CD4+ T cell depletion in HIV infection: mechanisms of immunological failure

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Summary

The hallmark of acquired immunodeficiency syndrome (AIDS) pathogenesis is a progressive depletion of CD4+ T-cell populations in close association with progressive impairment of cellular immunity and increasing susceptibility to opportunistic infections (OI). Disease progression in untreated human immunodeficiency virus (HIV) infection can take many years, and it was originally hypothesized to be a consequence of slow, viral-mediated CD4+ T-cell destruction. However, massive CD4+ memory T-cell destruction is now known to occur quite early in infection, almost always without overt immunodeficiency. In most individuals, this initial destruction is countered by CD4+ memory T-cell regeneration that preserves CD4+ T-cell numbers and functions above the threshold associated with overt immunodeficiency. This regeneration, which occurs in the setting of chronic immune activation and immune dysregulation does not, however, restore all functionally important CD4+ T-cell populations and is not stable over the long term. Ultimately, CD4+ memory T-cell homeostasis fails and critical effector populations decline below the level necessary to prevent OI. Thus, the onset of overt immune deficiency appears to be intimately linked with CD4+ memory T-cell dynamics and reflects the complex interplay of direct viral cytopathogenicity and the indirect effects of persistent immune activation on CD4+ memory T-cell proliferation, differentiation, and survival.

Keywords

Introduction

It has been 30 years since the discovery and identification of a family of deadly human lymphotropic retroviruses now known as human immunodeficiency viruses (HIV)(1–3). This new virus type was isolated from patients presenting with the then recently described acquired immune deficiency syndrome (AIDS), a syndrome characterized by the development of previously rare opportunistic infections (OIs) and/or malignancies in previously healthy young homosexual men and/or intravenous drug users (4). The earliest reported AIDS cases included subjects with *Pneumocystis carinii* pneumonia and/or Kaposi's sarcoma (5, 6), but subsequently, other AIDS-associated OIs were identified, including *Mycobacterium tuberculosis, M. avium intracellulare, Cryptococcus neoformans, Toxoplasma gondii*, cytomegalovirus, adenovirus, herpes simplex virus, and *Candida albicans* (7, 8). A common thread of impaired cellular immunity linked these OIs. In keeping with this observation, early laboratory studies documented that subjects with AIDS

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manifested marked lymphopenia, low lymphocyte proliferative responses *in vitro* after stimulation with antigens or mitogens, anergy to cutaneous skin tests, and an inversion in the ratio of T-helper cells to cytotoxic T cells (5–7). Subsequent studies confirmed that HIV selectively infected and killed CD4$^+$ T cells *in vitro* and that the numbers of circulating CD4$^+$ T cells in HIV$^+$ subjects predicted the onset of overt immunodeficiency (9, 10). Later still, it was found that suppressing HIV replication with antiretroviral therapy (ART) rapidly increased peripheral blood CD4$^+$ T-cell counts and reversed immunodeficiency (11, 12).

Overall, these observations provide strong evidence that a profoundly impaired cellular immune response due to depletion of CD4$^+$ T cells and loss of CD4$^+$ T-cell function was the underlying cause of immunodeficiency present in these patients. Further evidence for this conclusion came from analysis of experimental infections of nonhuman primates (NHPs) with certain strains of chimeric simian/human immunodeficiency viruses (SHIV). In these infections, systemic, acute, pan-CD4$^+$ T-cell depletion led to rapid development of an AIDS-like syndrome and death early after infection (13, 14). Taken together, these observations suggested a model of HIV pathogenesis in which viral-mediated destruction of CD4$^+$ helper T cells results in impaired immunity to pathogenic agents typically restricted by T-cell-mediated immunity, and ultimately, the emergence of one or more fatal OIs.

