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Research in Translation

Resisting Immune Exhaustion in HIV-1 Infection

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The human immune system is extraordinarily active against infection with HIV-1, yet never eliminates the virus and rarely controls viral replication for prolonged periods without the assistance of anti-retroviral therapy (ART). In order to harness the power of the human immune response in HIV therapy, we need a better understanding of the key elements of protective immunity against the virus and how and why these ultimately fail in chronic infection.

A New Study on Cytotoxic T Lymphocytes

Most investigators would nominate cytotoxic T lymphocytes (CTLs) as key players in the control of HIV-1 infection, based on data accumulated over the two decades since they were first described. This evidence includes the appearance of CTLs very early in HIV-1 infection coinciding with a profound drop in plasma viral load and the dramatic rise in viraemia following CTL depletion in monkey models of both acute and chronic infection with simian immunodeficiency virus [1].

In a new study in this issue of *PLoS Medicine*, Marcus Altfeld and colleagues describe the fate of CTLs responding to HIV-1 from the very earliest stages of infection—the time that most investigators believe is critical in determining the long-term outcome of HIV-1 infection [2]—through the transition to chronic infection [3]. Although the functionality and phenotype of HIV-specific CTLs showed variability both between and within patients, deterioration in the number of functions attributable to each individual T cell was consistently found in untreated patients. Thus in the 11 out of 18 patients who chose not to start ART in acute infection, the capacity of HIV-specific CTLs to secrete a range of anti-viral cytokines and chemokines as well as to generate cytotoxic granules in response to an encounter with HIV antigens declined in the face of continuing viral replication.

Deterioration of immune function as viral levels increase is well described at other stages of HIV-1 infection, but it is inevitably difficult to determine which is cause and effect in this scenario. In this new study, the authors were able to exploit another observation to examine the underlying causes of declining T cell function in their patients. By studying the evolution of the infecting virus in the first months of infection, they noted that in many instances there was an early accumulation of mutations in T cell epitopes that enabled the virus to avoid recognition by circulating CTLs. Not only did these mutations render virus-infected cells "invisible" to the responding T cells, but they also prevented repeated stimulation of the cells following contact with their target antigen. Even in untreated patients, the effect of removing CTLs from antigen exposure led to a very similar preservation of T cell function to that seen in those with a good response to ART. This maintenance of CTL function was particularly striking in untreated patients, for whom escape mutations were generated to some but not all of their repertoire of responding CTLs, thereby making it possible to discern the role of repeated antigenic stimulation in promoting T cell dysfunction.

These observations are also important in highlighting how early in HIV-1 infection immune pressure from CTLs can drive the emergence of escape mutations: this is well documented in the macaque model [4], but has not been studied systematically in human infection. CTL escape mutations were selected in nine of the untreated patients in Altfeld and colleagues' study and could be detected as early as 61 days after initial presentation.

Clinical Implications of the Study

What are the clinical implications of this study? If polyfunctional HIV-specific CTLs need to be preserved long term for the fight against HIV-1 infection, then this study suggests that such preservation is best achieved by suppressing HIV-1 replication both early and efficiently. The question of whether or not to start ART in acute HIV-1 infection has been controversial.

Related Research Article

Streeck H, Brumme ZL, Anastario M, Cohen KW, Jolin JS, et al. (2008) Antigen load and viral sequence diversification determine the functional profile of HIV-1–specific CD8+ T cells. PLoS Med 5(5): e100. doi:10.1371/journal.pmed.0050100

Marcus Altfeld and colleagues suggest that the exhaustion of virus-specific CD8+ T cells during chronic HIV infection likely results from the persistence of antigen.

Research in Translation discusses health interventions in the context of translation from basic to clinical research, or from clinical evidence to practice.

