OPINION

WHEN TO START ANTIRETROVIRAL THERAPY IN ADULTS: THE RESULTS OF HPTN 052 MOVE US CLOSER TO A 'TEST-AND-TREAT' POLICY

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When is the best time to initiate antiretroviral therapy (ART) in adults? This is a vital question in HIV treatment and prevention services. More specifically, is the 350 cells/µl CD4 count threshold recommended by current World Health Organization (WHO) guidelines sufficient, or should we move to a 'test-and-treat' approach in which anyone who tests HIV-positive is offered ART, irrespective of their CD4 count? The recently announced results of the HPTN 052 trial take us closer, but not all the way, to a test-and-treat approach.

There are several important questions in determining ART initiation criteria, including what is best for treating the HIV-positive individual, what is best for HIV and tuberculosis (TB) prevention at the population level, and the costs of the different options for initiating ART. While there is not yet enough evidence to confidently change policy to recommend universal ART for all HIV-positive individuals, there are certainly enough data to support the implementation and evaluation of 'test-and-treat' pilot programmes.

WHAT IS BEST FOR TREATING THE HIV-POSITIVE INDIVIDUAL?

Clinical trials have shown definitively that a CD4 threshold of 350 cells/µl for initiating ART results in lower morbidity and mortality than 200 cells/µl.[1,2] However, observational data on whether patients with HIV will benefit from initiating at a higher CD4 count are less clear.

Researchers from the North American NA-ACCORD cohort (including over 17 500 patients) found a nearly two times increased risk of death in patients who deferred ART to below 500 cells/µl.[3] This study is cited in US treatment guidelines that provide for early treatment. However, the study's statistical methods have been criticised.[4,5] Other evidence comes from the HIV-CAUSAL collaboration, which includes nearly 21 000 patients in Europe and America, including the NA-ACCORD patients. In this study no mortality benefit was observed for patients who started ART with a CD4 count above 500 cells/µl compared with those who started at 350 cells/µl. However, AIDS-defining illnesses were significantly more likely among patients who started treatment at lower CD4 counts.[6]

These studies do not offer conclusive evidence that initiating ART early (>500 cells/µl) will benefit patients. Both NA-ACCORD and HIV-CAUSAL are observational studies and subject to methodological limitations. The long-term side-effects of ART and the possible effect of treatment fatigue on adherence might mitigate against early initiation. Furthermore, participants in these studies were less likely to use sub-optimal drugs, such as stavudine, that are prevalent in many resource-limited settings.

It is hoped that two ongoing clinical trials will answer once and for all whether early treatment is beneficial. The Strategic Timing of Antiretroviral Treatment (START) trial is recruiting 4 000 volunteers. Patients with CD4 counts >500 cells/µl are randomised to either initiate immediately or defer to 350 cells/µl.[7] This international trial currently only has one site in sub-Saharan Africa, the Desmond Tutu HIV Centre at the University of Cape Town (UCT). START is due to complete in 2015, and clinicians in Cape Town should encourage their patients with high CD4 counts to consider enrolling at the UCT site.

In addition, the ANRS 12136 trial in Côte d'Ivoire is due to complete in 2013. The trial objective is to compare the benefits and risks of initiating ART according to the WHO guidelines versus the benefits and risks of initiating ART immediately among HIV-positive adults with CD4 counts >350 cells/µl.[8]

WHAT IS BEST FOR HIV AND TB PREVENTION AT THE POPULATION LEVEL?

Several observational studies show that there is a strong correlation between reduced HIV incidence and either increased ART coverage or lower viral loads in the community. In San Francisco, new HIV diagnoses decreased along with mean community viral load from 2004 to 2008.[9] In Taiwan, there was a more than 50% decrease in HIV infections ascertained by community surveillance after the introduction of free ART.[10] In British Columbia from 1996 to 2009, the number of people receiving ART increased from 837 to 5 413, while the number of new HIV diagnoses fell over 50% from 702 to 338 per year.[11]

Because of the possibility of confounding factors, these observational studies alone do not prove a causal effect, although they are strongly suggestive. This research was also conducted in populations where a large proportion of HIV-positive individuals are men who have sex with men (MSM), and the generalisability of the findings to heterosexual populations may be questioned. However, the recently terminated HPTN 052 study indeed demonstrates that ART reduces the risk of HIV transmission in serodiscordant predominantly heterosexual couples.

HPTN 052 was an international study that began enrolling in 2005. A total of 1 763 HIV-positive people in serodiscordant relationships and with CD4 counts from 350 to 550 cells/µl were randomised to either receive ART immediately (immediate group) or when their CD4 count fell below 250 cells/µl (delayed group). A total of 39 HIV infections

occurred, and genetic analysis demonstrated that most transmission was between partners enrolled in the trial. Only one HIV transmission took place from HIV-positive to HIV-negative partner in the immediate group versus 27 in the delayed group (hazard ratio (HR) 0.04; 95% confidence interval (CI) 0.01 - 0.27; $p<0.001$).[12] The study was due to complete in April 2015, but the Data Safety Monitoring Board terminated it in May 2011 because of the highly significant results.

