



FORUM

One size doesn't fit all: Tailoring adult antiretroviral treatment

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Advances in antiretroviral treatment mean that patients in the public health system can be given more options in the management of their treatment. Although public health programmes tend to offer one-size-fits-all approaches, patients might benefit from a more flexible approach. In particular, we propose that people with HIV should be given more choice with regard to when to start treatment, and patients who experience efavirenz side-effects should be encouraged to switch to other medications, which will be facilitated by faster registration and lower prices of newer antiretrovirals.

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In the past decade, the standard of care for HIV treatment in the public sector has improved considerably. Our increased knowledge of antiretroviral (ARV) medicines and the additional drugs in our treatment arsenal are an opportunity to give patients a greater number of options and improve the tolerability of treatment.

When the state's antiretroviral therapy (ART) roll-out began in 2004, the CD4⁺ initiation threshold for adults was 200 cells/ μ l and the first-line regimen included stavudine, a drug associated with severe side-effects. A decade later, the CD4⁺ threshold is 350 cells/ μ l,^[1] and will be increased soon to 500 cells/ μ l.^[2] Additionally, stavudine has been replaced with a safer alternative, tenofovir. While 10 years ago, adults on their first regimen had to take varied-dose combinations twice daily, today most patients are being prescribed one pill once daily. This progress has resulted in ART that is easier to manage and maintain.

Public health programmes need to standardise the care offered to patients. But a one-size-fits-all approach can be too restrictive, resulting in some patients receiving suboptimal care. There is scope to offer more options to patients with HIV, at least in some facilities, with the prospect of improving their quality of life. This increased individualisation of treatment is unlikely to overburden the public health system. While there are a number of factors that affect individualising treatment, here we focus on two that we believe can be adapted in public-sector ART programmes in South Africa (SA): (i) efavirenz tolerability; and (ii) treatment initiation.

Efavirenz tolerability

In 2014, ART options are relatively plentiful, but several important ones are, for the most part, beyond the public sector. Besides nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, integrase inhibitors are

now also available in the private sector, but access is limited to specific research and clinical scenarios in public facilities.

The current first-line regimen includes efavirenz, which is tolerated well by most patients. Given that over 2.5 million patients are receiving treatment in the public sector, about 2 million are likely to be receiving efavirenz. But some patients endure debilitating neurocognitive side-effects from this drug; recent data suggest a doubling of the suicide rate in people treated with efavirenz over other regimens.^[3] Patients should have the opportunity to modify their regimen by switching efavirenz for a protease or integrase inhibitor.

The concern is the price and availability of alternative drugs. The standard first-line efavirenz-containing regimen costs the state less than R100 per patient per month. Protease inhibitors cost more, but have become increasingly affordable. Raltegravir, however, is not readily available in the public sector, is on the state tender at R533 per patient per month,^[4] and is currently dosed twice daily. New integrase inhibitors like the daily-dosed dolutegravir are not yet available in SA, and the local price is as yet unknown.

The lag times between ARVs being approved by the US Food and Drug Administration, European Medicines Agency v. the Medicines Control Council (MCC) are extraordinarily long, especially considering that there is much greater need in SA and other sub-Saharan African countries than in North America or Europe. To improve treatment options for patients, clinicians, researchers and activists need to put pressure on pharmaceutical companies and the MCC to prioritise registration here (and in other African countries). Campaigning for lower prices of new ARV drugs must continue.

Treatment initiation

The HPTN 052^[5] and PARTNER^[6] studies show that HIV-positive people with suppressed viral loads and who are receiving

treatment will not transmit the virus to HIV-negative sexual partners. Also, clinical trial evidence shows that it is clinically beneficial to initiate treatment at a CD4⁺ count of 350 v. 250 cells/ μ l.^[7] But the optimal CD4⁺ threshold to initiate patients to maximise clinical benefit remains unknown. It is possible that the benefits of starting above 350 cells/ μ l may be undone by interrupted drug supplies or if poor adherence results in the emergence of drug resistance. Within the next 3 years, the START^[8] and TEMPRANO^[9] clinical trials are likely to provide a clearer answer on the clinical benefits and risks of initiating treatment above 350 cells/ μ l.

But without clear evidence that the clinical benefit of earlier treatment outweighs harm due to side-effects, patients should be given the opportunity to make an informed choice. Their pathophysiology, preferences and circumstances should be taken into account to determine when it is appropriate to initiate treatment. The question of when to start treatment has become contentious, and many experts differ on this issue. This is understandable, given the current lack of evidence about the clinical and the public health benefits of suppressing viral load in sexually active people with HIV.

There is increasing pressure on people with HIV to start treatment earlier, e.g. at 500 cells/ μ l. The World Health Organization raised the CD4⁺ threshold for initiating ART to 500 cells/ μ l in its 2013 treatment guidelines.^[10] The SA Minister of Health has announced that this threshold will also be used in SA from January 2015.^[2] In response to the Minister's announcement, the Southern African HIV Clinicians Society correctly wrote: 'We ... support an individualised approach in patients with a CD4⁺ count 350 - 500 [cells/ μ l]: after a discussion about the potential benefits, uncertainties, side-effects and need for impeccable [sic] adherence patients should only be prescribed ART in this CD4⁺ range if they are motivated for lifelong ART with the required adherence. If they do not feel ready yet, ART should be deferred until their CD4⁺ count is below 350 [cells/ μ l] with a plan in place for ongoing follow-up and CD4⁺ monitoring.'^[11]

Furthermore, the threshold of 500 cells/ μ l is arbitrary and not based on clinical trial findings. We therefore propose the following approach: ART should be offered to all people with HIV. As part of discussions between patients and providers, patients need to be given an informed choice.

Patients with CD4⁺ counts >350 cells/ μ l should be informed that the clinical benefits and risks of starting ART at high CD4⁺ counts are, as yet, unknown, and that taking treatment daily is likely to be a life-long commitment. Patients should also be informed that within a few years, more will be known about this.

Patients who are sexually active and want to minimise their risk of transmission to sexual partners should be informed that treatment can

reduce the risk of transmitting HIV considerably, at least once viral load becomes undetectable.

Based on this information, patients who wish to start at a high CD4⁺ count should be allowed to do so. There are caveats: Early ART is not a reasonable option in facilities still using stavudine or zidovudine as first-line treatment, nor in facilities prone to stock-outs. In resource-stretched facilities with high patient loads, patients with CD4⁺ counts <350 cells/ μ l must be prioritised. Ultimately, an approach that gives patients the opportunity to make informed choices respects the principle of patient autonomy. This could lead to increased adherence, and better outcomes for individual patient's and the public's health.

Conflict of interest. N Geffen is on the INSIGHT Community Advisory Board and receives a *per diem* for travel to INSIGHT meetings and an honorarium. INSIGHT is running the START trial. F Venter is on the Data Safety Monitoring Board for the START trial.

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