REVIEW

Preserving HIV-specific T cell responses: does timing of antiretroviral therapy help?

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Purpose of review

HIV-specific T cell responses are likely to have an important role in HIV cure strategies that aim for long-lasting viral control without antiretroviral therapy (ART). An important issue in enhancing virus-specific T cell responses is whether timing of ART can influence their magnitude and breadth.

Recent findings

Early ART is associated with lower T cell activation, preservation of T cell numbers, smaller DNA and RNA reservoir size, and, in a single study (VISCONTI), control of plasma viremia after treatment interruption. The prevention of T cell destruction by early ART is associated with relatively low anti-HIV CD8⁺ T cell responses but stronger CD4⁺ T helper function. The relatively lower CD8⁺ T cell response, which is presumably due to rapid lowering of HIV antigen burden after early ART, appears sufficient to control residual viral replication as well as viral rebound upon treatment interruption.

Summary

Available evidence of starting ART during acute or early HIV infection has shown benefit in both virologic and immunologic parameters despite the lower HIV-specific CD8⁺ T cell responses observed. Encouraging as this is, more extensive data are necessary to evaluate its role in combination with immunotherapeutic and latency activation strategies that are being assessed in various HIV cure-related studies.

Keywords

antiretroviral therapy, HIV, HIV-specific T cell response

INTRODUCTION

Effective antiretroviral therapy (ART) has improved the life expectancy of the HIV-infected population, [1–3] yet complete eradication of the virus has not been achieved. Viral persistence in the presence of ART continues to be an important barrier to HIV cure, and is hypothesized to be due to the presence of a long-lived reservoir of blood and tissue CD4⁺T cells with latent HIV infection. Although HIV eradication has been reported in a single patient after a CCR5Δ32/Δ32 stem cell transplantation [4,5], there have been no other cases to date that have shown similar outcomes. Apart from an ‘eradication cure’, other strategies that can lead to long-lasting viral control without ART and without residual immune dysfunction (functional cure) are currently being evaluated. In both approaches for HIV cure, effective HIV-specific immune responses are considered necessary for continued viral suppression off ART. Using an in-vitro model, Shan *et al.* [6] reported that after viral reactivation, the stimulation of antigen-specific cytotoxic lymphocytes (CTL) was necessary to kill the infected cells. Furthermore, HIV

controllers have been shown to have effective HIV-specific T cell responses related to undetectable or low levels of viremia despite not being on ART [7–10,11[■],12]. Indeed, a number of immunotherapeutic interventions to boost HIV immune responses continue to be evaluated in HIV cure-related studies.

An important issue in enhancing HIV-specific T cell immune responses is whether timing of ART can influence these responses. In primary HIV infection, HIV-specific CD8⁺ T cells expand and are associated with the initial control of viremia [13–15]. In the

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The case for early antiretroviral therapy (ART) towards a cure of HIV infection

KEY POINTS

- Although robust HIV-specific T cell responses in early infection are associated with initial decline of plasma viremia, viral escape and immune dysfunction occur, making adaptive immune responses unable to control virus during chronic infection.
- ART initiated during chronic HIV infection leads to an initial improvement in T cell responses and then a subsequent decline as the antigenic burden is suppressed.
- Early ART initiation does not result in a robust HIV-specific CD8⁺ T cell responses, but virologic and other immunologic effects such as lower levels of activation and stronger helper T cell responses provide evidence of the benefits of this strategy.

nonhuman primate model of simian immunodeficiency virus infection, loss of control of viral replication during primary infection occurs after CD8⁺ T cell depletion, [16] thus demonstrating a central role of HIV-specific T cell response in acute HIV infection. Is it possible then that early ART initiation can preserve these potent HIV-specific immune responses thereby leading to better viral control after reactivation of latent virus? In this article, we will briefly review the evolution of HIV-specific T cell responses during HIV infection as well the changes in these immune responses upon starting ART. We will also review recent studies evaluating the effect of early treatment on HIV-specific response and discuss whether timing of ART can preserve these responses.