The loss in CD4$^+$ T cells was initially thought to be a gradual process as the timing to overt immunodeficiency and AIDS in untreated patients was typically within 10–12 years from primary infection (15–17). However, the concept that HIV disease progression results from slow, viral-mediated CD4$^+$ T-cell destruction was brought into question by a number of observations. First, HIV replication was shown to be continuous and high throughout the course of infection, despite the slow progression to end-stage disease (12, 18). Second, because of the use of CCR5 as a viral co-receptor (CCR5 tropism), infecting strains preferentially infect memory CD4$^+$ T cells (particularly the more differentiated effector memory subset) and these preferentially targeted cells, which compromise the majority of CD4$^+$ T cells in extra-lymphoid effector sites such as the intestinal mucosa, are rapidly and profoundly depleted during acute HIV infection, long before the onset of AIDS (19–22). Third, the level of immune activation in HIV-infected subjects predicts disease progression as well or better than the levels of virus replication (23–26). Taken together, these observations suggested that AIDS pathogenesis was not well explained by the direct viral killing hypothesis and must involve a more complex interplay between the host immune system and both direct and indirect effects of active viral replication. Indeed, the discovery that the simian immunodeficiency virus (SIV) infections of African NHPs (the larger viral family from which HIV originated) are largely nonpathogenic vividly illustrates this conclusion. The SIVs that infect these natural hosts are just as cytopathic to NHP CD4$^+$ T cells as HIV is to human CD4$^+$ T cells, but in the vast majority of these animals, CD4$^+$ T-cell depletion is not progressive and AIDS does not ensue (27–31). These hosts have obviously adapted to viral replication and CD4$^+$ T-cell destruction, whereas pathogenic infections (HIV infections of humans and SIV infections of Asian NHPs) reflect cross-species transmission of infection to non-adapted hosts, a situation in which genetically determined differences in host response result in vastly different outcomes from otherwise similar viral infections.

Over the past decade, a more nuanced and dynamic model of AIDS pathogenesis has emerged. In this model, viral replication drives pathogenesis but does not directly cause immunodeficiency. Instead, immunodeficiency results from dysregulation and ultimately failure of host homeostatic mechanisms and cellular immune networks. Here, we review the evolution of this new model, with the hope of providing a better explanation for why a rapidly replicating, cytotoxic virus causes such a slowly progressing disease.

Cellular dynamics of HIV/SIV infection

One of the more critical discoveries in the investigation of AIDS pathogenesis was the demonstration that HIV entry (and therefore, the targeting of the infection) is dependent not only on expression of a primary receptor, CD4, but also on expression of co-receptors. These co-receptors, which were shown to be chemokine receptors, typically CCR5 or CXCR4, are differentially expressed on CD4$^+$ T cells (21, 32). CXCR4 is highly expressed on the vast majority of peripheral T cells and can indeed mediate a generalized infection and destruction of all CD4$^+$ T cells in infections with viruses using CXCR4 as co-receptor, as demonstrated by the profound generalized CD4$^+$ T-cell destruction and acute onset of AIDS in NHPs infected with a CXCR4-using SHIV (13, 14). However, this co-receptor is not used by transmitted strains of HIV, and ′CXCR4-tropism′ typically develops only in a proportion of infected individuals very late in infection, a switch in co-receptor usage which, in keeping with CXCR4 distribution, is often observed in association with profound pan-CD4$^+$ T-cell depletion and end-stage disease (33–36). As implied by this late switch, transmitted strains of HIV use CCR5 as co-receptor, which confers ′CCR5-tropism′. Importantly, CCR5 is not expressed by all CD4$^+$ T cells, but rather, in keeping with its role in direction of the migration of effector-differentiated T cells to extra-lymphoid sites of inflammation or host defense, its expression is upregulated as part of the late differentiation of effector and effector memory T cells. It is therefore predominantly expressed by CD4$^+$ T cells in effector sites like the *lamina propria* of the intestinal mucosa (37, 38). CCR5-tropism is not accidental. It represents a fundamental adaption of the virus that allows infection of a subset of CD4$^+$ T cells (effector-differentiated cells in extra-lymphoid effector sites and their immediate precursors in secondary lymphoid tissues) that can be rapidly regenerated from less differentiated, CCR5$^−$ precursors (20, 39–41). This adaptation provides the virus with a large initial target population (CD4$^+$ T cells in effector sites), and once these are depleted, the host courteously provides a continuous stream of new targets that maintain infection over the long-term and increase the likelihood of viral transmission.

The importance of this selective targeting in AIDS pathogenesis was first demonstrated in the SIV model of pathogenesis in rhesus macaques (RMs), where it was shown that highly pathogenic, CCR5-tropic SIV infection was associated with widespread infection and massive destruction of CD4$^+$ T cells in intestinal *lamina propria* and other extra-lymphoid effector sites during the first 2–3 weeks of infection (22, 42–44). The wholesale destruction of CD4$^+$ T cells in these sites has been attributed to both direct infection and Fas/Fas ligand-mediated apoptosis (42). Studies in HIV-infected patients have since shown a similar pattern of preferential and profound depletion of CD4$^+$ T cells within the gastrointestinal tract during acute infection (20, 45, 46). These findings demonstrated that depletion of HIV/SIV viral targets (CD4$^+$CCR5$^+$ memory T cells) is not slow, as originally hypothesized, but rather early and profound.

