

Trying to cure HIV with immunotherapy: not so simple

Great interest exists in curing HIV or at least achieving prolonged remission while off combination antiretroviral therapy, because current treatment is lifelong, expensive, has side-effects, and needs substantial compliance to prevent emergence of drug resistance. Recruitment the immune system to assist in elimination or control of HIV replication is an area of active study, with hopes boosted by recent exciting results showing that immune clearance of cancers, such as melanoma, is possible.¹

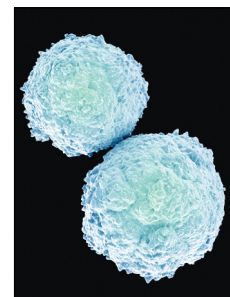
Reduced antigenic load resulting from antiretroviral therapy leads to substantial loss of T-cell immunity to HIV and, to a lesser extent, humoral immunity. This quiescent HIV-specific cytotoxic T-cell response with antiretroviral therapy is not capable of recognising reactivated latently infected cells in vitro.² Activation of T-cell immunity against HIV with a therapeutic vaccine could theoretically help to eliminate HIV reservoirs and control viral replication off treatment. The unusual T-cell response induced by cytomegalovirus vector vaccines against simian immunodeficiency virus in macaques can slowly mop up residual infection.³

In *The Lancet HIV*, Chad Achenbach and colleagues report the results of a small study in which they united combination antiretroviral therapy intensification and a potentially therapeutic vaccination.⁴ 28 adult patients with chronic HIV-1 infection were randomly assigned to receive ritonavir and maraviroc antiretroviral therapy intensification either alone or combined with injections of HIV DNA prime vaccine followed by HIV recombinant adenovirus 5 boost vaccine. This preliminary study had the unusual primary endpoint of reducing total HIV DNA by about threefold in at least one participant (a 0.5 log₁₀ or greater decrease in HIV DNA in 10⁶ peripheral blood mononuclear cells at week 56). The vaccines did induce T-cell immunity and, in fact, one patient in the control group who received treatment intensification alone did reduce their HIV DNA levels by the preset level; however, no overall reduction in HIV DNA levels was detected in either group and the authors therefore concluded that the treatments did not reduce the latent HIV reservoir overall. More sophisticated assays of the HIV reservoir or treatment interruption analyses were not pursued. In this trial, the latent HIV reservoir would have

remained hidden from immune surveillance; the use of latency-reversing drugs to first reactivate the reservoir before a therapeutic immunisation (a so-called shock and kill approach⁵) might more effectively target the HIV reservoir than the methods used.

This study adds to the published literature about the difficulties involved in translating therapeutic vaccination for HIV into a clinical benefit. Related DNA and adenovirus vector vaccines induce quite strong T-cell responses but have not been able to prevent HIV infection.⁶ Immunity induced by DNA, adenovirus, and similar HIV vaccines might be insufficiently broad to cope with the huge diversity of HIV strains and the propensity of the virus to escape cytotoxic T-lymphocyte immunity. Indeed, recent work shows that most HIV strains within the latent reservoir have already escaped from the host's cytotoxic responses,⁷ which is consistent with a substantial turnover of this reservoir.⁸ Even stimulated cytotoxic T-lymphocyte responses were poorly capable of recognising and eliminating the reactivated latently infected cells unless unmutated cytotoxic T-lymphocyte epitopes were still present.⁷ Wild-type cytotoxic T-lymphocyte epitopes are more likely to remain if combination antiretroviral therapy is started very early during acute infection before antigen escape—such patients would be interesting to study in future trials because boosting of their T-cell responses could be capable of recognising and eliminating their reactivated latent HIV reservoir.

In addition to T-cell immunity, humoral immunity could also play a part in eliminating reactivated latently infected cells. Recent work in murine models showed that a combination of latency-reversing drugs and neutralising antibodies helped to reduce latent HIV.⁹ Neutralising antibodies are typically regarded as having the role of controlling free virus, but some of the more potent recently identified broadly neutralising antibodies such as the PGT121 antibody can stop cell-to-cell transmission of virus and also mediate antibody-dependent cellular cytotoxicity functions.¹⁰ Infusions of such neutralising antibodies substantially reduce both viral RNA and DNA levels in macaques infected with simian-human immunodeficiency virus.¹¹ Antibody-dependent cellular cytotoxicity responses also decrease during combination antiretroviral therapy¹² and could



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be amenable to boosting with regimens similar to those used in the Thai RV144 trial.¹³ Non-neutralising antibodies, such as those involved in antibody-dependent cellular cytotoxicity, seem to have played a part in the modest protective immunity reported in that trial.¹³ However, in a similar way to neutralising antibodies and cytotoxic T-lymphocyte responses, antibody-dependent cellular cytotoxicity antibodies also force immune escape¹⁴ and strategies to boost responses to strains within the existing HIV reservoir of patients, although complex, might ultimately be needed.

The process of harnessing the immune system to cure or control HIV is not straightforward, as illustrated by Achenbach and colleagues' study. Carefully designed trials are still needed to pursue this goal.

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I declare no competing interests.

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