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Mechanisms of CD8+ T cell-mediated suppression of HIV/SIV replication

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Abstract

In this article, we summarize the role of CD8+ T cells during natural and ART-treated HIV and SIV infections, discuss the mechanisms responsible for their suppressive activity, and review the rationale for CD8+ T cell-based HIV cure strategies. Evidence suggests that CD8+ T cells are involved in the control of virus replication during HIV and SIV infections. During early HIV infection, the cytolytic activity of CD8+ T cells is responsible for control of viremia. However, it has been proposed that CD8+ T cells also use non-cytolytic mechanisms to control SIV infection. More recently, CD8+ T cells were shown to be required to fully suppress virus production in ART-treated SIV-infected macaques, suggesting that CD8+ T cells are involved in the control of virus transcription in latently infected cells that persist under ART. A better understanding of the complex antiviral activities of CD8+ T cells during HIV/SIV infection will pave the way for immune interventions aimed at harnessing these functions to target the HIV reservoir.

Keywords

CD8 T cells; cytotoxicity; HIV; immune response; infectious disease

Introduction

Human immunodeficiency virus (HIV) is the causative agent of the acquired immunodeficiency syndrome (AIDS) [1, 2] and infects an estimated 36.7 million people worldwide. Based on UNAIDS estimates, 1.8 million new HIV infections are projected to occur annually and as well as one million AIDS-related deaths [3]. While antiretroviral therapy (ART), the standard care for HIV infection, has dramatically reduced the mortality and morbidity of HIV infection, there is still no cure for this infection.

The main obstacle in the development of an HIV cure is the presence of a reservoir of HIV-infected cells containing integrated DNA but not expressing the virus, defined as latently infected cells, that seem to persist indefinitely in ART-treated HIV-infected humans [4–7]. This population is termed “HIV viral reservoir” and occurs primarily within resting memory CD4+ T cells [4, 8]. It appears that over time there is a progressive reduction in the size of

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the HIV viral reservoir around a core of less differentiated memory subsets: central memory (T_{CM}) and stem cell memory (T_{SCM}) [9]. These cells are long-lived, capable of self-renewal (*in vitro*) and have an estimated half-life of >44 months [7, 10]. It was recently described that the HIV viral reservoir is established early during infection [11, 12] and is responsible for the viral rebound observed after ART interruption [13, 14]. Therefore, strategies additional to ART are necessary to cure HIV, and novel therapies targeting the HIV viral reservoir are of utmost importance.

SIV infection of rhesus macaques (RM) is similar to pathogenic HIV infection of humans with establishment of peak and set point viremia, depletion of CD4+ T cells, onset of AIDS, and suppression of viremia by ART [15]. Therefore, certain experimental limitations of studying HIV infection of humans can be overcome using the nonhuman primate (NHP) with simian immunodeficiency virus (SIV) infection model [reviewed in [15–17]. NHP studies allow for control of the infecting virus strain, timing of infection, more aggressive tissue sampling, selection of specific MHC class I genotypes, and elective necropsies with unlimited tissue collection. Crucially, the NHP/SIV model allows the testing of risky in vivo immune interventions, such as those combining various immunomodulatory approaches, which are virtually impossible to conduct in HIV-infected humans. As such, NHP SIV studies are an important tool used for further insight into HIV pathogenesis, prevention, and treatment in humans.

CD8+ T cells in HIV and SIV pathogenesis

Acute infection

HIV can be transmitted via blood, breast milk, semen or vaginal secretions from infected individuals [18]. Systemic infection is established with the spread of the virus to lymphoid tissues throughout the body including, but not limited to, the thymus, the spleen, peripheral lymphoid organs, mucosal lymphoid tissues, and the brain [19]. Acute HIV infection of humans is characterized by a transient peak in viremia (2-3 weeks) followed by a post-peak decline to a viral set-point level of viremia that is a strong predictor of the ensuing rate of progression to AIDS [20]. Subsequently, HIV-infected patients experience a slow decrease in CD4+ T cells and gradual deterioration of immune function, including exhaustion of CD8+ T-cells, loss of immune function in the lymph nodes and mucosal tissues and chronic immune activation, leading to increased susceptibility to opportunistic infections and cancer [21], [22, 23].

Several lines of evidence suggest that CD8+ T cells play a significant role in the control of virus replication during the acute phase of HIV and SIV infection. First, the post-peak decline of viremia only occurs after the emergence of virus-specific CD8+ T cells, suggesting that CD8+ T cells are involved in the initial control of infection [24, 25]. In support, depletion of CD8+ T cells during acute SIV infection of RM results in the abrogation of the post-peak decline of viremia [26, 27], confirming a critical role in the initial resolution of viral control. In addition, during the first weeks of infection viral mutants capable of escaping the CD8+ T cell response begin to appear and rapidly become fixed in the overall virus population, thus demonstrating a strong evolutionary pressure posed on the virus to escape immunological recognition by CD8+ T cells [28–31]. Overall, these observations indicate that CD8+ T cells play a significant role in the control of acute HIV infection.

Interestingly, unlike with other viral infections, the initial expansion of the effector CD8+ T cell pool is not limited to HIV-specific cells and of the total CD8+ T cell pool expanded during the acute infection, only about 10% are HIV-specific CD8+ T cells [32, 33]. CD8+ T cells specific for persistent pathogens, such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV), and non-persistent pathogens, such as influenza and adenovirus, may reactivate, thus suggesting that CD8+ T cell expansion is capable of occurring through antigen-independent mechanisms [34–36]. The exact cause of such “bystander activation” remains unclear.

Persistent exposure to HIV antigen during the natural course of HIV infection leads to the progressive dysfunction and “exhaustion” of virus-specific T cells. T cell exhaustion is characterized by altered differentiation, impaired function, and decreased proliferation [reviewed in [37]]. Of note, T cell exhaustion begins soon after peak HIV viremia and persists for the remainder of the infection [38, 39]. In the early stages of exhaustion, HIV-specific T cells have an impaired ability to proliferate in response to antigen, as well as reduced expression of interleukin-2 (IL-2), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), chemokine ligand-4/macrophage inflammatory protein-1α (CCL4/MIP-1α) and the degranulation marker CD107a [40]. The upregulation of exhaustion marker programed death-1 (PD-1) on HIV-specific CD8+ T cells from viremic patients is associated with impaired cytokine production, proliferation, survival, and turnover [41–44]. Other markers of T cell exhaustion include co-inhibitory receptors LAG-3, CD160, and Tim-3 [45–47]. It was recently shown that while virus-specific CD8+ T cells are initially capable of cytolytic activity, the potential is significantly reduced after acute infection [48, 49]. Thus, while HIV-specific CD8+ T cells appear to be necessary for the post-peak decline in viremia during the acute infection, persistent exposure to antigen and chronic inflammation results in an exhausted phenotype, in which cells are no longer capable of amounting an appropriate response against HIV and the infection remains.