CCR5-expressing CD4$^+$ T cells in blood and secondary lymphoid tissues are also infected and destroyed in acute infection, but these cells comprise only a subset of CD4$^+$ T cells in these sites, and both the CD4$^+$ naive (T$_N$) and central memory (T$_{CM}$) T-cell compartments in these tissues are relatively spared from destruction in acute infection. Indeed, within a few days of peak effector memory (T$_{EM}$) CD4$^+$ destruction in acute SIV infection of RMs, proliferating CD4$^+$ T$_{CM}$ and early transitional effector memory (T$_{TrM}$) T cells are observed, and these cells migrate to extra-lymphoid effector sites and either stabilize or partially regenerate CD4$^+$ effector memory cells in these sites (39). Indeed, among RMs infected with CCR5-tropic SIV, early collapse of the CD4$^+$ memory T-cell regenerative response is strongly associated with rapid disease progression (onset of AIDS in the first 6 months of infection), whereas robust CD4$^+$ memory T-cell regeneration is associated with survival into the chronic phase of infection (22). Our recent observation that regeneration is preserved in

RMs with experimental ablation of the $CD4^+$ T_N compartment prior to SIV infections indicates that the $CD4^+$ T_{CM} population is the critical population in this regenerative response (47).

These observations together indicate that the use of CCR5 as the major HIV/SIV co-receptor results in the ability of the virus to target the terminally differentiated $CD4^+$ T_{EM} population, while leaving relatively intact a precursor $CD4^+$ T_{CM} population capable of continuous, high level production of new T_{EM} (Fig. 1). As a result, the virus is assured of a continuous supply of new targets, most of which are expendable to the host, as long as the production of new T_{EM} cells is sufficient to maintain effective immunity (39–41). This would suggest that the profound depletion of $CCR5^+CD4^+$ memory T cells (viral targets) during acute infection would not lead to AIDS progression if the regenerative potential of the $CCR5^-CD4^+$ T-cell compartments (T_{CM} and T_N) could be effectively maintained over the long term. Indeed, this seems to be the case with non-pathogenic SIV infections of African monkeys ('natural hosts'). Via a variety of adaptations that both allow for more efficient sparing of $CD4^+$ T_{CM} populations (48, 49) and provide for effective long-term $CD4^+$ memory T-cell regeneration, these NHPs are able to regenerate and maintain nearly normal $CD4^+$ T-memory compartments after SIV infection, allowing them to tolerate levels of cytopathic SIV replication that are as high or higher than in pathogenic infections of humans and RMs (27, 29, 50–52).

Connecting $CD4^+$ T-cell depletion with chronic disease progression

These observations suggest that $CD4^+$ T-cell depletion in HIV/SIV infection might be considered a three-stage process: (i) initial profound destruction of optimal $CCR5^+$ viral targets (effector-differentiated $CD4^+$ memory T cells), (ii) a regeneration of the $CD4^+$ T_{EM} compartment from $CD4^+$ T_{CM} precursors, and (iii) progressive $CD4^+$ memory T-cell homeostatic failure in which declining $CD4^+$ T_{CM} populations ultimately lead to $CD4^+$ T-effector cell insufficiency and overt AIDS. As described above, the massive depletion of $CD4^+$ effector-differentiated T cells in infections with CCR5-tropic SIVs (which typically result in AIDS after 1–2 years of infection) is closely followed by a dramatic increase in $CD4^+$ T_{CM} proliferation and $CD4^+$ T_{EM} production that partially regenerates depleted mucosal compartments and prevents early onset of overt immune deficiency. However, this regenerative process does not completely restore immunity and is not stable over time. Unlike T-cell homeostasis in healthy uninfected RMs, in which proliferating cells are predominantly long-lived, the regeneration in SIV infection is a high-turnover process driven by immune activation that produces short-lived cells (53). Extraordinarily high levels of proliferation are necessary to maintain effector memory compartments even at subnormal levels, and not all functionally important $CD4^+$ subsets are regenerated to the same degree (see below). It is now appreciated that apparently healthy monkeys in early chronic phase SIV infection manifest major changes in their intestinal 'virome', including multiple subclinical invasive viral infections, consistent with covert immune deficiency (54).

