The hallmark of acute HIV-1 infection is overwhelming viral replication in CD4+ T cells that results in high levels of viremia. The initial peak of viral replication begins to decline simultaneously with the appearance of HIV-1–specific T cells, implicating the strong antiviral activity of these responses during acute infection [1, 2]. Several recent studies have demonstrated that the function of both HIV-1–specific CD4+ and CD8+ T cells is subsequently compromised in the presence of ongoing viral replication. Most dramatically, the ability of HIV-1–specific T cells to proliferate in response to antigenic stimulation is lost during the first years of viral infection [3–6], and this proliferative defect is associated with the loss of interleukin (IL)-2–producing HIV-1–specific CD4+ T cells [7]. Studies that have demonstrated a functional impairment of the cellular immune response early during the course of infection have provided a rationale for the initiation of antiretroviral therapy (ART) during acute infection to protect these HIV-1–specific T cell responses. Indeed, studies of individuals treated with ART during acute HIV-1 infection have demonstrated a preservation of T cell functions, most notably the ability of virus-specific T cells to secrete IL-2 and to proliferate in response to viral antigen [3–7]. However, the HIV-1–specific CD8+ T cell responses in individuals treated during acute infection remain at a low magnitude overall and are restricted to a limited number of viral epitopes [3, 8, 9]. In addition, HIV-1–specific T cell responses decline further in patients treated with ART, probably because of an absence of viral antigen to drive these responses [10–12]. On the basis of these observations, therapeutic immunization of individuals treated during acute HIV-1 infection has been proposed, with the hope that these measures will boost waning T cell responses—or engender new T cell responses—and lead to immunologic control of viral replication after discontinuation of ART.

In terms of possible therapeutic vaccine candidates, many HIV-1 immunogens have been developed during the previous 2 decades, including the 2 tested in the QUEST study, published in this issue of the Journal of Infectious Diseases [13]. ALVAC-HIV (vCP1452) is a canarypox vector modified to express the HIV-1 env and gag genes along with individual optimal CD8+ T cell epitopes from the nef and pol genes. Remune is an inactivated gp120-depleted HIV-1 immunogen emulsified with incomplete Freund’s adjuvant. ALVAC-HIV vectors have been previously studied in HIV-1–uninfected subjects, and both immunogens have been tested in HIV-1–infected subjects. In early studies in HIV-1–uninfected subjects, immunization with a canarypox–HIV-1 vector, vCP1521, and recombinant gp120 proteins induced CD8+ cytotoxic T cell responses in ~25% of subjects, but these responses were often transient [14]. In HIV-1–infected subjects who received ART early during the course of infection, vaccination with ALVAC-HIV (vCP1452) and recombinant gp160 protein induced persistent HIV-1–specific CD8+ T cell responses in 78% of subjects but only transient virus-specific CD4+ T cell responses [15]. Remune, in contrast, has been shown to augment HIV-1–specific CD4+ T cell responses in ART-treated HIV-1–infected subjects [16–20]. Induction of CD4+ T cell responses by Remune has also been associated with a correction in the functional defect in HIV-1–specific CD8+ T cell proliferation that is common in patients with chronic progressive HIV-1 infection [6]. Thus, ALVAC-HIV increases virus-specific CD8+ T cell responses, whereas Remune increases HIV-1–specific CD4+ T cell responses (and, indirectly, the ability of virus-specific CD8+ T cells to proliferate in response to HIV-1 antigens). The QUEST study sought to determine whether immunization with either ALVAC-HIV (vCP1452) alone or ALVAC-HIV and Remune in subjects who received ART during acute HIV-1 infection results in induction of
HIV-1–specific T cell responses and control of HIV-1 replication after discontinuation of ART.

In the QUEST study, a randomized, double-blind, placebo-controlled trial, 79 HIV-1–infected subjects treated with ART during early acute HIV-1 infection (defined as ≤3 bands on an HIV-1 Western blot) who had received continuous suppressive ART for ≥72 weeks were randomized to receive either ART alone with placebo vaccines (arm A); ART and ALVAC-HIV (arm B); or ART, ALVAC-HIV, and Remune (arm C). Both HIV-1–specific CD4+ and CD8+ T cell responses, measured using an interferon (IFN)-γ enzyme-linked immunospot assay, were significantly increased in individuals who were vaccinated with ALVAC-HIV or ALVAC-HIV and Remune (arms B and C). However, overall HIV-1–specific T cell responses were of low magnitude after immunization: a median of 180 spot-forming cells (sfc)/10^6 peripheral blood mononuclear cells (PBMCs) for p24-specific CD4+ T cells and 275 sfc/10^6 PBMCs for Gag-specific CD8+ T cells. These responses were considerably lower than the T cell responses reported in some individuals with long-term nonprogressive HIV-1 infection [21, 22]. Surprisingly, HIV-1–specific CD4+ T cell responses did not differ between arm B and arm C. However, the study did not report whether there were differences in the ability of these HIV-1–specific CD4+ T cells to secrete IL-2 or to proliferate in response to HIV-1 antigen. Despite these modest, but significant, differences in the HIV-1–specific T cell responses, no differences were observed between arms A and B/C in terms of viral control after discontinuation of ART. Overall, 14 (17.7%) of 79 subjects controlled viremia at levels ≤1000 HIV-1 RNA copies/mL at week 24 after discontinuation of ART (primary end point), and there was no significant difference between arm A (6/27 [22.2%] subjects) and arms B/C (8/52 [15.4%] subjects). In addition, no significant differences in plasma viral load, CD4+ or CD8+ T cell counts, or cell-associated HIV-1 RNA or DNA load were observed between arms A and B/C at 24 weeks after discontinuation of ART. The study also found no evidence for a correlation between HIV-1–specific CD4+ or CD8+ T cell responses and viral load after discontinuation of ART. These results are consistent with those from a small, nonrandomized study of subjects treated with ART during early acute HIV-1 infection who received ALVAC-HIV (vCP1452) and gp160 before discontinuation of ART [23]. Overall, the data from the QUEST trial suggest that immunization with ALVAC-HIV with or without Remune has no effect on viral control in individuals who receive ART during early acute HIV-1 infection.