HIV-SPECIFIC T CELL RESPONSES DURING UNTREATED HIV INFECTION

Primary HIV infection corresponds to the first 6 months of infection and is characterized by high levels of viral replication in blood as well as dissemination into lymphoid tissue [17] leading to a depletion of CD4⁺ T cells predominantly in the gastrointestinal tract [18,19]. After a period of approximately 10 days from the time of infection (eclipse phase), plasma viremia becomes detectable and continues to increase within the next 10–20 days, after which the level decreases over the next 4 to 5 months until it reaches a 'viral setpoint' [20,21].

The viral replication and processing by professional antigen presenting cells in the initial stages of HIV infection presumably provides the foreign antigen burden required to trigger a corresponding virus-specific, adaptive T cell immune response.

Early studies of T cell-specific responses showed that in individuals with acute retroviral syndrome or during seroconversion, significant major histocompatibility complex-restricted responses are generated to HIV-specific peptides, with response to Env peptides being the most dominant [13,22]. HIV-specific responses to one or more peptides are detected in 94% of individuals within the first 4 months of infection [23]. Although the breadth and magnitude of the total CD8⁺ T cell response are limited during acute infection [24], the antiviral pressure exerted by this initial immune response is evident by its association with the initial control of viremia [14,25] as well as the rapid selection of CTL escape virus [26,27]. With viral escape, these initial CD8⁺ T cell responses decrease and leave behind or are followed by responses to epitopes which escaped more slowly or were invariant [25]. This loss of CD8⁺ T cell function correlates with progressive infection [28]. New CD8⁺ T cell responses are generated following viral escape but are no longer associated with significant decreases in plasma viremia [29] despite the increase in the breadth of HIV-specific reactivity following early primary infection [23,30]. For CD4⁺ T cells, Env-specific and Gag-specific responses are detected within the first 30 days of infection [31]. The peak frequency of Gag-specific CD4⁺ T cells has been observed at 28 days post-Fiebig I/II staging [32] and continues to be detected during early chronic infection [31].

Differences in the characteristics of the initial T cell response have been associated with varying clinical outcomes. Higher frequencies of CD8⁺ T cells with polyfunctional responses to Gag and Nef are associated with lower viral setpoints [33[¶]]. A higher frequency of CD8⁺ T cells specific for Gag during acute infection correlates with delayed progression and a higher CD4⁺ T cell setpoint [34[¶]]. Some studies have shown that HIV-specific CD4⁺ rather than CD8⁺ responses in primary infection correlate with disease outcome. In the Short Pulse Anti-Retroviral Therapy at HIV Seroconversion (SPARTAC) trial [35], a CD4⁺ T cell interferon gamma (IFN γ) enzyme linked immunospot (ELISPOT) response to HIV-1 p24 detectable prior to ART was associated with higher baseline CD4⁺ T cell counts and slower clinical progression [36[¶]]. Induction of Gag-specific CD4⁺ T cell responses in acute infection also inversely correlates with viral setpoint in chronic infection, and individuals who have CD4⁺ T responses that target Gag over Env during acute infection remain off ART significantly longer [37[¶]].

In chronic infection, memory CD8⁺ T cell responses that target different variants reach a nadir

by 8 years from the time of seroconversion [38[•]]. Continued decreases of CD4⁺ T cells and impairment of function impact helper T cell capabilities [39,40[•]]. As with other chronic viral infections [41,42], impairment in function of T cell responses during chronic HIV disease can be attributed to expression of a number of inhibitory receptors leading to T cell exhaustion. Expression of the programmed death 1 receptor (PD-1) is upregulated in HIV-1-specific T cells and significantly correlates with viral load and a reduced proliferation and cytokine secretion that is reversible [43,44,45[•]]. This increased expression, which is significantly higher in HIV-specific T cells in lymphoid tissue than in blood, is believed to be driven by viral replication [46]. Indeed, within an epitope-specific response, the most dominant clonotypes tend to have the highest level of PD-1 expression [47]. Apart from PD-1, expression of other inhibitory receptors, such as CTLA-4 on HIV-specific CD4⁺ T cells [48] and TIM-3 in CD8⁺ T cells [49], also show reversible impaired immune dysfunction. Coexpression of two or more receptors on virus-specific T cells has also been reported [50,51].

