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The wind is in our sails

The publication in May, with much fanfare, of the results of the HPTN 052 Randomised Control Trial (RCT) of when to start HIV-positive people on ART was music to SACEMA's ears (1). Prof Myron Cohen and colleagues carried out a trial involving HIV discordant couples all of whom had $CD4^+$ cell counts between 350 and 550/µL at recruitment. In the treatment arm, the HIV positive partner was started immediately on anti-retroviral therapy (ART); in the control arm, people were started on ART when their CD4 cell count fell below 250/µL, as currently advised by the World Health Organization (2). The trial was designed to evaluate whether immediate versus delayed use of ART by HIV-infected individuals would reduce transmission of HIV to their HIV-uninfected partners and potentially benefit the HIV-infected individual as well.

The answer was a resounding "yes"; early treatment cut transmission by 96% and the incidence of TB by 82%. While there were also fewer deaths among those that started ART immediately the reduction was not statistically significant. The data safety and monitoring board stopped the trial four years before it was due to be completed because the evidence of impacts was so overwhelming that it became unethical to refuse early treatment to the control arm.

The HPTN 052 was the first randomised controlled trial of the effect of early treatment ($CD4^+$ > 350 to 500/µL) versus delayed treatment ($CD4^+$ < 350 /µL) and confirmed a number of earlier studies which showed clearly that high levels of compliance with ART reduces the viral load by 1,000 times or more (2,3), probably reduces the risk of HIV by about 95% (4), reduces the risk of TB by about 60% (4) and almost certainly reduces overall mortality by about 75%, even among those with very high $CD4^+$ cell counts (5).

None of this came as a great surprise to SACEMA colleagues. Brian Williams, Senior Research Fellow at SACEMA, was the moving spirit behind a 2009 ground-breaking paper promoting the idea of annual HIV testing and immediate initiation of HAART as a way of massively reducing incidence in high prevalence settings to the extent that we could feasibly see an end to the HIV pandemic by 2050 (3). Others, in particular Julio Montaner (2) and Mari Kithata (6) had also shown that early treatment not only improves the prognosis for infected individuals but greatly reduces the likelihood that they will infect others. Despite the immense international interest in the Lancet paper - and the resulting flurry of grant proposals from many workers keen to test the idea of Treatment as Prevention (TasP) - it took the irrefutable results of HPTN 052 to give the idea the stamp of scientific respectability.

Now that it is beyond dispute that treatment dramatically reduces individual infectiousness, the remaining concerns about TasP are operational, since we now need to determine how such large treatment programs be safely and effectively managed, and cost, since this would require a substantial up-front investment even though it will be cost-saving in the long run (3,7). It is time for the scientific world and funding agencies to consider how best to spend the vast billions still available for work on AIDS, in particular, whether to support preferential channelling of funds towards urgently required operational research into the many facets of TasP that need to be investigated before nation-wide roll-outs can be considered?

It will also be important to consider how to get the maximum benefit from the funds that are available for TasP. In this regard a recent analysis by SACEMA workers of data from Zimbabwe are of importance. It was shown that postpartum women who are HIV positive are at significantly increased risk of dying even when they have $CD4^+$ counts in excess of the levels typical of HIV negative mothers (5, 8, 9). In African settings then, how can it be ethical *not* to offer HAART to all HIV positive pregnant and postpartum women? Given that pregnant women in Africa are, increasingly, being routinely tested for HIV, this provides immediate access - at no added cost - to a large pool of infected persons who can be offered HAART immediately. Not only will this significantly reduce their mortality, it will prevent their children from being infected at or soon after birth and it will provide easier access to their male partners who are themselves likely to be HIV positive.

Demonstration trials could show, in less time than it takes to run a large community level randomised controlled trial, whether and how TasP gives us the tools to end AIDS, save millions of lives and, in the long term, actually *save* money.

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