Chronic infection

CD8+ T cells continue to exert some level of control over HIV and SIV replication after the acute phase of infection, as shown by studies in which depletion of CD8+ T cells during chronic SIV infection results in increased viral replication [50–52]. Additionally, viral escape mutants against CD8+ T cell responses continue to appear during the chronic phase of infection [53]. However, the combination of virus escape and progressive T cell dysfunction and exhaustion makes HIV− or SIV-specific CD8+ cells increasingly less able to successfully control virus replication [40, 54–59]. This loss of CD8+ T cell-mediated control of virus replication is associated with disease progression in chronically HIV-infected individuals [41, 46]. Interestingly, continuous activation of CD8+ T cells in the absence of effective antiviral activity may lead to disease progression [60], as first suggested by the classical observation that the level of CD8+ T cells expressing the activation markers CD38 and HLA-DR are most closely associated with shorter patient survival than viral load or CD4+ T cell count [61].

Natural control of HIV infection

It has long been recognized that a small group of HIV-infected individuals (<1% of the population) are capable of controlling HIV infection independent of ART. These individuals, termed elite controllers (EC) are able to maintain plasma viremia below the limit of detection of standard PCR assays in absence of ART . EC typically have stable CD4 counts without decline and progression to AIDS. Post-treatment controllers (PTC) are HIV-infected individuals who control virus below the limit of detection after interruption of long-term ART [62]. Intriguingly, the non-pathogenic phenotype of natural SIV infection in sooty mangabeys, a natural host species, is associated with relatively low CD8+ T cell responses to the virus [63, 64].

It is now understood that host factors, as opposed to viral factors, largely mediate control of HIV infection in EC and that CD8+ T cells play a prominent role in this phenomenon [reviewed in [65]]. In fact, depletion of CD8+ lymphocyte from controller rhesus macaques resulted in a transient increase in viremia [66]. Another study found that EC have very high levels of escape mutations, suggesting that CD8+ T cells put great selective pressure on the virus [67]. The identification of specific differences in host factors between chronic progressors and EC has defined potential targets for *in vivo* manipulation of HIV/SIV-specific CD8+ T cell-specific responses to achieve better immunological control of the infection. Among these host factors a key role is played by specific MHC class I alleles whose presence is significantly more frequent in the EC population [49, 68–71]. Specifically, HLA-B*27/*57 EC possess HIV-specific CD8+ T cells restricted by these class-I molecules that throughout chronic infection continue to show *in vitro* proliferation, whereas the majority of HIV-specific CD8+ T cells restricted by other HLA alleles lose this proliferative capacity [72–74]. Proliferative capacity of CD8 T+ cells in EC is associated with the up-regulation of perforin and therefore associated with enhanced cytotoxic capabilities [72]. In addition, HIV-specific CD8+ T cells from EC synthesize greater amounts of cytotoxic granule components, thus increasing their ability to kill infected cells [75–77] and are found to exceptionally up-regulate T-bet expression, which increases the production of perforin and granzyme B [78, 79].

Of note, EC are not different from CP on the basis of the frequencies of HIV-specific CD8+ T cells in peripheral blood, the antigen specificity or breadth of this response, nor the differences in the functional avidity [32, 80–82]. Together this data strongly suggests that CD8+ T cells play an important role during natural control of HIV and SIV infection.

Cytolytic versus non-cytolytic activities of CD8+ T cells during HIV infection

Cytolytic activities

CD8+ T cells have long been characterized by their cytotoxic T lymphocyte (CTL) activity during viral infection. CTL activity is mediated via formation of TCR-dependent immunological synapses in an antigen-dependent manner. CD8+ T cells kill target cells through the secretion of the granule-bound cytolytic molecules perforin and granzyme [83–85]. Granzymes are serine proteases that induce apoptosis by cleaving caspases [86, 87]. Perforin forms pores in the membrane of the cell, which also leads to apoptosis and allows for delivery of granzyme [88, 89]. The balance between the transcription factors Eomes and T-bet seems to dictate the differentiation and CTL functional pathways of the cell [90–94]. Together these transcription factors regulate the differentiation and CTL effector function of CD8+ T cells [95–97]. While T-bet positively regulates perforin and granzyme B expression, as well as genes associated with effector function [78, 98], Eomes positively regulates genes associated the maintenance of memory CD8+ T cells [90, 95, 97, 99].

The specific contribution of CTL responses to the control of HIV infection remains incompletely understood. HIV-specific CD8+ T cells are able to suppress HIV replication *in vitro* by direct cytotoxicity as well as by secretion of soluble factors [100–102]. During the acute phase of HIV and SIV infections, the CD8+ T cell pool is highly activated and primed for strong cytotoxic effector activity, however, this capacity decreases in the chronic phase of infection [49]. HIV-specific CD8+ T cells lose their ability to upregulate perforin after the resolution of peak viremia, a characteristic that also coincides with reduced expression of T-bet, but not of Eomes [49]. During chronic HIV infection, a T-bet^{hi}Eomes^{hi} population predominates the HIV-specific CD8+ T cell pool, exhibiting reduced differentiation, decreased functionality, enhanced exhaustion, and little to no expression of perforin [78, 92]. The loss of HIV-specific CD8+ T cell cytolytic function during chronic infection is thought to be a contributing factor to progressive HIV infection [75, 76, 103–105]. As mentioned above in describing the EC phenotype, control of viremia is associated with the ability of CD8+ T cells to proliferate and upregulate granzyme/perforin expression in response to *in vitro* antigen exposure [76]. In addition, it has also been shown that the ability of CD8+ T cells to upregulate perforin following *in vitro* stimulation correlates inversely with viral load [75]. Overall this complex set of experimental data suggests that CTL activity by CD8+ T cells is present and likely very important during the acute phase of HIV/SIV infection and in determining the relatively rare EC phenotype, while its role during chronic progressive infection is not clear and possibly much less important.

