

Very early antiretroviral therapy permits CD8 T cells to keep HIV reservoirs at bay

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Human immunodeficiency virus (HIV) infection is defined by a profound immune dysfunction and an abrogated T cell homeostasis (1). The gradual loss of CD4 T cells is associated with disease progression in the absence of treatment. On the other hand, CD8 T cell count becomes very elevated at the earliest phase of infection and plateaus during the chronic phase up until the very late phase, when major depletion of all T cell subsets occurs (2). In the majority of patients living with HIV, antiretroviral therapy (ART) suppresses HIV replication, reduces the risk for AIDS and non-AIDS events and contributes to an improved health status (3). Usually, an optimal CD4 T cell reconstitution (>500 cells/ μ L) is achieved a few years after treatment depending on CD4 T cell count at the time of treatment initiation (1).

Temporal dynamics of CD8 T cells responses during HIV infection

In contrast to the CD4 T cell decline, the elevation of CD8 T cells persists in absence of treatment and only partially decreases even after a decade of treatment. Despite the control of viral replication on ART, normalization of CD8 T cell counts is rarely observed even with optimal CD4 T cell reconstitution. Such persistence of elevated CD8 T cell counts independent of CD4 T cell reconstitution has been linked with an increased risk of non-AIDS-related clinical

events, including renal diseases, cardiovascular disorders, neurocognitive dysfunction and cancer (2,4). Indeed, only early initiation rather than prolonged duration of ART contributes to the normalization of CD8 T cell counts (2,5). These observations in treated HIV infection have led to consider the CD4/CD8 ratio as a better marker than CD4 or CD8 T cell counts in predicting risk of inflammatory non-AIDS events, level of immune exhaustion and HIV reservoir size (6).

Temporal dynamics of HIV specific CD8 T cell responses during HIV infection

Antigen-specific CD8 T cells represent a major component of defense system against invading viruses, by recognising and killing infected cells harboring non-self-proteins. Crucial step in this process involves T cell receptor (TCR) recognition of virus-derived peptides presented on the surface of infected CD4 T cells by molecules of the human leukocyte antigen (HLA) class I.

The HIV specific CD8 T cells constitute a small fraction of the total population of CD8 T cells and are primed at the early phase of infection when viremia bursts. Then primed HIV-specific CD8 T cell responses gain partial control over viral replication and establish a viral set point that further dictates the speed of disease progression. Even in the rare individuals who spontaneously control viral replication,

called elite controllers, clearance is not achieved. Thus, despite their partial ability to control viremia, HIV-specific CD8 T cells are unable to clear HIV infection. Understanding the factors limiting CD8 T cells' ability to kill infected cells measured by their cytotoxic function has been a research priority for years. We first learned that after undergoing rapid expansion following acute HIV infection, CD8 T cells waned and became hypo-functional or "exhausted" after a few months of infection (7). The quality of CD8 T cell response contributes to the establishment of a viral set point in each patient that in turn has been shown to predict the time of the development of AIDS events and CD4 T cell decay (8,9). Furthermore, the contribution of CD8 T cell function was illustrated by the ability of a fraction of elite controllers carrying distinctive HLA-B57 or HLA-B27 alleles to suppress viral replication (10); and by viral escape due to the immune pressure observed after early infection. It is now established that such emergence of HIV specific response have been temporally associated with plasma viral load decay following the peak of viremia during the acute infection. The temporal dynamics of HIV specific CD8 T cell cytotoxic response to become exhausted remains poorly defined (11).

Influence of early ART initiation on the dynamics of HIV specific CD8 T cell responses

Conversely to other viral specific responses (for example infection with cytomegalovirus), HIV-specific CD8 T cell responses following primary infection, rapidly wane following ART initiation and are linked with an irreversible cell surface expression of an immune checkpoint receptor called programmed cell death protein 1 (PD-1) leading to a persistent cellular memory defect (7,12).

To gain further insight on the dynamics of CD8 T cell function on the control of viremia under ART, Cartwright and Silvestri *et al.* conducted a very elegant study showing that antibodies blocking CD8 T cells led to a viral rebound in viremic simian immunodeficiency virus (SIV)-infected macaques a few months after ART initiation at the time of infection (13). They further showed that repopulation of CD8 T cells was associated with prompt reestablishment of viral control. These study findings highlighted the role of SIV-specific CD8 T cells on both viral production in blood and SIV reservoir size measured in tissues (14). Such animal model experiments demonstrated the role of CD8 T cell function on the control of pre ART viremia and size of viral reservoir (total DNA load) following early ART.

Can a similar observation from SIV-infected macaque be observed in very early treated HIV-infected patients? Our limited understanding of the contribution of CD8 T cell functional dynamics in early HIV infection is due to the inability to recruit and treat patients within the first week of infection as the mean time to participation in acute HIV infection research cohorts is around one to three months after infection (5,11,15). Such limitation was recently overcome by establishing a unique cohort (RV254/SEARCH010) in Thailand (16). This cohort was implemented after frequent screening of thousands of individuals in HIV voluntary counselling and testing centers who were invited to be treated within days of acquiring HIV infection.