What important lessons can we learn from this study? First, the discontinuation of ART appeared to be safe, which has important implications for ongoing trials of other therapeutic HIV-1 vaccines. Although the median decline in CD4+ T cell count after discontinuation of ART was 139 cells/mm^3, no subject progressed to an AIDS-defining condition or had a CD4+ T cell count <200 cells/mm^3. The reason for the lack of clinical progression is most likely because of the high CD4+ T cell count at entry in all 3 study arms (median, >700 cells/mm^3). Also, no subject in this study had severe acute retroviral syndrome; in other treatment-interruption studies, the frequency of this complication is <5% [24]. Whether subjects in this trial had viral suppression when ART was resumed is not specified; most subjects in previous treatment-interruption trials achieved an undetectable viral load when treatment was resumed [24].

Second, several of our present assays of immunogenicity do not predict control of HIV-1 replication. In the QUEST study, there was no significant correlation, on the basis of the quantification of Gag-specific IFN-γ–producing CD4+ and CD8+ T cells, between the measures of immune responses in the vaccine recipients and viral load after discontinuation of ART. This finding is in accordance with those from recent studies suggesting that the number of HIV-1–specific IFN-γ–producing T cells does not correlate with control of viremia in infected subjects [21, 25, 26], and the restriction of the immunological analysis to the quantification of IFN-γ–producing T cells alone represents a major limitation of the QUEST study [27]. In some studies that used assays to assess the functionality of T cell responses against HIV-1, such as the number of virus-specific IL-2–producing CD4+ T cells or the extent of antigen-specific ex vivo T cell proliferation, stronger correlations were found between these values and low plasma viral load [6, 7, 28]. In future randomized trials, it will be important to evaluate whether augmenting HIV-1–specific T cells with these functions by use of novel vaccines will lead to enhanced control of HIV-1 replication.

Perhaps the most important lesson to learn from this study is that future therapeutic vaccine trials should not only establish that an approach is immunogenic but also assess the effect of the vaccine and functional vaccine-induced immune responses on HIV-1 replication. Several scenarios might account for a lack of an effect on viral replication despite the detection of vaccine-induced immune responses, as was observed in the QUEST study. The overall immunogenicity of the vaccine used may be limited, which results in HIV-1–specific T cell responses that are not sufficiently strong to control viral replication. Alternatively, the vaccine may induce significant immune responses that lack important antiviral functions needed for the control of viral replication [29]. Finally, because of the dramatic sequence heterogeneity in the viral population, the immune responses induced by a vaccine may be restricted in their repertoire to the sequence of the HIV-1 immunogen used and may not cross-react sufficiently with the autologous viral strain in the
infected individual [30]. Taken together, these scenarios highlight the importance of assessing both immunologic and virologic end points in therapeutic vaccine trials, as was done in the QUEST trial.

Although immunization with the vaccines in the QUEST trial did not result in the control of viral replication, recent data on new strategies may offer more encouragement in the search for a vaccine. Chronically HIV-1–infected subjects who were vaccinated with autologous dendritic cells (DCs) pulsed with chemically inactivated HIV-1 reportedly had a significant reduction in HIV-1 RNA load [31]. A subsequent study that used a different method of obtaining and inactivating virus found that 4 of 12 HIV-1–infected subjects immunized with DCs pulsed with heat-inactivated HIV-1 had a reduction in HIV-1 RNA load of >0.5 log_{10} copies/mL, compared with their pretreatment viral load [32]. These studies suggest that HIV-1 RNA load may be decreased at least transiently by therapeutic immunization, although larger randomized and controlled studies must be completed before this correlation is conclusively established. Thus, although therapeutic vaccination in HIV-1 infection remains investigational, we believe that future studies of this strategy will contribute to our understanding of how the immune system controls HIV-1. This knowledge, informed by both basic and clinical science, will be a critical step forward in our quest for a therapeutic HIV-1 vaccine.

References

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