The quasi-stable equilibrium between viral- and immune activation-mediated $CD4^+$ T-cell destruction and host efforts to regenerate these populations appears to degrade over time as the substrate population, lymphoid tissue-based $CD4^+$ T_{CM} cells, decline, resulting in progressively reduced regenerative capacity. Indeed, the progressive failure of $CD4^+$ T_{CM} homeostasis and the consequent inability to maintain $CD4^+$ T_{EM} cell production appears to play a major role in setting the tempo of disease progression and the timing of progression to overt immunodeficiency in pathogenic SIV infection (39) (Fig. 2). The mechanisms responsible for the instability of the $CD4^+$ T_{CM} compartment in progressive CCR5-tropic HIV/SIV infection are not yet completely defined. The immune activation-induced high turnover state does not, by itself, explain $CD4^+$ T_{CM} homeostatic failure as $CD8^+$ T_{CM}

turnover is similarly increased, but $CD8^+$ memory T-cell homeostasis remains stable over the course of progressive infection (39). While $CD8^+$ and $CD4^+$ T_{CM} populations obviously differ in the fact that cells in the latter population, even with low CCR5 expression, can be killed by direct viral infection, this mechanism, by itself, would only be able to account for progressive $CD4^+$ T_{CM} cell decline if the rate of $CD4^+$ T_{CM} cell infection and direct destruction increased over time (otherwise homeostatic regeneration would maintain a stable equilibrium). In this regard, $CD4^+$ T_{CM} cell decline has been observed in animals with stable viral replication dynamics and stable or even declining levels of $CD4^+$ T_{CM} cell infection (39).

The slow nature of $CD4^+$ T_{CM} cell homeostatic failure in progressive SIV infection suggests that either $CD4^+$ T_{CM} cells have intrinsic or extrinsic limitations in their ability to self-renew or that the balance between their self-renewal and their production of effector-differentiated progeny is dysregulated, ultimately leaving the $CD4^+$ T_{CM} cell population too small to maintain the level of continuous effector cell production necessary to maintain minimal levels of immune competence. With respect to the former, it has been shown that the secondary lymphoid tissue microenvironments that support T_{CM} cell homeostasis are damaged by the ongoing inflammation associated with progressive infection, with the highly organized reticulin structure of the sites replaced by disorganized scarring (55, 56). Such microenvironmental destruction would limit T_{CM} cell access to IL-7, resulting in a reduction in the size of the total body T_{CM} cell population that can be maintained (39). It has also been suggested that over time, T_{CM} cells undergo proliferative senescence due to telomere shortening, resulting in an inability to maintain the cell division necessary to keep the population from declining. It remains controversial whether telomere shortening actually occurs in the $CD4^+$ T_{CM} cells responsible for maintaining $CD4^+$ memory T-cell homeostasis or whether induction of telomerase maintains the proliferative potential of this population (57–59).

If microenvironment destruction and/or proliferative senescence were solely responsible for $CD4^+$ T_{CM} cell homeostatic failure, the expectation would be that as HIV or SIV infections progress to AIDS, there would be an absolute limitation in $CD4^+$ memory T-cell regeneration, even if viral replication were suppressed. This does not seem to be the case, as anti-retroviral therapy of end-stage infections can result in a rapid burst of regeneration (60–63)(Fig. 3A,B). Thus, dysregulation of homeostatic mechanisms almost certainly plays a major role in disease progression. Negative regulators such as the programmed death-1 receptor (PD-1) is highly expressed on $CD4^+$ and $CD8^+$ memory T cells in chronic HIV and SIV infection as a consequence of persistent viral replication and hyperimmune activation (64–67). While it is generally appreciated that engagement of PD-1 and other negative regulators with their ligands dampens T-cell receptor-mediated signaling and activation, downmodulating pathogen-specific T-cell responses (64, 68), it is possible that these negative regulators have a more generic effect on the homeostasis of the memory compartment. Indeed, antibody-mediated blockade of the PD-1 pathway in chronically SIV-infected RMs induces robust $CD4^+$ T_{CM} cell proliferative responses and an increase in $CD4^+$ memory T-cell numbers, indicating that these pathways strongly inhibit $CD4^+$ T_{CM} homeostasis (Okoye, *et al.*, manuscript in preparation). Induction of negative regulator expression by $CD4^+$ T_{CM} cells is not the only mechanism by which chronic immune activation might dysregulate $CD4^+$ T_{CM} cell homeostasis. The proinflammatory cytokines associated with this immune activation drive effector differentiation (69–72), and by this mechanism lead to an imbalance between $CD4^+$ T_{CM} cell renewal and T_{CM} to T_{EM} cell differentiation, ultimately leading to smaller $CD4^+$ T_{CM} populations and an overall reduction in effector cell production.