In contrast, T cell function is maintained in chronic infection among HIV controllers [7]. HIV-specific CD8⁺ T cells continue to have high proliferative capacity and increased perforin expression [12] that is inversely related to viral load [52]. The ability of CD8⁺ T cells from HIV controllers to suppress the virus is stable over time and is associated with the magnitude of Gag-specific responses [53]. Mucosal CD8⁺ T cell responses are also stronger and complex with a dominant Gag-specific response in rectal mucosa [8,54]. Regarding CD4⁺ T cell responses, HIV controllers have a higher frequency of CD4⁺ T cells with polyfunctional response to Gag antigen [10] even at minimal amounts [9]. Furthermore, targeting of distinct Gag peptides is associated with spontaneous HIV control [55]. Gag-specific CD8⁺ and CD4⁺ T cell responses observed with HIV controllers are consistent with evidence showing better virus control with Gag-specific response [55,56].

HIV-SPECIFIC RESPONSES DURING ANTIRETROVIRAL THERAPY

The advent of highly active ART in the mid-1990s allowed suppression of plasma viremia to levels below that detected by commercial assays, as well as subsequent improvement in the life expectancy and quality of life of HIV-infected individuals [3]. With the initiation of ART in adults, rapid fluctuations in HIV-specific CTL response are observed

within 1 to 2 weeks of treatment [57] followed by a several month enhancement [58] and then a rapid decline in the immune response as the viral load and antigenic burden is suppressed [57,59]. Among HIV-infected children initiating therapy, higher Gag-specific memory CTL results in greater reductions in plasma viremia suggesting a synergy between T cell responses and antiretroviral activity [60]. Similarly, improvement of these immune responses is no longer observed in those individuals whose circulating levels of HIV are fully suppressed. The initial improvement in anti-HIV CD8⁺ T cell responses coincides with the decline in expression of PD-1 [61]. With declining levels of plasma viremia and subsequent suppression, levels of Gag-specific and Pol-specific CTL precursors decrease and these correlate with decreased CD8⁺IFN γ responses [62]. Not only is there a decrease in the frequency of epitope-specific T cells, but also in the number of T cell clonotypes within epitope-specific T cell repertoires [63]. With declining plasma viremia on ART, CD4⁺ T cell frequencies increase in blood and gut mucosal tissue within the first 9 months after starting ART [64[•]]. The frequency of interleukin-2-secreting and IFN γ /interleukin-2-secreting HIV-specific CD4⁺ T cell also expand after treatment initiation [65]. However, continuous virologic suppression leads to a time-dependent reduction in the frequencies of Gag-specific memory CD4⁺ T cells [66]. Compared to HIV-infected individuals who control plasma HIV-1 RNA to less than 3000 copies/ml off ART, T cell IFN γ responses to HIV peptides by ELISPOT assay are not detected in those on ART [67]. Moreover, HIV controllers with undetectable plasma viremia off ART have higher proliferative capacity and polyfunctionality of HIV-specific CD8⁺ T cells than patients on ART. These results are consistent with an earlier study [68] showing that in HIV progressors an antigenic threshold is necessary for maintaining virus-specific responses at a measurable level. It is important to note that despite virologic suppression on ART, CTL escape mutations have been shown to still develop [69]. It is possible that this seeming enigma is a result of the decreasing HIV-specific responses during ART. Interestingly, some studies have observed detectable HIV-specific T cell responses despite virologic suppression. Significant CD8⁺ and CD4⁺ T cell responses to Nef have been detected even after 4 years on ART [70]. These residual T cell responses are inversely correlated with pretreatment viral load [71]. Thus, for a majority of HIV-infected individuals, although ART can initially improve HIV-specific T cell function, the rapid decline of antigen also leads to decreased frequencies of these virus-specific T cells.