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Abbreviations: ART, anti-retroviral therapy; CTL, cytotoxic T lymphocyte; IL-2, interleukin-2; PD-1, programmed death-1; STI, structured treatment interruption

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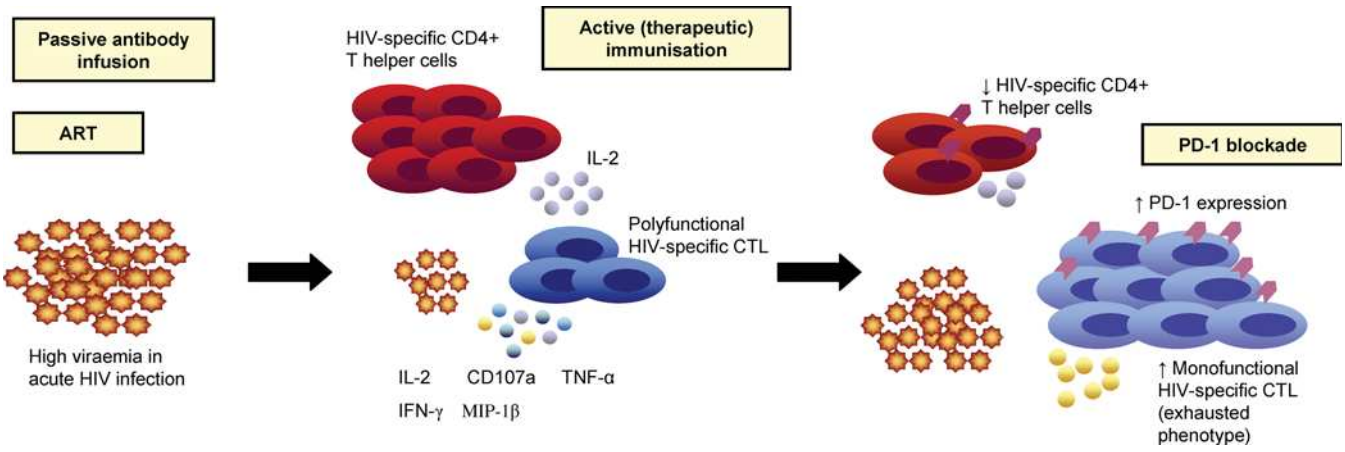

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Figure 1. Sequence of Events from Acute to Chronic HIV Infection and Potential Interventions to Combat T Cell Exhaustion
IFN, interferon; MIP, macrophage inflammatory protein; TNF, tumour necrosis factor

Acute HIV-1 infection is characterised by high levels of viral replication, dissemination of virus to lymphoid tissue reservoirs, and gradual depletion of circulating HIV-1–specific $CD4^+$ T lymphocytes [5,6]. Evidence from the study of gut-associated lymphoid tissue (GALT) in animal models suggests that there is massive infection of memory $CD4^+$ T cells in GALT and subsequent loss of over half the total memory T cell pool within two weeks of experimental simian immunodeficiency virus infection [7]. If this situation is mirrored in human infection, as suggested by the extensive depletion of GALT T cells in biopsies taken in chronic HIV-1 infection [8], the implication is that very early intervention would be needed to preserve memory T cell function. Although the use of ART in chronic HIV infection undoubtedly results in significant reductions in morbidity and mortality, reconstitution of the host immune system is rarely achieved. For example, HIV-specific $CD4^+$ T helper cell responses, which crucially augment effector HIV-specific $CD8^+$ responses, are poorly restored by ART in chronic infection [9,10]. Taken together, these data lead to the inevitable question of whether starting ART in acute HIV infection, and thereby minimising virus dissemination and damage to mucosal-associated lymphoid tissue, could facilitate the development and preservation of enhanced HIV-specific immunity and thus favourably alter the future course of disease.

Slow restoration of a polyfunctional CTL phenotypic profile similar to that observed by Altfeld and colleagues can also be achieved in chronic HIV-infected patients treated with ART [11]. However, the clinical significance of this improvement remains unclear in the face of evidence that suggests cessation of ART during treatment interruption in chronic HIV-1 infection results in rapid viral rebound and no long-term change in viral set point [12]. HIV-specific CTLs with strong ex vivo proliferative capacity are a feature of HIV long-term non-progressors [13], and can also be detected in acutely HIV-infected patients during the peak of viraemia, but gradually diminish during the first year of infection in the absence of therapy [14]. Preservation of CTL proliferative capacity and effector function appears to be critically dependent on interleukin-2 (IL-2) production from HIV-specific $CD4^+$ T cells [14]; this production in turn can be preserved by early institution of ART [15].