An additional important finding from HPTN 052 is that patients in the immediate initiation arm had fewer treatment endpoints, defined as first serious HIV-related clinical event or death (HR 0.59; 95% CI 0.40 - 0.88; $p=0.01$). The difference was driven by the fact that three participants in the immediate arm versus 17 in the delayed arm developed extrapulmonary TB ($p=0.002$). However, given the wide CI and the fact that the treatment initiation threshold was 250 cells/µl (not 350 cells/µl), this is not conclusive evidence of the benefit of early treatment to the patient.

Existing research suggests that a test-and-treat approach is likely to reduce HIV incidence. It is of course not a panacea: test-and-treat will seldom identify patients with primary HIV infection and therefore will not eliminate transmissions during primary HIV infection. Infections due to virological failure should also be expected, and there is the inevitable decline in efficacy when moving from trial conditions to programmes serving entire populations. Nevertheless, combined with scaled-up male medical circumcisions and condom distribution, we now have a formidable arsenal for reducing sexually transmitted HIV infections.

A further public health benefit of test-and-treat is the effect on the TB epidemic. Observational data also show a correlation between ART scale-up and reduced TB incidence. For example, one study in Masiphumelele township in Cape Town found that pre-ART adult TB notifications increased by an average of 212 cases per 100 000 people per year, while post-HAART, adult cases decreased by 116 per 100 000 per year.[13,14]

WHAT DOES THIS MEAN FOR GUIDELINES?

While 'test-and-treat' policies might still be a few years away, it is perplexing that the South African treatment guidelines still use an ART initiation threshold of 200 cells/µl except for pregnant women and people with TB (in which case 350 cells/µl is the initiation threshold). This is not a minor issue. A study by Médecins Sans Frontières of a Lesotho cohort found that the 639 patients who initiated above 200 cells/µl were 68% less likely to die and 39% less likely to be lost to follow-up than patients who initiated below 200 cells/µl. Only 56 patients were pregnant and 66 had TB, and thus would have been started on treatment according to the South African guidelines.[15] By failing to update our guidelines to the WHO standard, i.e. offering ART to all patients at first CD4 count below 350 cells/µl, we are probably losing lives.*

WHAT ABOUT COSTS?

Costing and operational issues are major concerns in implementing a 'test-and-treat' strategy on a large scale. One analysis presented at the International AIDS Conference in 2010 estimates the cost of using ART for prevention in South Africa. This analysis concluded that expanding ART to all CD4 levels, beyond the recommended WHO threshold of 350 cells/µl, would add $700 million to the cost of the programme, but that this would prevent 681 000 new infections over time, and consequently allow the cost of the programme to break even by 2022.[16]

*This policy was changed after this article was accepted. Now all HIV-positive patients with CD4 counts <350 cells/ µl are eligible for ART. – Editor

Another analysis by the Health Economics and Epidemiology Research Office (HERO) has examined the cost of ART using the WHO guidelines compared with a CD4 initiation of 200 cells/µl (South Africa's old guidelines). The cost of first-line tenofovir-based regimens is estimated to be R4 320 per patient for the first 6 months of treatment followed by R6 126 per patient per year.[17] The ASSA2008 model estimates that there are 5.6 million people with HIV and 1.2 million on treatment.[18] If hypothetically it were possible to initiate 1 million people on ART with CD4 counts >350 cells/µl who pass through the HCT programme over the next year as part of a test-and-treat programme at an average of R7 000 per patient for the first year, the additional cost of ART would be R7 billion – a substantial burden on the state's finances. However there are also potential cost savings due to reduced HIV infections and possibly reduced opportunistic infections. The potential of reducing the cost of treatment by lowering ART prices, task-shifting, and the potential for the private sector to absorb a greater part of the cost of treatment than it currently does should also be considered.

The HERO study suggests that if task-shifting were implemented and optimal reference prices were paid for ART regimens, the WHO 350 cells/µl initiation threshold including tenofovir-based regimens would cost less to implement than using the old 200 cells/µl threshold with stavudine (without task-shifting and optimal reference prices). Analyses like this demonstrate that it is not necessarily guideline improvements that stand in the way of making programmes more affordable, but rather sub-optimal drug prices and programme design and staffing plans. In this light, it is possible that 'test-and-treat' approaches could be made highly cost-effective, and analyses of the costs and benefits of such an approach are clearly needed.

CONCLUSION

While we do not yet have sufficient data to change guidelines to adopt test-and-treat, there are sufficient data to support preliminary programmes to research this approach. The HPTN 052 results suggest that 'test-and-treat' may present an opportunity to reduce HIV incidence in South Africa. Nationally, we need to consider piloting in some health facilities the offer of ART to HIV-positive people in serodiscordant relationships, heterosexual or homosexual, irrespective of CD4 count. Such an operational research cohort would help us estimate the cost of a test-and-treat approach and identify its practical challenges and opportunities.

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