Non-cytotoxic activities

CD8+ T cells may suppress active HIV replication *in vitro* via non-cytolytic mechanisms that are related to the secretion of soluble factors [106–111]. Immunological factors able to suppress HIV/SIV replication include the β-chemokines CCL3, CCL4, and CCL5 (also known as MIP-1α, MIP-1β, and RANTES, respectively), which block the entry CCR5-tropic viruses [102, 112–114]. In fact, characterization of CD8+ T cells with a MIP-1β expression profile has been identified as a correlate of virus control and inhibition [115–117]. HIV/SIV-specific CD8+ T-cells also secret IFN-γ, which may play a role in the noncytolytic immune response, however, there is no demonstrable correlation between IFNγ expression and viral load, viral set point, viral clearance, or chronicity, with considerable variation between patients [118–120]. Despite a significant effort in the laboratory of Dr. Jay Levy, relatively little is known about the exact nature or specific identity of another secreted factor termed CD8+ Antiviral Factor (CAF) [121–123] that appears to suppress LTR-mediated gene expression in CD4+ T cells [124]. CAF does not block viral entry, integration, or reverse transcription, nor is it MHC-restricted [122–125]. In addition, CAF is not lentivirus-specific as it was also shown to suppress promotors of other viruses [126] and it is not produced exclusively by CD8+ T cells, which led to the hypothesis that CAF is part of the innate immune response [126, 127]. Of note, CAF lacks identity with IFN-α, IFN-*β*, TNF-*α*, IL-4, IL-6, and the *β*-chemokines [111, 121, 128, 129], and it remains possible that CAF is the activity of multiple factors [127]. The CD8+ T cell-specific noncytolytic mechanisms responsible for the suppression of HIV have yet to be fully understood. Studies have found evidence CD8+ T cells suppress replication by inhibiting viral transcription [130] and proviral gene expression[131, 132].

Strong support in favor of the hypothesis that non-cytolytic mechanisms of antiviral activity by CD8+ T cells are important in controlling HIV and SIV replication was provided by two independent studies in which the *in vivo* lifespan of productively infected cells was measured in CD8+ lymphocyte-depleted versus non-depleted SIV-infected RM [133, 134]. In both studies, SIV-infected RM were initiated on ART immediately after depletion of CD8+ T cells and the *in vivo* lifespan of productively infected cells was calculated based on the rate of viremia decline under ART using established mathematical models [135, 136]. Interestingly, both studies showed that the viral decay dynamics at the onset of ART was very similar between CD8+ lymphocyte-depleted RM and non-depleted animals, thus demonstrating that the relatively short *in vivo* lifespan of productively SIV-infected cells cannot be attributed to cytolytic activity of CD8+ T cells (Figure 1 A and B). Instead, the results of both studies are compatible with the hypothesis that non-cytolytic mechanisms that do not impact on the lifespan of a productively infected cell are involved in CD8+ T cell-mediated suppression of SIV replication.

The main conclusion of these experiments was independently confirmed by three studies. In the first study, al Basatena et al., sough to determine if the consistent observation of viral escape proves that HIV/SIV-specific CD8+ T cells kill infected cells or could this also be the result of a non-cytolytic control [137]. To this end, these authors developed a 3D cellular automaton model of HIV infection that captures both spatial and temporal dynamics, and reproduces *in vivo* viral dynamics at the cellular and population level. Using this model, al Basatena et al. demonstrated that non-cytolytic effector mechanisms can select for viral escape variants. Intriguingly, those viral variants selected by non-cytolytic mechanisms of suppression have a slower outgrowth and a lower frequency as compared to those escaping from a cytolytic response, thus suggesting that non-cytolytic responses can provide more durable control of HIV/SIV replication. In the second study, Balamurali et al. investigated the mechanisms of virus-specific CD8+ T cell control during immune escape in vivo by using a RT-PCR assay that differentiates wild type (WT) virus from escape mutants (EM) and studying the dynamics of immune escape in early SHIV infection of pigtail macaques. These authors reasoned that for immune escape mediated by cytolysis, the death rate of WT infected cells would be faster than EM-infected cells. However, Balamurali et al. found no significant difference in the rate of decay of WT virus compared with EM virus, thus consistent with an epitope-specific, MHC class I-restricted, noncytolytic mechanism of CD8+ T cell control of both WT and EM variants of SHIV [138]. In the third study, Spits et al., tried to identify correlation(s) between markers of CD8+ T cell function that are associated with CTL activity *ex vivo* and the calculated *in vivo* lifespan of productively infected cell as calculated by measuring the kinetics of virus decline under ART. The apparently "negative" result that they obtained, i.e., that the lifespan of productively infected cells is similarly short even in patients with the arguably "worst" CTL responses, is consistent with the hypothesis that non-cytolytic mechanisms are involved in the anti-HIV effect of CD8+ T cells [139].

In conclusion, a number of independent experimental investigations and mathematical analyses suggest that conventional CTL activity does not fully explain the antiviral role of CD8+ T cells in HIV/SIV infection. The possibility that the “CD8 effect” is due to alternative, non-cytolytic mechanisms of viral suppression is quite plausible. However, at this time it remains unclear what specific antiviral mechanisms are involved in this phenomenon, and what is the relative contribution of these non-cytolytic mechanisms to the control of HIV or SIV infection *in vivo*.

CD8+ T cells during ART-treated infection and HIV reservoir activity

ART does not restore CD8+ T cell compartment to pre-infection state

ART is unable to completely reverse the immune dysfunction bequeathed during the untreated infection, especially in the CD8+ T cell compartment. Although long-term ART results in some restoration of CD8+ T cell polyfunctionality and at least partial downregulation of activation and exhaustion markers, it does not fully restore CD8+ T cell cytotoxic and proliferative capabilities [41, 140–147]. Similarly, the bystander activation and expansion of the CD8+ T cell compartment does not return to normal despite virologic control [148, 149]. Interestingly, initiation of ART during early infection is associated with greater CD8+ T cell count reduction when compared to ART initiation during chronic infection [150, 151].

CD8+ T cells are unable to eliminate the HIV viral reservoir preserved during ART

