Published in final edited form as:
Lancet Infect Dis. 2014 April ; 14(4): 258–259. doi:10.1016/S1473-3099(13)70329-3.

End of the debate about antiretroviral treatment initiation

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COMMENT

The impact of plasma HIV RNA levels on disease progression to AIDS or death in untreated individuals has been well understood since the mid-1990s.[1] With the subsequent advent of highly active antiretroviral therapy (HAART), which is able to reduce plasma HIV RNA to undetectable levels, dramatic decreases in morbidity and mortality have also been clearly demonstrated among HIV infected persons.[2] With these observations, the optimal time to initiate HAART has been a subject of longstanding debate.

While studies have suggested a clear survival benefit when HAART is initiated before the CD4 cell count falls below 200 cells/mm^3, there has been persistent uncertainty regarding the optimal timing of HAART in asymptomatic patients with higher CD4 cell counts.[3] Without clear evidence regarding the optimal time to initiate HAART, clinicians have had to balance the risks of delaying treatment until such time as benefits have clearly been demonstrated[4] against the possible harms associated with premature exposure to HAART, including side effects, pill burden, cost and potential for avoidable antiretroviral resistance.[5] Other debates saw those in favour of expanding HIV treatment access pitted against those in favour of expanding proven and less expensive HIV prevention strategies.[6]

These debates became increasingly complicated and saw the potential for public health goals to conflict with individual patient clinical needs with the original publication of the HPTN 052 trial, which demonstrated a dramatic reduction in HIV transmission among HIV-serodiscordant couples randomized to earlier HAART initiation.[7] In this issue of *Lancet Infectious Diseases*, Grinsztejn and colleagues report on the latest data from the HPTN 052 trial.[8] Their results demonstrate clear clinical benefits in addition to the public health benefit previously described. Patients initiating HAART at a CD4 cell count between 350 and 550 cells/mm^3 experienced fewer primary clinical events, fewer AIDS-related events and a lower incidence of tuberculosis in comparison to patients randomized to HAART when the CD4 cell count fell below 250 cells/mm^3. Contrary to placing public health goals (i.e. reduced HIV transmission) in conflict with individual patient needs (i.e. avoiding unnecessary HAART exposure), these data demonstrate clear patient benefits of starting HAART even when the CD4 count is well above 400 cells/mm^3.

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With the debate concerning the value of earlier HAART initiation now settled from both a patient and public health perspective, urgent questions remain regarding how to optimally roll out HIV treatment programs.[9] Several challenges still exist. The first relates to early detection of existing HIV cases. As many asymptomatic individuals are unaware of their HIV-positive status,[10] the implementation of universal screening programs is an urgent a priority. As demonstrated by Grinsztejn and colleagues,[8] such a strategy not only benefits the health of patients who might otherwise go undetected until late in the course of their infection, but also benefits the health of others to whom they may inadvertently transmit the virus. Early detection also permits earlier initiation of HAART therapy, the benefits of which have now been made clear.[7, 8] Other prevailing challenges that require further attention include the facilitation of immediate linkage to HIV care upon initial diagnosis to prevent loss to follow-up[11] and the implementation of strategies to ensure high adherence rates to HAART to ensure long-term virological suppression and prevention of antiretroviral resistance.[12] Unfortunately, these challenges are complicated in many settings where stigma towards persons with and at risk for HIV infection remains extremely high.[13] As a result, individuals are often reluctant to get tested for HIV, are often lost to follow-up before HAART is initiated, or experience structural barriers that impede access to HAART and/or optimal HAART adherence. [13]

With these challenges at the forefront of the HIV/AIDS agenda, the results of the HPTN 052 trial place humanity at a remarkable crossroads where there is now a clear understanding of the role of plasma HIV RNA levels on HIV disease progression and the considerable benefits of early HAART initiation on reducing HIV transmission[7] while also protecting patients from significant clinical endpoints.[8] Translating this knowledge into a global public health response remains an urgent challenge.

Acknowledgments

This research was undertaken, in part, thanks to funding from the Canada Research Chairs program through a Tier 1 Canada Research Chair in Inner City Medicine, which supports Dr Evan Wood, and the US National Institute on Drug Abuse [grant number R01-DA021525].

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