

**FORUM**

World Health Organization guidelines should not change the CD4 count threshold for antiretroviral therapy initiation

N Geffen

Centre for Social Science Research, University of Cape Town
N Geffen, MSc

Corresponding author: N Geffen (nathangeffen@gmail.com)

The World Health Organization (WHO) currently recommends that HIV-positive adults start antiretroviral therapy (ART) at CD4 counts <350 cells/ μ l. Several countries have changed their guidelines to recommend ART irrespective of CD4 count or at a threshold of 500 CD4 cells/ μ l. Consequently, WHO is currently revising its treatment guidelines and considering recommending ART initiation at CD4 counts <500 cells/ μ l. Such decisions are critically important, as WHO guidelines inform healthcare policies in developing countries and are used by activists in their advocacy work. Changing the CD4 initiation point from 350 to 500 cells/ μ l would, however, be premature and have profound cost implications on Global Fund, President's Emergency Plan for AIDS Relief (PEPFAR) and developing country health budgets. We should be willing to campaign for such a change in guidelines despite cost implications, *if supported by evidence*. However, the evidence remains outstanding.

S Afr J HIV Med 2013;14(1):6-7. DOI:10.7196/SAJHIVMED.906

The World Health Organization (WHO) currently recommends that adults living with HIV start antiretroviral therapy (ART) when their CD4 counts fall below 350 cells/ μ l. Several countries have changed their ART guidelines to recommend treatment irrespective of CD4 count or at treatment thresholds of 500 CD4 cells/ μ l.^[1] WHO is currently revising its treatment guidelines and considering recommending that treatment start at 500 cells/ μ l. The decisions taken by WHO on ART guidelines are extremely important, as these guide healthcare policies in developing countries and are used by activists in their advocacy work.

To understand the impact of the WHO guidelines, it is important to consider that there are more people living with HIV in Nigeria alone than in the whole of North America, Western Europe and Australia combined. Even a small country such as Zimbabwe has more HIV-positive people than in the whole of Western Europe.^[2] Countries in sub-Saharan Africa, the Caribbean and Asia are strongly influenced by the WHO guidelines, much more so than by the Department of Health and Human Services (DHHS) guidelines published in the United States of America. This is especially the case for countries where treatment is primarily provided through funding from the Global Fund to Fight AIDS, TB and Malaria (GFATM) or the United States President's Emergency Plan For AIDS Relief (PEPFAR).

The evidence for changing CD4 initiation thresholds

When considering changing the CD4 threshold for ART initiation, or dispensing a threshold entirely, we need to

consider the evidence to support such a change, for both an individual patient's health and for HIV prevention efforts at a population level.

Prevention

The HPTN 052 trial showed that ART greatly reduces the risk of an HIV-positive person transmitting HIV to his/her partner. This finding was consistent with compelling observational data.^[3] There is also evidence from several places, including San Francisco, Vancouver and Taiwan, that reducing community viral load reduces HIV incidence.^[4-6] There is also indication from mathematical models that ART may be reducing HIV incidence in South Africa.^[7] WHO subsequently published guidelines regarding the role of ART in HIV prevention efforts.^[8]

Nevertheless, in many settings it is not clear whether changing the CD4 initiation threshold to 500 CD4 cell/ μ l would have a significant effect on HIV incidence. In contrast to places in North America where reduction in community viral load has been shown to reduce incidence, the distribution of HIV in many sub-Saharan African cities is characterised largely by heterosexual epidemics of a much broader scale. It is likely that reducing viral load through widespread ART use will reduce incidence in sub-Saharan Africa, but this is not a given. Moreover, this approach has to be proven to policy makers, because there are enormous cost implications associated with this type of expanded treatment. Studies currently underway in African countries are looking at whether initiating treatment earlier does reduce community incidence.