A number of HIV cure strategies, collectively defined under the term “shock & kill” are based on the premise that, in ART-treated individuals, HIV/SIV-specific CD8+ T cells will recognize and eliminate virus-infected CD4+ T cells in which virus transcription and production has been reactivated by latency reversing agents [152]. While virus specific CD8+ T cells persist under ART, their number remains lower than prior to ART initiation, and the presence of virus immune escape variants as well as persistent dysfunction and/or exhaustion of HIV/SIV-specific CD8+ T cells may negatively affect their ability to clear the reservoir [53, 153–157]. Theoretically, during ART-treated HIV/SIV infections viral evolution ceases and, under this assumption, viral reservoirs preserve the pre-ART quasi-species with their escape mutations [158]. Overtime the ability of CD8+ T cells to recognize viral reservoirs appears to decline at a rate dependent on the time between infection and ART initiation [159]. In fact, a recent study demonstrated that more than 98% of proviruses in patients treated during chronic infection harbored escape mutations in dominant epitopes that were unrecognizable to CD8+ T cells, but subdominant CD8+ T cell responses against non-escaped epitopes were still found in each of the patients [160]. These findings raise the possibility that the epitopes targeted by CD8+ T cells under ART are suboptimal [70, 161–164]. Antigen sequestration has also been postulated to limit the ability of CD8+ T cells to clear the virus reservoir under ART. Most effector CD8+ T cells lack the proper chemokine receptors to enter the B cell follicle of the lymph node [165–169]. In the context of HIV, CD4+ follicular helper (T_{FH}) T cells have been shown to be 30-fold more likely to harbor latently-infected virus than peripheral CD4+ T cells [170], perhaps as a consequence of the inability of CD8+ T cell localization to the germinal center. Another point of discussion is whether and to what extent HIV latency per se poses as a barrier to CD8+ T cell-mediated eradication [159]. CD8+ T cells can detect even a single MHC-peptide complex on a cell surface [171] implying that even small levels of HIV translation can expose latently infected cells to CD8+ T cell killing. However, it is unclear how efficiently RNA transcripts that are often found in low levels in HIV/SIV-infected cells that persist under ART are translated – or, alternatively, their transcription is limited by retention in the nucleus, transcriptional interference, or "read-through" transcription [172] [173].

In conclusion, while CD8+ T cell recognition of the HIV viral reservoir is possible, especially in the setting of interventions that reactivate virus transcription and translation (i.e., latency reversing agents), the effectiveness of these CD8+ T cells may be limited by functional defects and/or residual exhaustion, presence of viral immune escape variants, and limited anatomical access to the latently-infected cell populations.

CD8+ T cells are required for maintenance of HIV viral reservoir suppression under ART

Recent evidence suggests that CD8+ T cells remain an essential component of virus control in ART-treated SIV-infected RMs [174]. In this study, depletion of CD8+ T cells from SIV+ ART-suppressed RM resulted in a rebound of viremia in 13 out 13 depleted animals and the reemergence of viral control was consistently coupled to the reconstitution of CD8+ T cells (Figure 1C). While in this study the depleting antibody used also depleted NK cells, there was no association between reconstitution of the NK cell pool and re-establishment of virus control. As part of this study, longitudinal viral sequencing by single-genome amplification (SGA) of SIV_{mac239} Env was performed on plasma samples collected during peak viremia (day 10 post-infection), immediately prior to ART initiation (day 56), and at the time of virus rebound after CD8+ lymphocyte depletion. Interestingly, the viral sequences derived from plasma following CD8+ lymphocyte depletion were similar to those obtained at the time of peak viremia and did not include in any case, the mutations that have emerged in the plasma by the time the SIV-infected RMs were started on ART. This observation supports the hypothesis that the source of the rebounding viremia after CD8+ lymphocyte depletion is the reactivation of virus transcription from a pool of long-lived, latently infected cells that were infected prior to ART initiation. In addition, the study found a significant direct correlation between the level of cell-associated SIV DNA in CD4+ T cells before CD8+ lymphocyte depletion and both the peak and the area under the curve of plasma viremia after depletion. This suggests that the size of the viral reservoir maintained under ART before CD8+ T cell depletion is a determinant of the ensuing amount of virus production.

In this study, as well as other experiments involving *in vivo* depletion of CD8+ lymphocytes, a modest increase in CD4+ T cell proliferation was observed likely as a result of homeostatic proliferation of T cells [50, 63, 174]. These observations raised the possibility that the observed increases in viral load were a passive consequence of this increased level of CD4+ T cell activation and proliferation, as opposed to the removal of a direct antiviral effect of CD8+ lymphocytes. To address this possibility, our group depleted CD4+ T cells from eight ART-treated SIV-infected RM and found that while the CD4+ T cells that survived depletion underwent strong homeostatic proliferation (as measured by increased expression of the proliferation marker Ki67) and increased cellular activation (as measured by increased expression of the markers CD25 and HLA-DR), plasma viremia remained below the limit of detection in all animals and at all time points (Kumar et al., manuscript in preparation) (Figure 1D). Thus, the results of these studies of CD4+ T cell depletion fully support the hypothesis that CD8+ T cells play a previously unappreciated but important direct role in the control of virus production and/or replication in ART-treated SIV-infected RM. Further studies with longer follow-up will determine if this effect of CD8+ T lymphocytes is present only in the first several months of ART or persists for longer periods of time under treatment.

It is important to note that in the natural history of HIV and SIV infections both cytolytic (i.e., CTL) and non-cytolytic (i.e., block of virus entry via beta-chemokines and suppression of virus transcription) activities result in reduction of virus production and replication, thus acting synergistically in promoting better virus control, with the most obvious example represented by the EC phenotype. However, in the setting of ART treatment and in terms of impact on virus persistence and the size of the reservoir, CD8+ T cell mediated CTL activity and CD8+ T cell-mediated suppression of virus transcription may have divergent effects. In particular, while clearance of infected cells via CTL activity will result in a net decrease of the reservoir size, the active suppression of HIV or SIV transcription may paradoxically increase the reservoir size by actively promoting latency. This latter point is of practical importance if we think of ways to manipulate these antiviral roles of CD8+ T cells in ART-treated HIV-infected individuals. In this regard, CTL activity could be enhanced by interventions such as therapeutic vaccinations and/or co-inhibitory blockade. On the other hand, CD8+ lymphocyte depletion could be viewed as a potentially very powerful way to reactivate latent HIV or SIV infection (i.e., latency reversing agent). Further studies aimed at better elucidating the relative *in vivo* contribution of cytolytic vs. non-cytolytic mechanisms of virus suppression under ART, as well as the molecular pathways that regulate the prevalence of either function of CD8+ T cells, will be crucial to design immune-based interventions that are best suited to reduce the reservoir size in ART-treated HIV-infected individuals.