Dysregulation of CD4^{+} T-cell functional heterogeneity

Up to this point, we have discussed mechanisms leading to depletion of the overall CD4^{+} T-cell memory compartment. Of course, the CD4^{+} memory T-cell population is not functionally homogenous but rather is comprised of a number of distinct subsets, Th1, Th2, Th17, T-follicular helper (Tfh), and T-regulatory (Treg), among others, with highly specialized immunologic functions and differing requirements for homeostasis and regeneration. These subsets differentially contribute to host defense against a wide variety of invading pathogens as well as prevention of autoimmunity by regulating tolerance to self-antigens, and a functional deficiency in any one of them could potentially lead to immune insufficiency or other immunopathology. Thus, to understand the mechanisms responsible for progression to AIDS, it is necessary to understand the impact of viral replication and immune activation not only on the overall CD4^{+} memory T-cell compartment but also on the dynamics and homeostasis of each of these functional CD4^{+} memory T-cell subsets, with particular attention to the effect of infection on the specific factors that mediate development and maintenance of these subsets.

CD4^{+} Th17 cells are important mediators in the hosts′ defense against extracellular pathogens such as bacteria and fungi, and in the intestinal mucosa, these cells are associated with maintaining the integrity of the gut epithelial barriers. They are characterized by expression of the transcription factor retinoic acid-related orphan receptor-γt (RORγt) and secretion of the IL-17 family of cytokines. Th17 cells promote neutrophil recruitment and induce the production of antibacterial defensins. They also promote tissue repair by inducing the proliferation and survival of epithelial cells (73). Th17 cells appear to play a central role in HIV pathogenesis (74). They are susceptible to direct viral infection *in vitro* and *in vivo* and the massive loss of CD4^{+} memory T cells from the gut early after infection results in significant alterations in CD4^{+} Th17 homeostasis. CD4^{+} Th17 cells are depleted in HIV-infected patients, resulting in a skewing in the fraction of CD4^{+} memory T-cell subsets in the gut from a Th17 to more of a Th1 phenotype (75). Studies in NHPs have shown similar results. In healthy animals, the fractions of Th17 cells are higher in mucosal tissues (lung, colon, jejunum) than in the blood or peripheral lymph nodes. However, after SIV infection, the fraction of Th17 cells in the gut decrease significantly and are never restored. As the infection progresses, CD4^{+} Th1 cells become the dominant population in the gut mucosa (75, 76). These observations suggest that the conditions of CD4^{+} memory T-cell regeneration in HIV/SIV infection are not conducive to Th17 regeneration, leaving infected individuals with persistent defects in the functions mediated by this subset. Besides increasing susceptibility to bacterial and fungal infections, loss of this subset may compromise intestinal mucosal integrity, increasing permeability to microbial products and contributing to the chronic immune activation that drives pathogenesis (51, 77, 78).

Another CD4^{+} helper T lineage subset of primary importance to HIV pathogenesis are Tfh cells. Tfh cells interact with antigen-specific B cells within specialized structures known as germinal centers (GCs) of secondary lymphoid tissues. This interaction enhances antibody affinity maturation and the differentiation of follicular B cells into long-lived memory B cells and/or plasma cells. Crucial to Tfh cell development is the expression of the transcription factor Bcl-6. They are further characterized by expression of the chemokine receptor CXCR5, PD-1, ICOS, and IL-21 secretion. Tfh cells are predominantly located within secondary lymphoid tissues (e.g. lymph nodes, spleen, tonsils, Peyer′s patches) (79, 80). A number of groups have recently shown significant alterations in Tfh cell dynamics in HIV and SIV infection. Like Th17 cells, Tfh are susceptible to infection *in vivo* and can support active viral replication and production *in vitro* (81, 82). Localization within secondary lymphoid tissues exposes them to high concentrations of HIV particles that are trapped within GC resident follicular dendritic cells (FDCs) in the form of immune