Trautmann *et al.* who previously reported on progressive exhaustion of cytolytic function of HIV-specific CD8 T cells, after two to four months of HIV infection (17), now assessed such response within days of infection in participants of the Thai cohort. These participants received treatment during very early HIV infection and were grouped as stage 1, 2 and 3 with a median of 14, 16 and 19 days post-infection, respectively (18). They were able to show that the magnitude of HIV-specific CD8 T cells and their proliferative capacity were delayed on ART during stages 1 and 2 occurring before the peak of viremia. Despite very early appearance of HIV-specific CD8 T cells, their expansion and function were abrogated with treatment. These results are in line with previous findings in SIV model where similar low CD8 T cell responses were observed in mucosal tissues following early infection (19). Conversely, at the time of the peak viremia (stage 3, median of 23 days post HIV-infection) a massive expansion of HIV-specific CD8 T cells occur concomitant to the burst of cytokine response and symptoms of acute infection (20). The fully differentiated HIV specific CD8 T cells led to a shorter time to control viral replication compared to groups 1 and 2. Most importantly, an elevated capacity to maintain HIV specific CD8 T cell function was linked to a lower viral reservoir size measured by HIV DNA PCR. Globally, these study findings showed that HIV specific CD8 T cell response contribute to the reduction of the pool of HIV producing cells as well as the HIV reservoir size in early ART treated patients.

Such study findings, which represent a *tour de force*, pave the way for the development of strategy that could enhance HIV-specific functions. However, the generalizability of this study is limited as the median age of the participants was 27 years, most were male (89%), and 76% harboured a clade

CRF01_AE HIV which is known to have a faster disease progression than clade B (21). Furthermore, this study was confined to the analysis of blood samples, opening avenues to analyze lymph node and gut associated lymphoid tissues where the majority of HIV reservoir resides. However, access to the human tissue samples remains an issue in HIV clinical research and needs to balance the risks/benefits to the participants (22). Lastly, this type of comprehensive research infrastructure like the one in Thailand allowing frequent screening for HIV acquisition combined with a very early treatment is not scalable.

Future directions

As the peak of viremia predicts viral set point, indicating that very early events are at play before CD8 T cells kick in (23). Innate immune response that occurs within hours induces production of type I interferons (IFNs), which regulate many immune pathways including the function of CD8 T cells. It is well established that in acute lymphocytic choriomeningitis virus (LCMV) infection mice model, IFNs helps to clear infection, while in chronic HIV infection higher levels of type I IFN signaling is correlated with immune activation, disease progression and reduced CD4 T cell recovery on ART. More information on the “IFN paradox” and CD8 T cell response in early infection is warranted (24).

Barouch *et al.* in a landmark study analyzed the earliest events following mucosal SIV infection of rhesus monkeys (25). They evaluated SIV CD8 T cell responses in blood and in several tissues on day 0, 1, 3, 7 and 10 post-infection. The earliest SIV specific CD8 T cell responses were observed on day 7 in female reproductive tract, gastrointestinal mucosa and bone marrow. Such early responses were not observed in lymph nodes and blood. Subsequently all monkeys exhibited high-frequency of specific CD8 T cell responses on day 10 in all tissues except blood.

These results demonstrate that during acute infection SIV specific responses first develop in tissue effector sites prior to the emergence of responses into the periphery, thus occurring “too little and too late” to block the viral swarm (19). They further assessed the transcriptomic signatures and observed direct strong correlation of SIV-specific CD8 T cell responses with metabolic pathways in tissues where such pathways are involved in T cell activation. They further observed an inverse correlation of immunosuppressive cytokine transforming growth factor

beta 1 (TGF- β 1) response genes with the magnitude of CD8 T cell responses on days 7 and 10 in gastrointestinal tissues demonstrating the inhibition of effective CD8 T cell responses at the very sites of early virus replication. These results further indicate that effective HIV-specific CD8 T cells play an important role in the reduction of HIV-producing cells and more importantly latent reservoirs in patients receiving early ART. In these lines, use of latency reversing agents *in vitro* such as vorinostat has been shown to create a window of vulnerability by inducing production of viral protein on the cell surface allowing for subsequent clearance of latently infected cells by an array of effector mechanisms including *ex vivo* autologous CD8 T cells (26).

Globally, all these findings in SIV and HIV infections established a pathogenesis link between CD8 T cell function and both viral load and size of HIV reservoir on ART. However, only comprehensive integrated strategies that will encompass enhancing innate cells, IFNs, antibodies and specific CD8 T cell responses with adequate CD4 T cell help (27) will provide long-term viral control or an HIV cure.

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Footnote

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