Conclusion

It is well established from the numerous studies discussed in this review that CD8+ T cells are key players in the antiviral response to HIV and SIV during each stage of infection, including when the infection is treated with ART. Recent studies have shown that (i) CD8+ T cells are required for maintenance of viral suppression under ART, and (ii) that the longitudinal analysis of viral sequences is compatible with a CD8+ T cell-mediated suppression of virus production at the transcriptional level. These findings suggest that CD8+ T cells may paradoxically contribute to persistence of the HIV reservoir and thus pose as a barrier to HIV cure. It is conceivable that while CTL activity occurs early during infection and results in a net reduction of the reservoir size, CD8+ T cells are also capable of maintaining latency via non-cytolytic mechanisms that suppress HIV replication. However, the relative contributions of cytolytic and non-cytolytic activities of CD8+ T cells in suppressing virus production remain unknown. A deeper understanding of these activities would contribute to the design of therapeutic vaccines capable of harnessing and boosting specific antiviral activities or downregulating others in the hopes of targeting and eliminating the HIV viral reservoir. Heightening the ability of CD8+ T cells to recognize and kill virally infected cells, especially during ART treatment, is a promising strategy to eliminate virally infected cells, including the viral reservoir. If the non-cytolytic activities of CD8+ T cells contribute to the establishment and persistence of the viral reservoir via inhibition of viral transcription or translation, strategies aimed at decreasing these capacities could also contribute to the elimination of virally infected cells.

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Abbreviations:

HIV:	Human immunodeficiency virus
SIV:	Simian immunodeficiency virus
AIDS:	Acquired immunodeficiency syndrome
ART:	Antiretroviral therapy
RM:	Rhesus macaque
EC:	Elite controller
CP:	Chronic progressor
CTL:	Cytotoxic T lymphocyte

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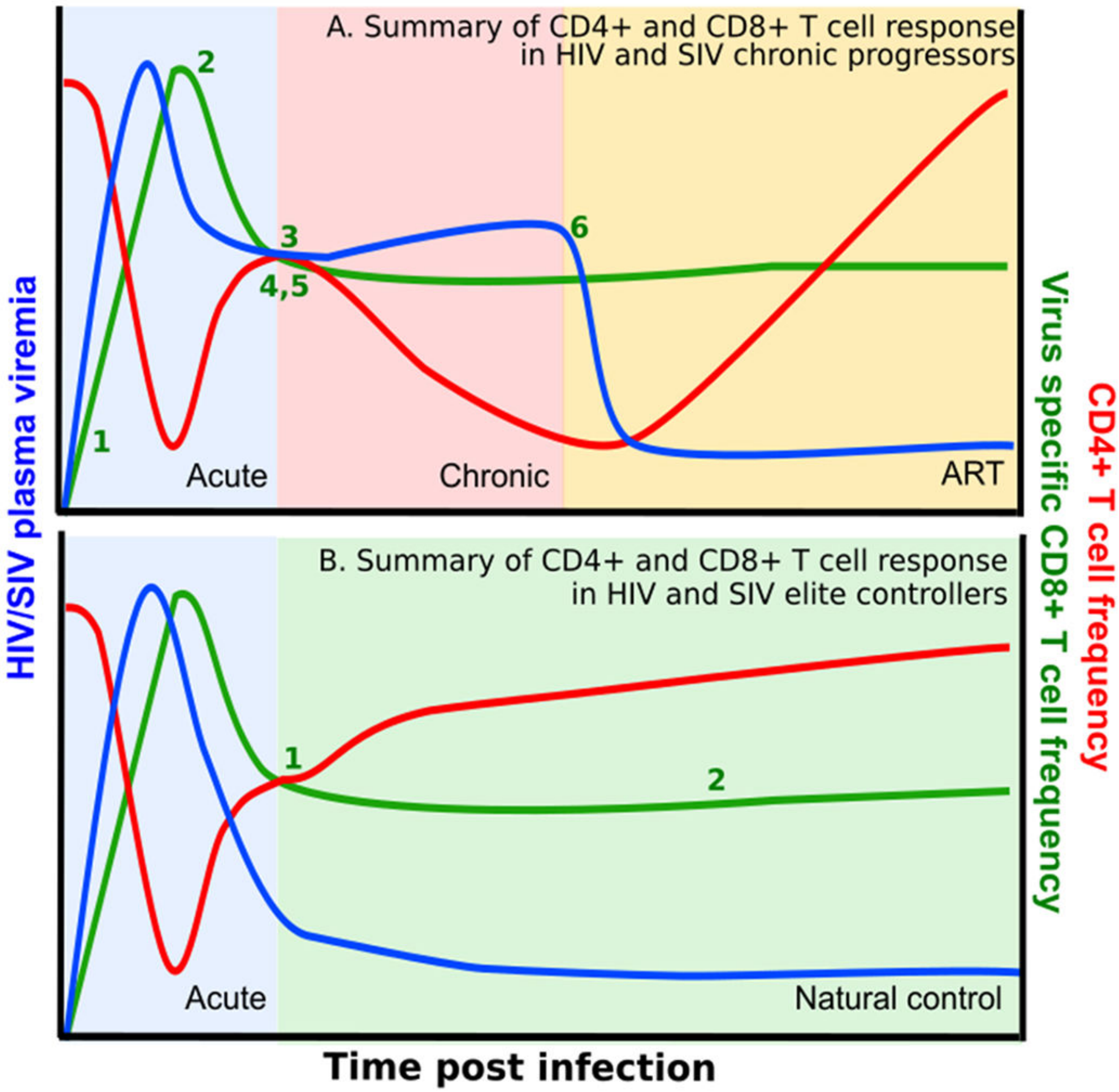

Figure 1:

Summary HIV and SIV infection in chronic progressors and elite controllers. **A.** Summary of CD4+ and CD8+ T cell response in HIV and SIV chronic progressors. 1. Acute HIV infection induces activation and expansion of all CD8+ T cells, including virus-specific CD8+ T-cells. 2. After an initial lag period, 3. expanded CD8+ T cells control peak viremia and chronic infection follows. 4. HIV specific CD8+ T-cells become exhausted and contribute to disease progression during chronic infection. 5. Emergence of CD8 escape mutants indicating selective pressure by CD8+ T-cells. 6. Despite ART, CD8+ T-cell function is not fully restored. (B) Summary of CD4+ and CD8+ T cell response in elite controller. Elite controllers have similar expansion of CD8+ T cells which leads to control of peak viremia and subsequent viral control and restoration of CD4+ T cells. 1. Specific MHC class I alleles are associated with viral control, indicating CD8 selective pressure. 2. HIV specific CD8+ T cells maintain high levels of polyfunctionality, proliferative capacity and maintenance of cytolytic potential throughout infection. Abbreviations: SIV, simian immunodeficiency virus; HIV, human immunodeficiency virus; ART, antiretroviral therapy; MHC, major histocompatibility class.