complexes (with antibody and/or complement) (83). FDCs also play a role in recruiting and retaining antigen-specific Tfh cells within the GC (84). Our group has recently shown that the persistence of live attenuated SIVs (LAV) was associated with their ability to selectively replicate in CD4+ Tfh cells in lymph nodes. At necropsy, secondary lymphoid tissues contained significantly higher levels of cell-associated viral RNA and DNA than bone marrow or tissues from extra-lymphoid effector sites (jejunum, liver, and lung), suggesting lymph node-resident CD4+ Tfh cells serve as a sanctuary for LAV persistence (85). In chronic HIV infection, Tfh cells are enriched for HIV-specific cells and contain a high proportion of HIV DNA+ cells (81, 82). Interestingly, the fraction of Tfh cells in peripheral lymph nodes is significantly increased in HIV and pathogenic SIV infection (81, 86). It is not clear the extent to which this relative expansion of Tfh in infected individuals is due to the preservation of these cells from viral-mediated destruction or the selective expansion of these cells after infection, although both likely have a role. Increases in plasma IL-6, a proinflammatory cytokine that regulates Tfh differentiation, suggests IL-6-mediated signaling could play a role in driving Tfh differentiation and expansion in HIV/SIV infection (70, 86). Overall, these observations suggest that the ratio of Tfh to other CD4+ memory T-cell subsets within secondary lymphoid tissues is significantly skewed resulting in higher frequencies of Tfh with progressive infection (81, 82, 86, 87). In both HIV infection of humans and pathogenic SIV infection of RMs, expansion of Tfh cells was associated with increased gammaglobulinemia and a high frequency of GC B cells. Expansion of Tfh cells, which parallels the follicular hyperplasia and hypergammaglobulinemia observed early in infection, might predispose infected individuals to autoimmunity commonly associated with AIDS progression. Indeed, it has been shown that the generation of autoreactive antibodies targeting platelet glycoproteins, phospholipids, and T-cell antigens in SIV-infected macaques was associated with severe pathologic outcomes including the depletion of CD4+ T cells (88).

HIV/SIV infection also affects the dynamics of CD4+ Tregs. Tregs represent a regulatory subset within the CD4+ T-helper lineage involved in suppressing the activation, proliferation, and cytokine production of effector T cells. They are important in the maintenance of immune tolerance and the control of immune activation. Their differentiation is regulated by the transcription factor forkhead box protein 3 (Foxp3) and is characterized by expression of the α chain of the IL-2 receptor CD25, Foxp3, and low expression of the IL-7 receptor CD127. Tregs are susceptible to HIV infection *in vitro* and are rapidly depleted from the gut during acute infection resulting in a reduction in Treg suppressor activity (89). In chronic SIV infection, there is a progressive decline in absolute Treg cell counts in the blood. Animals with high plasma viral loads manifested low numbers of circulating Tregs. This depletion was not preferential but reflected the overall loss of CD4+ memory T cells (90). In HIV-infected patients, a higher frequency of Tregs was observed in the blood, despite an overall decline in CD4+ T-cell counts. These frequencies were mostly normalized and returned to baseline levels in patients on ART or individuals with elite control of viral replication (91, 92). These observations would suggest progressive HIV/SIV infection alters the dynamics of peripheral CD4+ T-cell subset distribution resulting in higher frequencies of circulating Tregs at the expense of other CD4+ helper T-lineage differentiation and subsequent production of their effector-differentiated progeny. In SIV-infected pigtail macaques, the onset of systemic immune activation and disease progression was associated with a loss in the balance between Th17 and Tregs during acute infection. This loss in the normal ratio of Th17/Treg was not observed in nonpathogenic SIV infection of African green monkeys (AGM) (93). HIV disease progression is also associated with a loss in Th17/Treg balance, which was linked with the induction of indoleamine 2,3-dioxygenase 1 (IDO1) (94). IDO1 is a rate-limiting enzyme for tryptophan catabolism that plays a role in maintaining immune tolerance. IDO1 is induced during inflammation by interferons (and other agents), and its activity has been linked with the induction of Foxp3

expression and Treg differentiation while subsequently suppressing Th17 development (95). Thus, as Th17 cells are progressively depleted during the course of HIV/SIV infection, increased IDO1 activity does not support their regeneration but instead favors a suppressor Treg phenotype. Apart from the negative effects associated with Th17 deficiency (as discussed earlier), higher frequencies of Tregs could lead to delayed or diminished virus-specific immune responses, potentially impairing the ability of the host to limit HIV or SIV replication, as well as effectively respond to developing OIs.

Dysregulation of CD4$^+$ memory T-cell homeostasis and immune reconstitution after anti-retroviral therapy