Treatment

The benefit to the patient should be the salient consideration in the WHO treatment guidelines (as opposed to guidelines for sero-discordant couples, where preventing infection of the HIV-negative partner is the primary consideration). When empirical data on this question are appraised rigorously, as in the British HIV Association's guidelines, it emerges that the evidence for initiating treatment at a CD4 count >350 cells/μl is poor.^{19]}

One widely circulated myth that needs to be discredited is that the HPTN 052 trial showed a reduced disease progression when ART was initiated above 350 CD4 cells/μl: the initiation threshold was 250 CD4 cells/μl, and not 350 cells/μl. Data from clinical trials had previously shown that a treatment threshold of 250 cells/μl was inferior.^{10,11]} The question of whether a threshold of 350 CD4 cells/μl is optimal remains unanswered.

Guidelines in some wealthy countries have changed to-and-fro over the last decade and a half on the issue of when to initiate ART: from the 'hit hard, hit early' strategy promoted in the 1990s, to postponing ART initiation until lower CD4 thresholds more recently. This is precisely why the Strategic Timing of Anti Retroviral Therapy trial (START) (funded by the United States National Institute of Health) and the Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-positive Adults trial (TEMPRANO) (funded by the French National Agency for Research on AIDS and Viral Hepatitis) are being conducted: to answer once and for all when the best point is for patients to start ART.

There are three likely outcomes of the START and TEMPRANO studies: (i) that earlier treatment reduces disease progression; (ii) that there is no difference between the earlier v. later treatment arms; or (iii) that earlier treatment is harmful due to increased side-effects or reduced adherence. If the latter two outcomes emerge but WHO has already recommended earlier treatment, it will undermine the WHO treatment guidelines in general. At best, there would have been serious cost implications for developing country health budgets; and at worst patients might have been harmed. If WHO keeps its threshold recommendation unchanged and the first of the aforementioned outcomes is validated, then the organisation would have taken the correct action by having waited for the evidence.

Although clinicians and AIDS activists have different expectations of the trial results, these personal prejudices do not matter. The evidence is simply not yet available, and in this case, WHO needs to wait.

The issue of cost

Cost is profoundly important when considering public health interventions, and should always be a concern for activists. To ignore such implications is poor activism, not only because policy makers do not take activists who ignore cost seriously, but also because it is morally problematic. Public health policy involves making choices determined by cost. As ART becomes more nuanced, the relative cost per disability adjusted life-year (DALY) saved becomes higher and the arguments for using the money elsewhere become harder to refute. As an example of how cost has informed activism in a developing country, the Treatment Action Campaign (TAC) has been cognisant of cost in its campaigns, despite demanding that the South African (SA) government implements treatment and prevention programmes. In a court case that dealt with prevention of mother-to-child transmission of HIV in 2002, the TAC included an affidavit that showed that the intervention would be cost-saving.^{12]} The TAC later published research showing that ART

would be affordable for the SA government. By considering cost, the TAC was able to make compelling arguments for the implementation of life-saving interventions.

The current WHO ART guidelines for adults and adolescents include two important changes, including provision (i) for ART to be initiated at 350 CD4 cells/μl; and (ii) for stavudine (d4T) to be replaced by tenofovir (TDF). Both of these changes have cost implications, but are supported by a very strong evidence base. Because the campaigns for these changes to be adopted by poor countries have been based on sound science, they have met some success. WHO guidelines should be seen as an achievable aspiration for poorer countries. Nevertheless, even today, several sub-Saharan countries initiate ART at 200 - 250 CD4 cells/μl with stavudine, largely due to resource limitations. This proves that cost is a critical factor – perhaps the most critical factor – in getting poorer countries to change their guidelines.

Conclusion

Changing the CD4 initiation point from 350 to 500 cells/μl in the new WHO guidelines would be premature. It would have profound cost implications on Global Fund, PEPFAR and developing country health budgets. We should be willing to campaign for such a change in guidelines despite cost implications *if* it was supported by evidence. But, the evidence is still outstanding. Expecting countries to move to a costly new CD4 threshold without sufficient evidence is a mistake.

Conflict of interest. The author serves on the Community Advisory Board of INSIGHT, the organisation that runs the START trial.

Acknowledgements. The author acknowledges assistance from Claire Rappoport, Simon Collins and Caroline Sabin.

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