Therapeutic vaccination in HIV infection

The concept of using a vaccine to induce or enhance HIV-specific immune responses in those with established HIV infection has been through alternating waves of enthusiasm and skepticism over the past three decades of the HIV epidemic. The earliest therapeutic vaccination trials were conducted in subjects with uncontrolled viremia or suboptimal therapy and the highly activated and dysfunctional immune environment of such individuals would significantly impede the efficacy of any immunostimulatory approaches. Contemporary antiretroviral treatment assures potent and sustained inhibition of HIV replication, reduces immune activation and restores a variety of specific immune functions. This provides the context for a renewed level of scientific interest in the possibility of inducing HIV-specific immunity that could clear virally infected cells, retain long lived memory, and help reduce latent reservoirs of HIV that cannot be eliminated by current drugs or intensification strategies.

To date the most studied approaches for vaccination have been based on viral vectors, plasmid DNA and more recently, autologous dendritic cells (DCs). Among the vectored vaccines, the recombinant canarypox vaccine ALVAC is the most extensively studied across more than 15 preventative vaccine trials, including as the prime to subtype B/E gp120 protein boost in the RV144 ‘Thai’ trial that reduced HIV acquisition by 31%1. Notably, there was no effect on levels of viremia and/or CD4 T cell count in vaccinated subjects who ultimately acquired HIV and in the therapeutic vaccination setting, results with ALVAC based vaccines have been contradictory. While an open label single arm study found that up to 11% of patients who stopped their antiretroviral treatment after vaccination could remain off treatment for 44 weeks2, the largest randomised, placebo controlled studies have shown either no effect on the level of


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rebound viremia after drug treatment interruption (TI)\textsuperscript{3} or even increased viral rebound and decreased time to resumption of treatment\textsuperscript{4}. A trial of a recombinant fowl pox vectored vaccine expressing subtype B Gag/Pol did show a lower viral rebound after TI but this was specifically associated with the vaccine’s inclusion of human IFNγ and production of IgG2 antibodies to p24 Gag\textsuperscript{5}. Constructs based on modified vaccinia ankara (MVA) or adenovirus showed promise in terms of eliciting CD8 and CD4 T cell responses with modest reductions of rebound viremia\textsuperscript{6,7}. One of the key risks of vectored approaches is anti-vector immunity, and the related possibility that broad non-specific immune activation can be harmful if it increases the susceptibility of CD4 T cells to HIV infection. Vector immunity played a role in the terminated ‘STEP’ prevention trial of a recombinant Ad5 HIV-1 gag/pol/nef vaccine, in which pre-existing immunity to adenovirus serotype 5 (Ad5) was a risk factor for early HIV acquisition in vaccinees\textsuperscript{8}. In this and two other trials of the same vaccine, HVTN 503 and 505, vaccination failed to reduce viral load in newly infected subjects\textsuperscript{9}. The vaccine induced far weaker magnitude T cell responses than that seen in average HIV controllers and responses were directed against very few epitopes in each subject. DNA-based vaccines avoid anti-vector immunity, can be administered repeatedly and can incorporate molecular adjuvants to be co-expressed with the HIV antigens to alter the magnitude, quality and even tissue homing pathways of HIV-specific effector T cells\textsuperscript{10}. Despite these theoretical advantages, human studies have been disappointing. The VRC HIV DNA 009-00-VP consisting of four plasmids encoding a subtype B Gag-Pol-Nef fusion protein was poorly immunogenic and failed to impact rebound viremia after TI\textsuperscript{11}. While eliciting strong HIV-specific CD8 T cell responses is the central goal of all these approaches, recent studies of a four HIV antigen (F4) protein vaccine formulated with AS01 controls respectively\textsuperscript{17,18}. A number of more recent studies using DC electroporated with mRNA encoding HIV-1 antigens have shown this to be a highly efficient loading mechanism, with successful induction of CD8 T cell responses, partial viral control in vivo and/or viral inhibition in vitro\textsuperscript{19-21}. Notably, the most positive results have been associated with use DCs matured ex vivo and combined with autologous HIV antigens, which suggests that suppression of particular variants unique to each individual, including immune escape variant epitopes, is important for antiviral control.

The future role of therapeutic vaccination in functional cure still remains closely tied to the success of strategies to limit or purge the latent reservoir, which are necessary to make HIV visible to immune recognition and clearance. It remains to be seen whether achieving immune control in the absence of antiretroviral drugs, even if not permanent, could find ‘niche’ applications in current models of life-long clinical care, such as a ‘one-off’ intervention available to patients at particular times when oral therapy would be otherwise interrupted for adherence or medical reasons or in paediatric patients where the challenge of life-long adherence is most burdensome. Key challenges include the need to improve the quality of vaccine-induced CD8 T cell responses in terms of central and effector-memory phenotypes, cytolytic ability and polyfunctionality. The fact that viral escape occurs in acute infection, or can be even transmitted in founder viruses, suggests that the precise epitope-specificity of vaccine-induced cytotoxic T cells is important and should not merely recapitulate responses to which vaccinees have already escaped in vivo. In this regard, consideration of immunogens that are more likely to promote responses against epitopes functionally or structurally constrained against mutation should be explored. Analytic treatment interruptions will be increasingly problematic as an outcome measure in clinical trials because of the known risks to both vaccine and placebo groups and therefore, vaccine efficacy will need to be measured by reliable surrogate markers of immunogenicity and viral burden and the field should standardise which assays and markers will be used to compare different platforms and products. For the moment, therapeutic vaccination remains in the realm of test-of-concept. However, in
incrementally helping to improve our understanding of the requirements for functional cure, research into therapeutic vaccination could perhaps be approached with neither wild enthusiasm nor undue scepticism but with a tempered optimism.

References

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A spectrum of (avoidable) HIV latency?

Long-lived latently HIV-infected cells present a major barrier to the eradication of the virus under ART. Current strategies are aimed at eliminating this reservoir of cells once it is established. However, it may be easier to prevent the formation of the reservoir rather than eliminate it.

Current anti-retroviral therapies are able to effectively suppress HIV replication and reduce viral levels. However, they are unable to eliminate a pool of cells that are infected with virus, but remain dormant after infection. This pool includes different cell types, such as CD4+ T cells and macrophages, that have integrated virus, but remain dormant after infection. This pool includes different cell types, such as CD4+ T cells and macrophages, that have integrated virus, but remain dormant after infection. Our current concept of latency is very much shaped by the problems caused by these extremely long-lived infected cells, persisting at fairly stable levels for many years on therapy and requiring the continuous administration of ART.

This particular view of latency has not always been the case. The observation that some cells only expressed viral antigens after a