Immune reconstitution with antiretroviral therapies in chronic HIV-1 infection

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Introduction

Human immunodeficiency virus 1 (HIV-1) infection is characterized by a progressive decline in both function and number of CD4+ T-lymphocytes secondary to ongoing viral replication. Without intervention, this ultimately leads to the development of the Acquired Immunodeficiency Syndrome (AIDS) that places persons at risk for the acquisition of opportunistic infections and neoplasms.1 In recent years, reconstitution of the immune system of HIV-1-infected patients has been achieved by suppression of HIV-1 replication through antiretroviral therapies (ART), resulting in a dramatic decline in HIV-1-related morbidity and mortality.2 Whereas in the short term, restoration of numbers of circulating CD4+ T-cells seems to largely protect persons from opportunistic infections, it is less clear that functional immune responses can be fully restored particularly in persons with advanced stages of HIV infection. Recent findings from clinical trials and epidemiological studies suggest that the timing of treatment initiation is a major determinant of the capacity of the immune system for reconstitution. Findings from these studies indicate that immune phenotype and function remain impaired over time in patients who initiate ART at lower CD4+ T-cell counts even if circulating CD4+ T-cell numbers are normalized. These data indicate that aspects of the complete immunological ‘repertoire’ are irreversibly lost with progressive HIV-1 disease.

Restoration of the circulating CD4+ T-cell pool on ART

Approximately 98% of the body’s lymphocytes are located in the lymphoid tissue, where ongoing HIV replication leads to a chronic state of inflammation with the increased expression of pro-inflammatory cytokines and adhesion molecules.3 Following suppression of viral replication with ART, increases in the peripheral CD4+ T-cell pool occur in two major phases.4 During the initial 8–12 week phase, lymphocytes that had been trapped at the site of inflammation in the lymphatic tissue are redistributed, leading to a rise in most lymphocyte populations, including CD4+ T-cells, in the peripheral blood. The first phase increase in the number of peripheral CD4+ T-cells has been attributed to an increase primarily in CD45 RO+ memory cells.5 Nonetheless, lymphocytes with T-cell receptor excision circles (TRECs) identifying recent thymic emigrants6 and representing mostly naive T-cells are also rapidly and selectively released from lymphoid sites during the first weeks following the initiation of ART.7 During the second phase, CD4+ T-cell increases are slower than during the first and these are mainly comprised of CD45 RA+ 62L+ phenotypically naive CD4+ T-cells.3

Restoration of the immune phenotype on ART is often incomplete, particularly if treatment initiation is delayed

Several prospective studies have documented that restoration of circulating CD4+ and CD8+ T-lymphocyte subsets is incomplete when ART is initiated during chronic HIV-1 infection and that numbers of CD8+ T-lymphocytes remain elevated even if therapy is started early in the course of the disease.4,5,8,9 Immune phenotypes in HIV disease may predict both outcome of infection and in vivo immune competence. As examples, expression of the activation marker CD38 on

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CD8+ T-cells is correlated with HIV RNA levels but may be a better predictor of disease outcome than plasma HIV RNA. CD28 is a critical co-receptor for T-cell activation that facilitates appropriate cellular activation after exposure to antigen. HIV infection is associated with diminished numbers, and proportions of CD4+ and CD8+ T-cells expressing CD28 and diminished CD28 levels predict a poor in vivo response to immunization in HIV infection.

We recently investigated the effect of longstanding continuous suppression of viral replication on the restoration of the immune phenotype in HIV-infected patients treated with ART. We found that even patients who were able to ‘normalize’ the numbers of circulating CD4+ T-cells after 3 years of therapy did not ‘normalize’ numbers of memory-phenotype CD4+ T-cells or numbers of CD4+ T-cells co-expressing CD28. Additionally, numbers of CD8+ T-cells expressing HLA DR and CD38 remained elevated in persons who initiated ART at advanced stages of HIV-1 infection. Importantly, among these patients with excellent virological and numerical CD4+ T-cell responses to antiretroviral treatment for HIV-1 infection, the likelihood of more complete phenotypic ‘normalization’ was directly correlated to the CD4+ T-cell count before initiation of ART. In a prospective study, AIDS Clinical Trials Group Protocol 375, patients with advanced HIV infection and suppressed viral replication were observed for a period of 3 years following the initiation of ART. Almost all immune restoration that was achieved in these patients with advanced disease occurred during the first year of therapy, whereas CD4+ T-cell rises in the peripheral blood during the second and third year were not significant. Although other patient groups have had better CD4 T-cell increases, the ACTG 375 group participants also had an extensive phenotypic examination, and in these subjects, normalization of CD28 expression on CD4+ T-cells and HLA DR CD38 expression on CD8+ T-cells was not achieved during the study period. The kinetics of the restoration of the immune phenotype as observed in these persons suggest that normalization of immune phenotypes may not be achieved by ART alone if therapy is initiated in advanced stages of HIV infection.