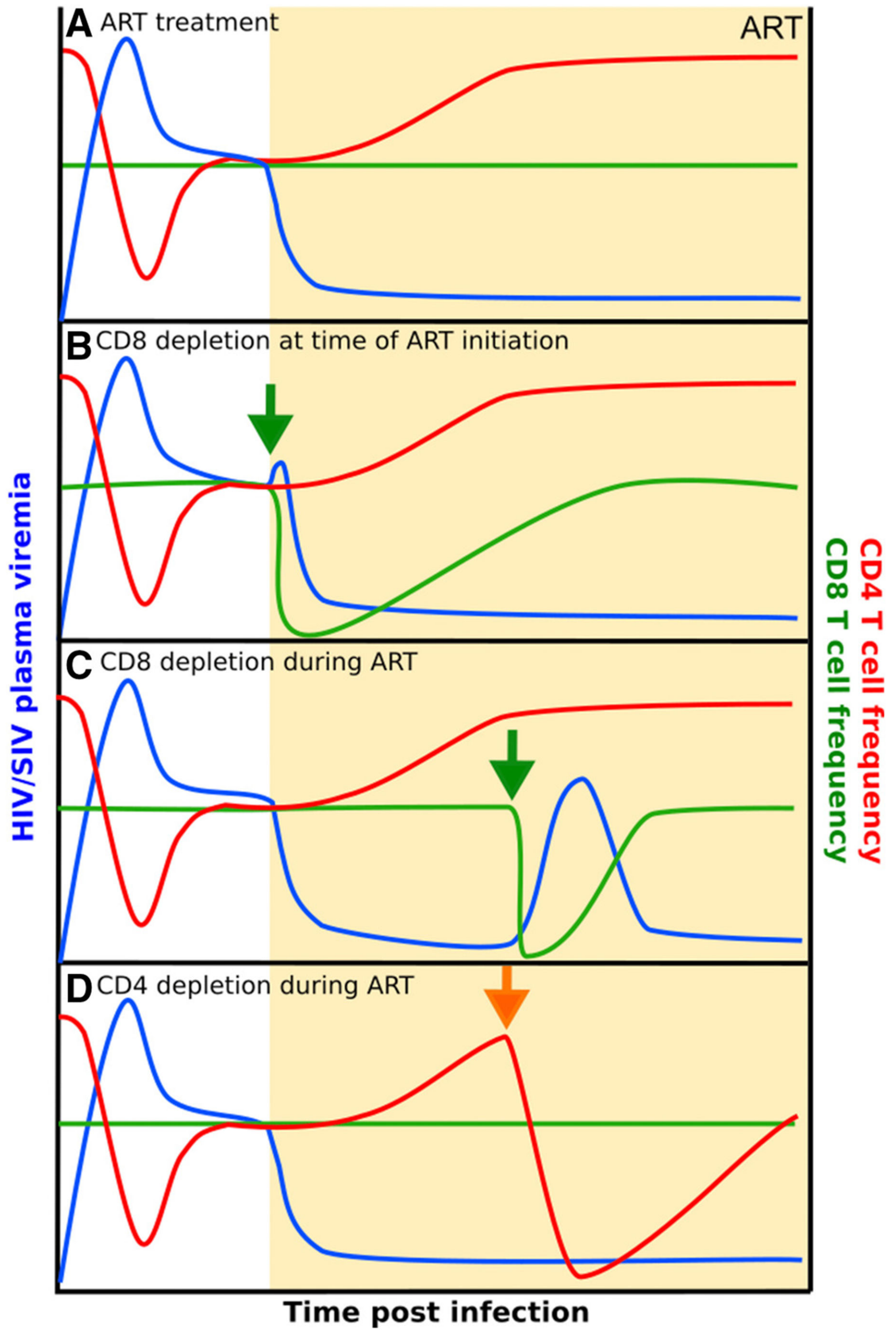

Figure 2:

Changes in viral load and T cell frequencies during CD8 and CD4 depletion studies in SIVmac239 infected, ART-treated rhesus macaques. The initiation of ART in the presence **(A)** or absence **(B)** of CD8+ T cells during SIV infection results in similar decay rates of plasma viremia. **(C)** Viral load increases upon CD8 depletion during short-term ART. **(D)** Depletion of CD4+ T cells after ART does not result in viral rebound. Key: green arrow represents CD8+ lymphocyte depletion and orange arrow represents CD4+ T cell depletion.

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Abbreviations: SIV, simian immunodeficiency virus; CD, cluster of differentiation; ART, antiretroviral therapy; P.I., post-infection.