Structured Treatment Interruptions

Clinicians have been understandably reluctant to commit patients diagnosed with acute HIV-1 infection to lifelong ART. An alternative strategy was based on the hypothesis that preservation of HIV-specific immunity could be achieved by starting ART in acute infection, followed by structured treatment interruptions (STIs), thereby allowing "immune boosting" by exposure to autologous virus.

This strategy involved restarting therapy if rebound plasma viraemia increased above set thresholds (more than 5,000 copies/ml for three consecutive weeks or more than 50,000 copies/ml on one occasion) and introducing further STIs once viral control was regained. Initial enthusiasm for this approach was fuelled by the observation that potent Gag-specific T helper cell responses develop in patients with acute HIV infection started on ART, at similar magnitudes to those seen in long-term non-progressors, and to significantly higher levels than are found in untreated patients with acute HIV infection or ART-treated patients with chronic HIV infection [15]. Although some patients subjected to STIs after starting ART in acute infection were initially able to control viraemia and maintain Gag-specific $CD4^+$ responses off therapy, a detailed longitudinal analysis (median 5.3 years from infection) of this cohort showed the effect to be transient, with viral breakthrough occurring ultimately in most patients, accompanied by a similar rate of $CD4^+$ cell loss as that seen in early chronic untreated HIV infection [16]. It seems, therefore, that although the immunological damage caused by acute HIV-1 infection may be reduced to some extent by early ART, this effect is limited to the duration of therapy and may not translate into long-term benefits.

Can Early ART Affect Risk of Future Disease Progression?

For clinicians to accept early and lifelong therapy for HIV-1 infection into routine practice, reliable data from controlled clinical trials are needed. To date, there have been no randomized

and adequately powered studies addressing the issue of whether early ART can affect the risk of future HIV-1 disease progression.

A number of observational studies of ART used for a limited period in early HIV-1 infection present contrasting conclusions. One multicentre observational study compared surrogate markers of disease progression at 24, 48, and 72 weeks of untreated observation in 58 ART-treated patients (13 with "acute" infection within two weeks of seroconversion and 45 with "early" infection within six months of seroconversion) and 337 untreated patients with primary HIV infection [17]. Lower viral loads and higher CD4 counts were observed at 24 weeks following cessation of ART in both the acute and early treatment groups, although a longer-term benefit at 72 weeks was less clear. Despite these promising results, the variable ART duration (median 1.5 years) and lack of randomisation, amongst other factors, make interpretation of this study difficult. In contrast, short-term ART (for 24 weeks) failed to show any benefit in CD4 counts or viral loads at six months after treatment discontinuation in a smaller observational study [18]. Enhanced interferon-γ and CD107a expression on HIV-specific $CD8^+$ T cells at 12 months in the treated group did not result in lower viral load set points.

Although these, along with other such studies, may hint at the potential benefits of using short-term ART in acute HIV-1 infection, data are needed from adequately powered and controlled studies, such as the ongoing Short Pulse Anti Retroviral Therapy at HIV Seroconversion (SPARTAC) study (http://www.ctu.mrc.ac.uk/studies/spartac.asp). This is an international randomised controlled trial comparing the effect of combination anti-retroviral therapy given for 48 weeks or 12 weeks, with a no-intervention arm.

If, as some of these studies suggest, the benefits of early ART are limited to the duration of therapy, then the question of using longer or even continuous periods of treatment must be considered. In a recent French cohort study where patients initiated therapy within 10 weeks of first acute symptoms and continued for a median of 2.3 years, 25% of treated patients remained aviraemic (more than 50 copies/ml) as far as 144 weeks after cessation of ART [19]. After three years of follow-up, only 6% of those in the treatment arm met eligibility criteria for ART, when compared with 64% of patients who did not receive ART in the acute stages of infection. An even more marked benefit from continuous treatment instituted within 90 days of primary infection was noted in an observational study, in which early and prolonged treatment was associated with significant protection against rapid progression to AIDS and opportunistic infections, as well as a substantially decreased frequency of more minor mucocutaneous and respiratory conditions [20]. Nevertheless, HIV-1 reservoirs in lymphoid tissue and latently infected $CD4^+$ T cells persisted, and side effects of combination therapy were common. Moreover, the lack of gut mucosal $CD4^+$ lymphocyte reconstitution despite prolonged and uninterrupted periods of ART initiated in acute HIV-1 infection may suggest that even at an early stage much of the immunological damage is irreversible [21].

