronic ART, irrespective of CD4+ count, for the 5 million or so citizens infected with HIV.

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