The advent of ART has dramatically improved the life span of HIV-infected individuals. These drugs are able to suppress viral replication to undetectable levels and significantly restore CD4$^+$ memory T cells in the blood, secondary lymphoid tissues, and extra-lymphoid effector sites. As viral replication is suppressed and chronic immune activation is resolved, at least in part, it is still unclear whether the homeostatic mechanisms associated with regulating CD4$^+$ memory T-cell homeostasis are fully normalized in patients on ART. As previously discussed, end-stage disease is often characterized by the severe depletion of optimal target cells (CCR5$^+$CD4$^+$ memory T cells) and a decline in the CD4$^+$ T$_{CM}$ proliferative response to below a crucial threshold required to maintain CD4$^+$ T$_{EM}$ in extra lymphoid effector sites (22). However, even at this stage of disease, ART induces a burst in CD4$^+$ memory T-cell regeneration with the production of new tissue homing CCR5$^+$CD4$^+$ T$_{EM}$ cells. This regenerative response is not solely due to suppression of direct virus-mediated cytopathicity, as CD8$^+$ memory T cells, which are resistant to infection and depletion, can also respond to ART (47) (Fig. 3C). In a large fraction of HIV-infected individuals, however, ART fails to effectively reconstitute CD4$^+$ T cells to pre-infection levels despite fully suppressed viral replication (96, 97). Although the mechanisms for this are unclear, recent evidence suggests that initiation of therapy during primary infection rather than later in chronic infection significantly improves the prospects for enhanced immune recovery. Patients treated within the first 4 months of infection significantly correlated with higher restoration of CD4$^+$ T-cell counts (>900cells/ml) in the blood (98). Interestingly, initiation of ART within this early (<4 month) time period coincided with the spontaneous restoration of CD4$^+$ T-cell counts observed in HIV-1-infected patients who were not receiving therapy. However, in patients who were not on ART, CD4$^+$ T-cell counts initially rebounded but then progressively declined. Patients who initiated ART in chronic infection were less likely to have enhanced CD4$^+$ T-cell recovery. In a different study, patients treated for 48 weeks with ART in primary infection were less likely to progress to disease (or have CD4$^+$ T-cell counts drop below 350 cells/ml) than patients treated for just 12 weeks or no treatment at all (99). Overall, these observations suggest that CD4$^+$ T-cell regenerative potential declines over time in untreated infection, likely due to the destructive effects of viral replication and chronic immune activation on cell substrates, homeostatic microenvironments, and the balance of regulatory mechanisms regulating CD4$^+$ memory T-cell regeneration. This concept would argue that early intervention aimed at preserving CD4$^+$ T$_{CM}$ cell regenerative capacity should lead to improved CD4$^+$ T-cell recovery and better long-term immune function in ART-treated subjects. This idea is supported by data showing that low CD4$^+$ T-cell nadir (baseline CD4$^+$ T-cell counts before ART) has been implicated with incomplete immune recovery after ART (100). In addition, Lederman *et al.* (101) showed that patients with immunologic failure (CD4$^+$ T-cell counts < 350 cells/ml) had diminished CD4$^+$ T$_{CM}$ and T$_{EM}$ cell populations, with high turnover rates and increased levels of immune activation despite suppressive ART. It is important to note that other factors such as age, ongoing viral replication (possibly due to viral sanctuaries), and duration

of therapy have also been linked to immune reconstitution in HIV-infected patients (97). Dysregulation in $CD4^+$ T cell homeostasis appears to be a key contributor to this process.

Viral persistence during optimally suppressive ART has also been linked with $CD4^+$ T-cell homeostasis. The major barrier to eradication of HIV is thought to be the pool of latently infected, long-lived, resting $CD4^+$ memory T cells, including both $CD4^+$ T_{CM} and T_{TrM} cells, that constitute the major cellular reservoirs for HIV persistence in patients on ART (102). Thus, the maintenance of the viral reservoir is intimately linked with the regulation of $CD4^+$ T_{CM} and T_{TrM} homeostasis. Homeostatic proliferation of these latently infected cells might lead to the regeneration and maintenance of the viral reservoir without cell death. Interestingly, it has been shown that patients with low $CD4^+$ T-cell nadir manifest the highest levels of cell-associated HIV-1 DNA (103). This observation suggests that the level of $CD4^+$ T-cell depletion prior to initiating therapy plays a role in determining the size of the viral reservoir. In addition, virally suppressed patients on long-term ART with low $CD4^+$ T-cell counts (<350 cells/ml) had significantly higher levels of cell-associated HIV RNA and proviral DNA than patients with high $CD4^+$ T-cell counts after therapy. Interestingly, patients with low $CD4^+$ T-cell counts had higher levels of PD-1 expression, predominantly in the $CD4^+$ T_{CM} compartment (104). These observations suggest that the homeostatic mechanisms associated with $CD4^+$ T-cell regeneration have a significant effect not only on the ability to reconstitute immunity after ART but also on the HIV reservoir that maintains infection and hinders therapies aimed at HIV cure.

