



# Editorial: Advances in T Cell Therapeutic Vaccines for HIV

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## Editorial on the Research Topic

### Advances in T Cell Therapeutic Vaccines for HIV

Despite significant advancements in our understanding of HIV persistence and immunology, long-term remission of HIV off antiretroviral therapy (ART) has not been achieved except in a few reported cases (1–3). Various strategies aiming to boost immune responses against the virus are currently being evaluated in several proof-of-concept studies and randomized clinical trials. These strategies include harnessing the activity of broadly neutralizing antibodies (bNAbs) (4), innate immune responses (5), and immune checkpoint inhibitors (6, 7). Although newer and more innovative immunotherapeutic approaches are constantly being introduced and evaluated in the HIV cure field, the strategy of therapeutic vaccination to enhance HIV-specific T cell immune responses has been around for over two decades ago and multiple clinical trials have assessed the efficacy of various iterations of these vaccines (8, 9). In general, these vaccines have been safe and well-tolerated, and some of the vaccine approaches had promising results with regard to increasing HIV-specific T cell immune responses. However, despite these results, the overall goal of ART-free HIV remission has remained elusive. The disconnect between clinical outcomes and assay results stress the importance of investigating different factors that could play a role in the success of therapeutic T cell vaccines and is the focus of this Research Topic. Investigating these factors continue to be an important priority in HIV cure research.

As it is with preventative vaccine research, the specific vaccine type constitutes an important factor that can contribute to the safety, tolerability, and efficacy of the vaccine. Previous studies have used DNA vaccines, viral vectors, inactivated whole virus depleted of gp120, and monocyte-derived autologous dendritic cells (DCs) (10). The strategy of DC-based vaccination capitalizes on the ability of these potent antigen presenting cells to coordinate and enhance T cell immunity and is indeed one of the most promising strategies (11–13). The review by Espinar-Buitrago and Munoz-Fernandez not only elucidates DC-T cell interactions but also strategies to better employ DC function, specifically discussing ways of introducing viral peptides to DCs such as the use of nanoparticles as delivery agents. Meanwhile, the randomized placebo-controlled clinical trial by Leal et al., evaluated the safety, immunogenicity, and virologic effects of three doses of ultrasound-guided intranodal infections of a monocyte-derived DC loaded with autologous heat-inactivated HIV every two weeks with or without 3 weekly doses of subcutaneously administered pegylated interferon (IFN)  $\alpha$ -2a, the first being given at the last DC vaccine dose. Participants then stopped ART at the last vaccine dose and were observed for viral rebound. The vaccine and the pegylated IFN  $\alpha$ -2a were safe and well-tolerated and generated higher HIV-specific IFN $\gamma$  ELISPOT responses compared to placebo. The study also showed a very modest decrease in viral load setpoint among

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vaccine recipients which correlated with the increase in HIV-specific T cell responses. Despite these findings, all participants had viral rebound within the 12-week treatment interruption period with a median time to rebound of 27 days.

Results of this clinical trial highlight the disconnect between the various immunologic and virologic assays used to evaluate vaccine response and the clinical outcome of viral rebound following ART interruption. Although development of innovative ways to optimize the ability of therapeutic vaccines to enhance cellular immunity is important, addressing this disconnect remains to be a critical gap in our understanding of this vaccination strategy. This would involve identifying which specific combinations of immunologic and virologic parameters would best predict time to viral rebound. This is one of the main objectives of the AIDS Clinical Trials Group (ACTG) study A5345 (14). Results of that study will be helpful in designing future clinical studies. In addition, developing newer highly reproducible assays that could provide immunologic readouts that significantly correlate with viral rebound is paramount so these could be used in therapeutic vaccine trials. In the paper by Xu et al., the investigators address the substantial variability observed in viral inhibition assays and describe ways by which they optimized the 7-day protocol. The modifications allowed improved reproducibility and also resulted in a larger assay dynamic range to detect % inhibition which could be beneficial in identifying changes in therapeutic vaccine trials. Interestingly, there was no correlation between this assay and magnitude of T cell responses measured using IFN $\gamma$  ELISPOT or cytolytic function using intracellular cytokine staining, two assays commonly used in vaccine trials. It would be important to assess the ability of this assay to predict rebound in completed or ongoing vaccine trials where participants undergo treatment interruption.

Finally, one approach to further enhancing immune responses against HIV is to employ several arms of the immune system. This immunotherapeutic strategy is currently being investigated in a number of ongoing clinical trials and studies in development. The study by Veenhuis et al. provide the supporting rationale for this

approach. In their paper, they describe the development of an assay that can measure effector functions of CD8+ T cells and bNAbs. The assay involves co-culture of isolated CD4+ T cells with HIV and bNAb immune complexes, infection of CD4+ T cells by spinoculation, and a suppression assay with CD8+ T cells. The authors show through this *in vitro* model that CD8+ T cells and bNAbs act synergistically in inhibiting HIV. This vaccinal effect of bNAb therapy has indeed been demonstrated in both nonhuman primate studies and clinical trials (15, 16). A study in development within the ACTG evaluating therapeutic vaccination together with bNAb therapy and which includes a treatment interruption phase will be crucial in determining whether this approach will indeed result in HIV remission. Other combination therapies which would include innate immune responses or strategies to reverse latency are also being evaluated in different clinical trials. These studies highlight the fact that since HIV pathogenesis affects various arms of the immune system, immunotherapeutic interventions targeting these different arms may be necessary in achieving the goal of long-term HIV remission off ART.

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