Functional immune restoration depends upon timing of treatment initiation

In addition to demonstrating quantitative cellular restoration and improvement in immune phenotypes, a number of prospective studies have shown improvement of immune function in HIV-1-infected patients who were treated with ART. We recently analysed a comprehensive panel of functional immune responses in a group of chronically HIV-1-infected patients with favourable responses to ART. Twenty-nine HIV-1-infected patients with ART-induced suppression of viral replication <400 copies/mL and normal CD4+ T-cell counts (median 730 cells/mm^3) who started ART at a broad range of CD4+ T-cell nadirs (0–618 cells/mm^3) were included in this study. We used a new scoring system to summarize responses to immunization by measuring antibody titres, lymphoproliferation and delayed-type hypersensitivity skin reactions to the vaccine antigens. Patients with the lower pre-treatment CD4+ T-cell nadirs had diminished responses to immunization despite normal CD4+ T-cell numbers. The functional immune response score was significantly correlated with the pre-treatment CD4+ T-cell nadir and the number of CD28+ CD4+ T-cells at the time of immunization, but not to the current CD4+ T-cell count.

These results indicate that both phenotypic and functional immune restoration remain incomplete with currently available treatment regimes despite ‘normalization’ of circulating CD4+ T-cell counts if initiation of ART is delayed. From a more clinical perspective, a collaborative analysis of 13 prospective cohort studies found that delaying ART as CD4+ T-cells fall is associated with a greater risk of opportunistic infection and death.

How much immune reconstitution is enough?

The incidence of AIDS-defining illnesses has decreased dramatically in the era of ART despite the fact that many patients do not normalize circulating CD4+ T-cell counts or suppress viral replication below the limit of detection of conventional assays. The risk of recurrence of opportunistic infections after discontinuation of secondary prophylaxis is generally very low once CD4+ T-cell counts have reached stable levels >200 cells/mm^3. Therefore substantial clinical benefit can be achieved without complete virological, phenotypic and functional immune restoration. On the other hand, the long-term risks of subclinical immune deficiency in this setting are unknown. In other settings, such as the immune deficiency associated with solid organ transplantation, the long-term risks of neoplasms exceed those in the general population.

Restoration of HIV-1-specific immunity on ART

Long-term non-progressors (LTNP), who have no or little disease progression in the absence of antiviral drug therapy, often exhibit strong CD4+ T-cell lymphoproliferative (LP) responses to HIV gag antigens in the absence of ART. These patients also maintain a high proliferative capacity of HIV-specific CD8+ T-cells that is linked to an enhanced effector cytotoxic T-lymphocyte (CTL) function. In contrast, the majority of patients with chronic HIV-1 infection develop functional impairments in both CD4+ and CD8+ HIV-
reactive T-cells with ongoing viral replication and decreasing CD4+ T-cell counts. In animal models of chronic viral infection, sustained function of CTLs, which are critical for the elimination of virus-infected cells,23 is dependent upon CD4+ T-cells.24 In most patients with chronic HIV infection, sustained viral replication results in diminished proliferation capacity (or loss) of HIV-specific CD4+ T-cells.25 Although HIV-1-specific CD8+ T-cell numbers are sustained by ongoing HIV-1 replication,26 CTL maturation may be skewed23 and the in vivo functional capacity of these cells is not clearly understood. Moreover, there is evidence that HIV is capable of mutation in sequences recognized by CD8+ CTLs resulting in escape from immune defences.27 Following suppression of viral replication on ART, HIV-1-specific CD4+ T-cell responses may increase in patients with chronic HIV-1 infection28 but HIV-1-specific CD8+ T-cell frequencies tend to fall as antigen levels decrease and these defences are rarely sufficient to prevent high-level HIV replication once ART is withdrawn.

There is recent evidence that an effective endogenous HIV-1-specific T-cell immunity may be preserved with therapeutic interventions very early in the course of HIV-1 infection.29 As HIV-specific CD4+ T-cells are preferentially infected by HIV in vivo,30 immunological control of HIV decreases with ongoing viral replication. Persistence of an effective HIV-1-specific immunity does not appear to be common in persons who start ART in more advanced stages of the disease.

**Conclusions**

Suppressing HIV replication with antiretroviral therapies results in a dramatic decrease in HIV-related morbidity and mortality, and increases in the quality of life of people living with HIV. Whereas immune reconstitution may remain incomplete when the initiation of ART is delayed, the optimal timing for treatment initiation to preserve the capacity for functional immune reconstitution still needs to be determined. Likewise the long-term consequences of subclinical immune deficiency in treated HIV infection are not yet known. In the clinic, the potential immunological benefits of earlier initiation of ART must be weighed against both short-term and longer term risks of drug toxicities as well as other factors such as cost, quality of life and perhaps even more complex factors such as potential effects on HIV transmission. Careful follow-up of large, well-studied cohorts of HIV-infected patients will be increasingly important in order to provide early recognition of the longer-term consequences of earlier versus later treatment initiation. Moreover, a better understanding of HIV-1-specific immunity and its failure is needed for the development of effective vaccines and immunotherapies that may one day lead to immune control of HIV-1 infection.

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**References**


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