The case for early antiretroviral therapy (ART) towards a cure of HIV infection

EARLY INITIATION OF ANTIRETROVIRAL THERAPY

HIV causes detrimental effects on various components of the immune system within the first few weeks of infection [17,72] resulting in alterations that can persist despite effective ART [73,74]. This has led to studies evaluating the effects of early initiation of ART on different virologic and immunologic endpoints. Among them are ACTG study A5217, in which participants within the first 6 months of HIV seroconversion were randomized to either receive 36 weeks of ART or no treatment [75], and the SPARTAC trial [35], in which a similar population of HIV-infected participants were randomized to 48 weeks of ART, 12 weeks of ART or no treatment. In A5217, early ART modestly delayed the need for subsequent treatment, whereas in the SPARTAC trial, longer duration of ART during primary infection was associated with higher probability of controlling virus during treatment interruption [76[■]]. Thus, both studies show a benefit of early treatment on disease progression. In the seminal article by Saez-Cirion *et al.* [77[■]], the authors describe 14 HIV-infected study participants of the VISCONTI study who were started on ART during primary HIV infection and were able to control plasma viremia for several years after treatment interruption. Although these participants had lower frequencies of HIV-specific CD8⁺ T cells compared to HIV controllers, they were able to control the virus for a median of 89 months. The authors also showed that early treatment resulted in lower CD8⁺ and CD4⁺ T cell activation, the latter potentially resulting in a lower number of target cells for virus replication. Other recent studies highlight the benefits of early treatment. Le *et al.* [78[■]] reported that treatment within 4 months of infection was associated with an enhanced likelihood of CD4⁺ T cell count recovery. Jain *et al.* [79[■]] further showed that early ART is associated with lower levels of T cell activation as well as a smaller HIV DNA and RNA reservoir size. Similarly, HIV-infected children started on ART within 6 months of age (median of 17 weeks) and who have been virally suppressed for a median of 6 years had a low frequency of T cells with integrated HIV DNA and none had detectable two long term repeater-circles [80[■]]. Interestingly, these children also had undetectable HIV-specific T cell responses. Cockerham *et al.* [45[■]] showed a 41% decrease in PD-1 expression on total CD8⁺ T cells within 1 year of ART in individuals who started treatment within 6 months of infection, similar to those who started ART at least 2 years after the estimated time of infection. An earlier article by Altfeld *et al.* [81] showed that individuals treated during acute (preseroconversion) infection had

narrower CTL responses of lesser magnitude, and a less diverse virus population, than those treated during within 180 days after infection (postseroconversion). Treatment during acute infection also led to stronger CD4⁺ T helper responses. Thus, although early initiation of treatment results in narrow, less robust HIV-specific CD8⁺ T cell responses, virologic and other immunologic effects such as lower levels of T cell activation and stronger helper T cell responses could contribute to better viral control.

CONCLUSION

Despite evidence of lower frequencies of HIV-specific responses with early ART, the responses can be sufficient to control residual viral replication and even viral rebound after treatment interruption as shown in the VISCONTI study. This favorable outcome may be because of a combination of both better CD4⁺ T cell help and less diverse virus population in individuals who are started on ART early in course of infection. In addition, the lower frequencies of HIV-specific responses despite HIV control may be because the current methods of determining HIV-specific responses still lack sensitivity and specificity for critical HIV epitopes that are conserved and cannot be readily mutated. As such, further research is needed to sort out which specific responses are important in posttreatment control in the setting of early ART. Furthermore, evaluation of strategies that boost the immune response of individuals treated during acute or early infection through immunotherapy alone or in combination with activating latent virus, may be a promising approach to HIV cure.

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Conflicts of interest

Dr B.J.C.M. and Dr C.R.R. have no conflict of interest to report.

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The case for early antiretroviral therapy (ART) towards a cure of HIV infection

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