The possibility that ART may need to be started as early as possible and continued indefinitely raises many concerns. How would clinicians balance the potential impact on disease progression against the cost, drug toxicity, and the risk of drug resistance entailed by prolonged ART, particularly at a time in early HIV-1 infection when most patients would be probably be asymptomatic without therapy? If it is important to treat within days of primary infection, how should we best identify newly infected patients at the optimum time for instituting therapy? The need to provide long-term therapy for participants in vaccine trials who acquire primary HIV-1 infection during the trial would have major cost and logistic implications that could make phase III vaccine trials virtually impracticable.

A Way Forward

Probably the best way forward would be to develop a therapeutic strategy that combines early viral suppression using ART with immunotherapy to augment HIV-specific immune responses in a way that does not expose the host immune system to the damaging consequences of continued HIV-1 replication (see Figure 1). Although both therapeutic vaccination and passive monoclonal antibody infusion in this setting have so far failed to show absolute benefit [22–24], there are some data to suggest that therapeutic vaccination in chronic HIV-1 infection can lead to a restoration of a broad and fully functional CTL response [25]. In Altfeld and colleagues' study [3], a reliable marker of failing CTLs was expression of the molecule

Five Key Papers in the Field

- **Streeck et al., 2008** [3] Epitope-specific $CD8^+$ T cells in acute HIV infection progressively lose their polyfunctional capacity following repeated exposure to antigen in acute HIV infection, but this exhausted phenotype is reversible either with anti-retroviral therapy or reduction in epitope-specific antigen load due to cytotoxic T cell escape mutations.
- **Day et al., 2006** [27] The inhibitory receptor PD-1 is significantly up-regulated on HIV-specific T cells in chronic HIV infection, and expression correlates with impaired cytotoxic T cell function and predictors of disease progression. Blockade of the PD-1 pathway enhances HIV-specific $CD4^+$ and $CD8^+$ cellular function.
- **Mattapallil et al., 2005** [7] 30%–60% of $CD4^+$ memory cells in most tissues are infected during the peak of experimental acute simian immunodeficiency virus infection in macaques, resulting in catastrophic early depletion of these cells by direct viral infection.
- **Lichterfeld et al., 2004** [14] The loss of HIV-specific $CD8^+$ T cell function in chronic HIV-1 infection correlates with disease progression and is critically dependent on IL-2 secretion from HIV-specific $CD4^+$ T helper cells. This functional deficit may be reversible with immunotherapeutic interventions.
- **Rosenberg et al., 2000** [15] Successful treatment of acute HIV infection with anti-retroviral therapy leads to preservation of HIV-specific $CD4^+$ T helper cell responses. Maintenance of virus-specific HIV $CD8^+$ and $CD4^+$ responses, along with viraemic control, can be seen in the short term even when therapy is subsequently stopped in STIs.

programmed death-1 (PD-1), which has been associated with "exhausted" and dysfunctional T cells in chronic infection [26]. Up-regulation of PD-1 on HIV-specific CTLs correlates with plasma viral load [27] and can be reversed when viral replication is controlled both in chronic and acute infection [3,28]. It has recently been shown in a murine model of lymphochoriomeningitis virus that a combination of therapeutic vaccination and blockade of PD-1's interaction with its ligand, PD-L1, both enhanced the function of responding T cells and significantly improved viral control [29]. Perhaps a similar strategy may enhance the response to therapeutic immunisation in early HIV-1 infection and facilitate long-term viral control without resorting to lifelong drug therapy. ■

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