End of the debate about antiretroviral treatment initiation

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Since the mid 1990s we have known that the amount of HIV RNA in plasma affects progression to AIDS or death in untreated individuals.[1] Highly active antiretroviral treatment (HAART) can make plasma HIV RNA undetectable, and use of this treatment leads to striking decreases in morbidity and mortality.[2] However, the best time to initiate HAART has been the subject of prolonged debate.

Although study findings show a clear survival benefit when HAART is initiated before patients' CD4 counts fall below 200 cells per μL, uncertainty surrounds the best time to initiate treatment in asymptomatic patients with higher CD4 cell counts.[3] Clinicians have to balance the risks of delaying antiretroviral treatment against the possible harms associated with premature exposure to HAART, including side-effects, pill burden, cost, and potential for avoidable antiretroviral resistance.[4] Other issues under discussion include expansion of access to HIV treatment versus augmented use of proven and cheaper HIV prevention strategies.[5] These debates are becoming increasingly complicated and risk public health goals conflicting with individual patients' clinical needs.

In *The Lancet Infectious Diseases*, Beatriz Grinsztejn and colleagues report the latest data from the HPTN 052 trial.[6] In this study, HIV-serodiscordant couples were randomly allocated to either early initiation of HAART (ie, at a CD4 count of 350–550 cells per μL) or delayed antiretroviral treatment (ie, starting treatment when their CD4 count fell below 250 cells per μL). Fewer individuals who were assigned to early HAART had primary clinical events (57 individuals *vs* 77 people allocated to delayed treatment; hazard ratio 0·73, 95% CI 0·52–1·03; p=0·074), new-onset AIDS events (40 *vs* 61; 0·64, 0·43–0·96; p=0·031), and tuberculosis (17 *vs* 34; 0·49, 0·28–0·89; p=0·018). These data show a clear benefit to patients of starting HAART early, when the CD4 count is well above 400 cells per μL. The debate about the value of early HAART initiation should now be viewed as settled from both patients' and public health perspectives.

Several challenges remain before we can consider the best approach for rolling out HIV treatment programmes.[7] First, many asymptomatic individuals who are HIV-1-positive are unaware of their HIV status;[8] thus, implementation of universal screening programmes is a priority. Such a strategy benefits not only the health of HIV-positive patients whose status might otherwise be unknown and undetected until late in the course of their infection but also the health of other people to whom they might inadvertently transmit the virus. Early detection also permits early initiation of HAART. Second, immediate linkage to HIV care on initial diagnosis is needed, to prevent loss to follow-up.[9] Third, strategies need to be implemented to ensure high rates of adherence to HAART, to ensure long-term virological suppression and prevention of antiretroviral resistance.[10] Unfortunately, these challenges exist in settings where stigma towards people with and at risk of HIV infection remains very high.[11] As a result, individuals are typically reluctant to be tested for HIV, are frequently lost to follow-up before HAART is initiated, or meet structural barriers that impede access or enable adherence to treatment.[11]

With these challenges at the forefront of the HIV/AIDS agenda, the results of the HPTN 052 trial place humanity at a crossroads, at which a clear understanding exists of the effect of plasma HIV-1 RNA concentrations on disease progression and of the benefits of early HAART initiation for reduction of HIV transmission, which protect patients from important clinical endpoints. Translation of this knowledge into a global public health response remains an urgent challenge.

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Shot in the HAART: vaccine therapy for HIV

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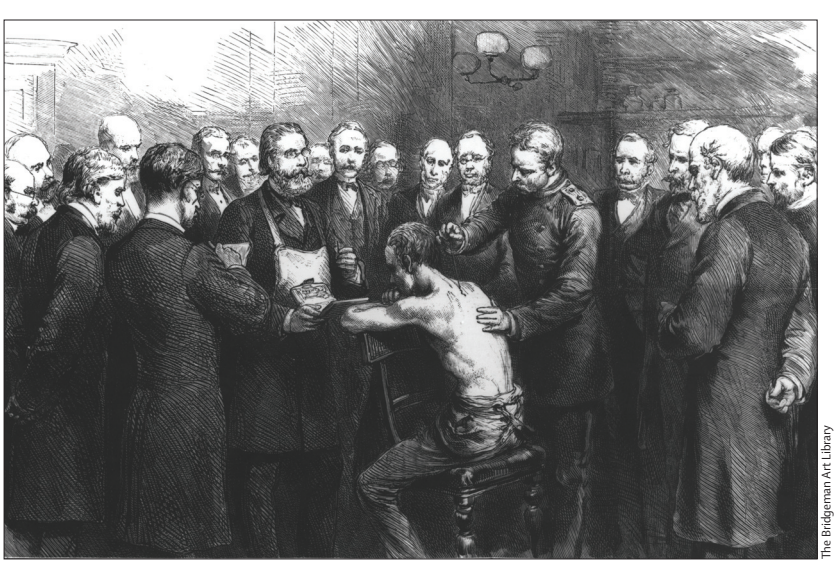
In 1890 *The Lancet* reported that Robert Koch was starting trials of a therapeutic vaccine for tuberculosis, noting that "we may be on the verge of a revolution".[1] A century later, vaccines for therapy in general or against infectious diseases in particular have not yet achieved revolutionary status, although the approval of sipuleucel-T for therapeutic vaccination of metastatic prostate cancer was an important milestone.[2] In *The Lancet Infectious Diseases*, Richard Pollard and colleagues[3] report that the Vacc-4x HIV Gag conserved peptide vaccine given during combination antiretroviral therapy (cART) was associated with lower setpoint viral load after analytical treatment interruption (ATI) than was placebo. Although there were no differences in primary endpoints of either the proportion of volunteers needing restart of cART or in postATI CD4 cell counts, this study represents one of the few successful randomised trials showing a favourable viral-load effect of therapeutic HIV vaccination.

Several studies in the era before cART examined the effect of vaccination on the outcome of HIV disease, CD4 cell count, or viral load, and although it was possible to use vaccination to alter immune responses in people infected with HIV, no effect on disease progression could be shown.[4,5] The advent of cART shifted the focus to cure strategies, using vaccination to augment host immune control of HIV during treatment to achieve a functional cure—ie, spontaneous and durable control of HIV disease after treatment interruption. These studies have shown equivocal effects.[6] Recently, a dendritic-cell vaccine given during cART with subsequent ATI was shown to transiently lower viral load.[7] If the use of the Vacc-4x conserved Gag-peptide vaccine improved natural responses to HIV and effected better control of replication during ATI, several questions accrue. Did the vaccine reduce the pool of latently infected cells? Was vaccination itself associated with bursts of replication and enlargement of the latent pool? Why did it take more than 12 weeks for the difference in viral-load setpoint to be evident when Felipe Garcia and colleagues[7] found a difference at 12 weeks? Was there a vaccine-induced correlate of control? Clearly future work with this sample set and new studies should focus on ways to address these issues.

In view of the prominence of the cure agenda, some aspects of the present study and the problems encountered by the investigators warrant comment. Immune modulators—vaccines, biologicals, drugs—might have a greater likelihood of achieving durable



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Robert Koch's treatment of tuberculosis