

Shot in the HAART: vaccine therapy for HIV



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 colleagues³ 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 colleagues⁷ 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.

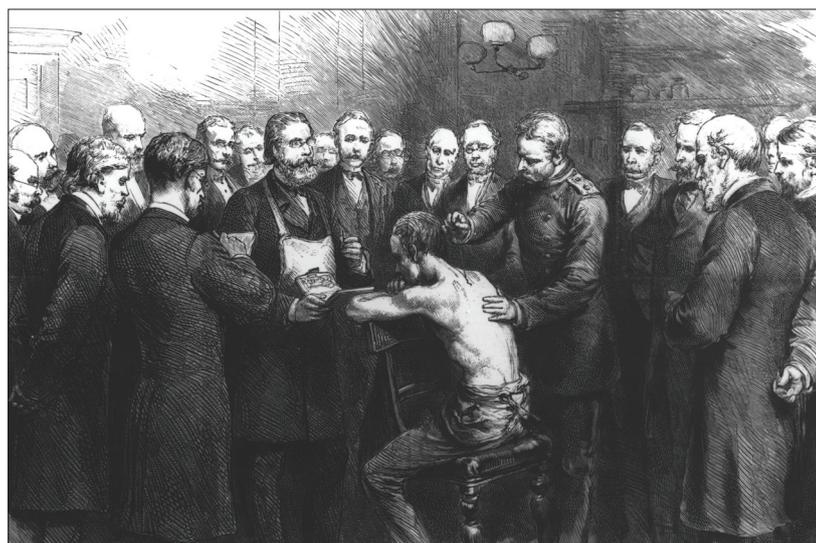
In view of the prominence of the cure agenda, some aspects of the present study and the problems encountered by the investigators warrant comment. Immune modulators—vaccines, biologicals, drugs—might have a greater likelihood of achieving durable functional (if not sterilising) cure if the pool of latently infected central memory T cells is small at the outset. Latently infected immune cells are long-lived, and prolonged treatment has not been able to purge this pool.⁸ A better study population might be people whose treatment was started during acute HIV infection (ie, from earliest detectable viral load) or in early infection (3–6 months after infection),^{9,10} in whom cART can reduce latently infected T cells to undetectable levels. This approach might reduce and qualitatively alter the latent reservoir and preserve or reconstitute CD4 cells in the gut-associated lymphoid tissue.¹¹ With a very limited pool of integrated viruses, vaccination or other immunomodulatory strategies might be more likely to succeed and generate useful information about correlates of cure.

The difficulties Pollard and colleagues faced in recruiting volunteers for this study might suggest a major problem for future studies. Importantly, the SMART study used CD4-driven interventions in chronically infected people who had a median nadir CD4 count of 250 cells per μL and many of whom (about 29%) had detectable viraemia at baseline.¹²

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Robert Koch's treatment of tuberculosis

Whether the conclusions of SMART apply to all ATI studies is unknown, but unlikely, because viral load, not CD4, can be the trigger for renewal of cART. Moreover, the unknown risk imposed by transient viraemia and lifelong HAART must be balanced against the potential benefit of functional cure, as recently shown in the VISCONTI study where 15% of patients had a viral load below 50 copies during treatment interruption.¹³

Whether future ATI studies will be allowed to progress to setpoint or whether an earlier viral-load threshold will trigger reinitiation of cART is an important scientific and ethical issue, and one that people on treatment should influence (through community advisory boards). The identification of surrogates for the latent pool, whether these be PCR, viral outgrowth, or a currently unknown viral or immunological biomarker will be a key to progress. Ultimately, failure to identify biomarkers that correlate with outcome (eg, if definitions of outcome are too stringent to explore partial responses) will hamper objective measurement of success.

The challenge of curing an infection that is not sterilised by natural immune responses, with a pathogen integrated into the genome of the host's long-lived, quiescent CD4 T cells is daunting. The suggestion by Pollard and colleagues of the potential for vaccine-induced immune responses to modulate viral setpoint during ATI might be an important proof-of-principle and a first tentative step to an effective set of immune interventions.

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