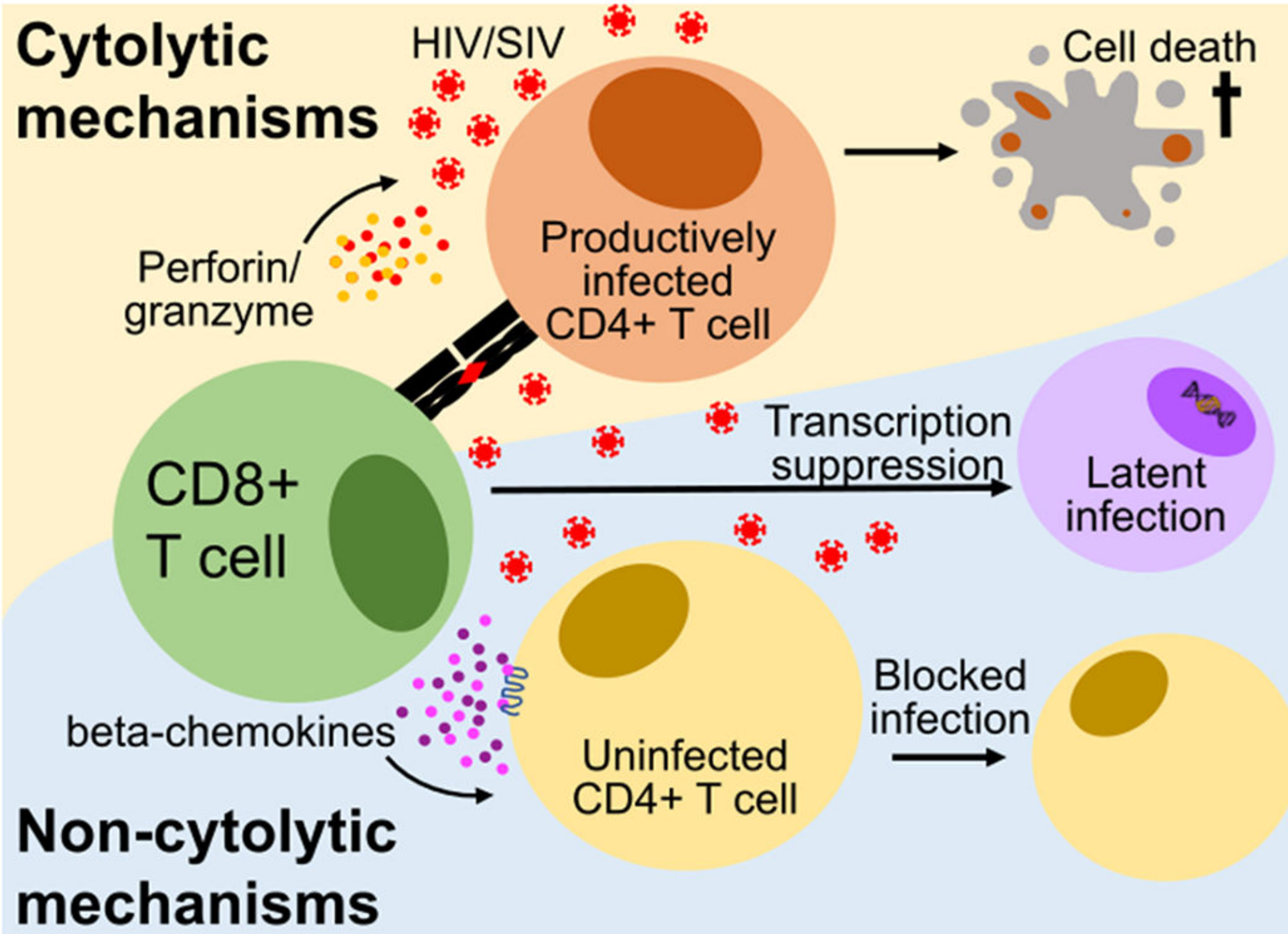

Figure 3:

Schematic representations of the association between CD8+ T cell frequency and SIV viral load. **A**. The initiation of ART in the absence or presence of CD8+ T cells during SIV infection results in similar decay rates of plasma viremia. **B.** Viral load increases when CD8+ T cells are absent during short-term ART. **C.** Viral load does not increase when CD4+ T cells are absent during short-term ART. Abbreviations: SIV: Simian immunodeficiency virus; CD: cluster of differentiation; ART: Antiretroviral therapy; P.I.: post-infection.

Table 1:

Summary of noteworthy studies providing evidence of cytolytic and non-cytolytic antiviral activity of CD8+ T cells during HIV/SIV infection during different phases of infection, including treatment and natural control. Abbreviations: HIV: Human immunodeficiency virus; SIV: Simian immunodeficiency virus; PBMC: peripheral blood mononuclear cell; ART: Antiretroviral therapy; RM: Rhesus macaque; EC: Elite controller; CP: Chronic progressor; CTL: Cytotoxic T lymphocyte; CD: cluster of differentiation; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; CCL: chemokine (C-C motif) ligand; CCR: chemokine receptor; PD-1: programmed death-1; HLA: human leukocyte antigen; MIP: macrophage inflammatory protein ; CAF: CD8 antiviral factor.

Phase	Finding	Evidence	Reference
Acute infection	CD8 T cells are required for the initial control of HIV viremia.	Depletion of CD8+ lymphocytes from RM at the time of SIV infection resulted in abrogation of post peak decline.	[26, 175]
	After initial lag period, HIV-specific CD8+ T cells massively expand and differentiate at the time of peak viremia.	HIV-specific CD8+ T cells exhibit a delay in expansion and differentiation until peak viremia when compartment becomes fully expanded and differentiation in response to systemic proinflammatory cytokine burst, allowing for effective killing of productively-infected cells.	[176]
	The emergence of HIV-specific CD8+ T cells is associated with partial control of acute infection.	Increasing frequency of precursor CD8+ T cells specific for HIV-1 gag, pol, and env viral proteins using PBMC from patients experiencing acute HIV infection was correlated with partial resolution of peak viremia.	[24, 25]
	CD8+ T cells are capable of exerting significant selective pressure on the HIV viral genome.	Identification of the rapid appearance of specific escape mutations in HIV genome.	[29, 153]
	Acute HIV infection induces massive activation and expansion of the entire CD8+ T cell compartment	CD8+ T cell frequencies increase during the course of infection in HIV+ individuals and do not return to normal.	[177]
		Activation marker CD38 is up-regulated on Epstein Barr-, Cytomegalovirus- and influenza-specific CD8+ T cells during acute HIV infection, although activation was highest in HIV-specific cells.	[178]
		HIV-specific CD8+ T cells represent less than 10% of the total CD8+ T cell pool expanded during the acute infection.	[32]
		During the acute infection as high as 80%-90% of the entire CD8+ T cell compartment becomes activated.	[55]
	CD8+ T cell expansion can occur through antigen-independent mechanisms.	Microbial products systemically translocated across the gut epithelium contribute to the chronic activation of CD8+ T cells.	[22]
		Lipopolysaccharide and inactivated HIV activate monocyte-derived dendritic cells, which are capable of activating CD8+ T cells via transpresentation of IL-15. Therefore, proliferation and activation of the CD8+ T cell pool is initiated by cytokines, most notably IL-15.	[179]
	HIV-specific CD8+ T cells become exhausted during the acute infection and do not recover.	HIV–specific CD8+ T cells proliferate rapidly upon encounter with cognate antigen in acute infection, but lose this capacity with ongoing viral replication.	[73]
		HIV-specific CD8+ T cells provide a very early, robust, and highly activated effector response with immediate cytotoxic potential (as measured by perforin expression), but the ability is quickly lost after resolution of peak viremia.	[49]
		After full differentiation and expansion, HIV-specific CD8+ T cells reach a hyperproliferation state that is “too strong for too long” and push them to terminally differentiated effector cells that contributes to exhaustion.	[176]

Phase	Finding	Evidence	Reference
Chronic infection	CD8+ T cells contribute to control during chronic HIV infection.	CD8+ T cell depletion during chronic infection results in an increase in viremia that is not controlled until reconstitution of depleted cells.	[50-52]
	Expanded CD8+ T cell population in chronically HIV-infected patients shows symptoms of immunosenescence.	HIV-specific CD8+ T cells lack of proliferative capability in response to cognate antigen (ex vivo), which could not be overcome by exogenous IL-2 or IL-15. These cells were associated with expression of CD57.	[46]
		Ex vivo analysis of virus-specific CD8 T cells shows that HIV disease progression correlates with increased proportions of highly differentiated CD8+ T cells, which exhibit characteristics of replicative senescence: CD57 expression, inability to proliferate in response to antigen, and shortened telomeres.	[55]
	The HIV-specific CD8+ T cell compartment has a skewed differentiation pattern towards effector memory during chronic infection.	70% of HIV-specific CD8+ T cells were found to be CD45RA-CCR7-, in contrast to cytomegalovirus-specific CD8+ T cells where only 40% are CD45RA-CCR7-.	[180]
	Expression of exhaustion markers on HIV-specific CD8+ T cells continues during chronic infection and contributes to disease progression.	Persistent antigen during chronic HIV infection contributes to the impairment of HIV-specific CD8+ T cells. HIV-specific CD8+ T cells show significant upregulation of PD-1. Expression correlates positively with impaired function, viral load and inversely with CD4+ T cell count.	[41, 42, 44]
		TIM-3 expression on CD8+ T cells correlates positively with viral load and inversely with CD4 counts during chronic HIV infection.	[140]
	PD-1 expression on HIV-specific CD8+ T cells is correlated with decreased survival, proliferation, and cytokine expression.	Ex vivo anti-PD-L1 treatment of CD8+ T cells from HIV+ donors led to changes in the ability of the cells to survive, expand, and secrete cytokines.	[42]
	HIV-specific CD8+ T cells exhibit reduced polyfunctionality during chronic infection.	HIV-specific CD8+ T cells from HIV+ donors exhibit decrease CD107, IFNγ, CCL4, IL-2, and TNFα expression after stimulation.	[40]
	HIV-specific CD8+ T cells exhibit impaired cytolytic function during chronic infection	Perforin expression was significantly lower in HIV-specific CD8+ T cells compared to CMV-specific CD8+ T cells of the same donor.	[57]
	CD8+ T cells secrete factors that are capable of suppressing replication of HIV through non-cytolytic mechanisms.	CD8+ T cells were found to release β-chemokines (CCL3, CCL4, and CCL5) with suppressive activities capable of blocking entry of M-tropic viruses.	[102, 112, 113]
		Replication of HIV in latently infected, resting CD4+ T cell reservoir is effectively suppressed in ex vivo coculture by autologous CD8+ T cells in EC and ART-treated patients but not ART-naïve patients.	[114]
		Identification of the characterization of CD8+ T cells with a MIP-1β expression profile as a correlate of virus control and inhibition.	[115, 116]
		CAF suppresses LTR-mediated HIV gene expression in CD4+ T cells.	[124]
		CD8+ T cells suppress replication by inhibiting viral transcription and proviral gene expression].	[130-132]
		SIV-infected RM were initiated on ART in the absence or presence of CD8+ T cells. The rates of viral decay did not differ between the two groups, suggesting that CD8+ T cells do not decrease the lifespan of productively infected cells. Thus, the antiviral mechanism of CD8+ T cells may be non-cytolytic.	[133, 134]
Natural control	CD8+ T cells are important during the control of SIV viral replication during RM controller infection.	Depletion of CD8+ lymphocytes in SIV controller RM resulted in a transient and significant increase in viremia and control was reestablished with the reconstitution of CD8+ T cells.	[66]

Phase	Finding	Evidence	Reference
	HIV-specific CD8+ T cells from EC maintain high polyfunctionality.	HIV-specific CD8+ showed increase function via expression of 5 functional markers: CD107 (degranulation), IFNγ, CCL4, IL-2, and TNFα.	[40]
	HIV-specific CD8+ T cells from EC show better maintenance of cytolytic potential compared to CP.	HIV-specific CD8+ T cells of EC exhibit greater cytolytic capacity compared to CP. The strong ability of EC to kill HIV-infected CD4+ T cells was mediated by the delivery of granzyme B to target cells, an observation not congruent in CP.	[76]
		During chronic infection, cytolytic potential is lost rapidly in most HIV-infected individuals, such that only around 15% of HIV-specific CD8+ T cells express perforin, whereas around 40% express perforin in EC.	[75]
	HIV-specific CD8+ T cells from EC have a higher proliferative capacity as compared to CP.	High proliferative capacity of HIV-specific CD8+ T cells EC is coupled to increases in perforin expression with relative absence of these functions in CP.	[72]
	Host factors related to CD8+ T cells contribute to the control of HIV infection observed in EC.	CD8+ T cells restricted by certain protective alleles (HLA-B27 and -B57) can resist replicative defects, which permits expansion and antiviral effector activities.	[74]
	HIV-specific CD8+ T cells of EC have a higher functional recall memory than CP.	The expansion of CD8+ T cells producing IFNγ alone or in combination with IL-2 in response to gag peptides presented on monocyte-derived dendritic cells is limited in CP compared to EC. This was not observed by CD8+ cells in response to influenza, cytomegalovirus, and Epstein Barr virus.	[181]
	HIV-specific CD8+ T cells put selective pressure on the virus during EC infection.	Sequencing of plasma viremia of EC shows a discordance between the genotypes of the plasma virus and provirus. Specifically, HLA-B*57-restricted Gag epitopes were present in plasma virus but rare in provirus.	[67]
Treated infection	CD8+ T cells are required for the maintenance of viral suppression under ART.	Depletion of CD8+ lymphocytes from SIV+ RM during short-term ART results in a rebound of viremia.	[174]
	HIV-specific CD8+ T cells decline in peripheral blood after the initiation of ART	The longitudinal responses to 95 HLA class I-restricted HIV epitopes were measured using intracellular staining in HIV+ patients beginning ART. A rapid decline in HIV-specific CD8+ T cell response was observed upon initiation of ART. Discontinuation of ART resulted in a rapid increase in HIV-specific CD8+ T cells.	[149]
	Dysfunction of HIV-specific CD8+ T cells is decreased, but not restored during ART.	In a longitudinal study of HIV-infected patients, ART initiation resulted in some restoration of cytokine secretion, increase of IL-7Rα and CD28 expression, and a decline of PD-1 on HIV-specific CD8+ T cells.	[147]
		Defective HIV-specific CD8+ T cell polyfunctionality, proliferation, and cytotoxicity are not restored by ART	[182]
	ART does not resolve CD8+ T cell compartment elevation.	ART does not restore ongoing elevation of CD8 counts despite normalized CD4 count, resulting in a persistently low CD4:CD8 ratio even during virological control. This phenotype is correlated with markers of T cell activation and innate immune active, immunosenescence, and serious non-AIDS events and mortality.	[183]
		Early initiation of ART during HIV infection, not prolonged duration of ART, contributes to partial normalization of CD8+ T cell counts.	[150]
	ART is able to partially reverse the exhaustion of virus-specific CD8+ T cells observed during chronic HIV infection.	ART-initiation reverses expression of PD-1 on HIV-specific CD8+ T cells, reversing the functional impairment of these cells that had been caused by the constant presence of HIV antigen.	[145]
		HIV-specific CD8+ T cells from ART-treated patients expressed significantly lower levels of TIM-3 compared with untreated patients and TIM-3 expression was positively correlated with viral load.	[144]