Concluding remarks

The development of AIDS in untreated HIV and pathogenic SIV infection has the paradoxical quality of being a slowly progressive pathogenetic process involving rapid, highly dynamic mechanisms, a continuously ′negotiated′ balance between direct and indirect effects on HIV/SIV replication that compromise $CD4^+$ memory T-cell survival or function and the ability of the host to replace these lost cells and maintain $CD4^+$ memory T-cell populations by cell proliferation and differentiation. This process leaves its imprint on all clinical aspects of HIV/SIV infection, including the degree to which immunity does or does not normalize after viral suppression with ART and the dynamics of the HIV reservoir in ART-treated subjects. A better understanding of these mechanisms and the development of approaches for their therapeutic manipulation will be critical for management of subjects for whom viral replication cannot be controlled, as well as the development of cure strategies for individuals whose infections are controlled by ART.

Acknowledgments

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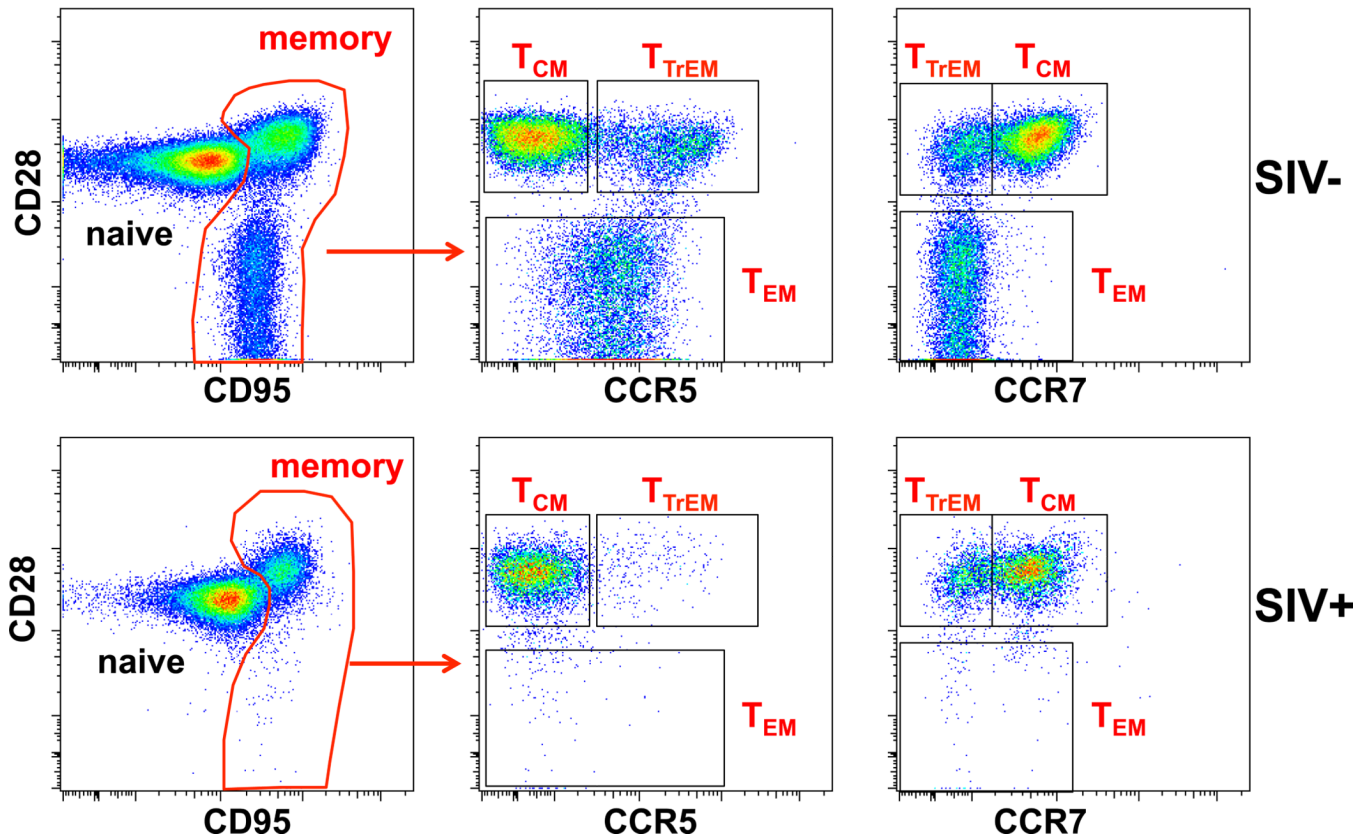
Fig. 1. CCR5$^+$CD4$^+$ memory T cells are primary targets for HIV/SIV
The figure shows CD28 versus CCR5 or CCR7 on gated CD4$^+$ memory (CD95$^+$) T cells from the peripheral blood of a healthy normal RM (SIV$^-$) and the same animal during chronic infection with the CCR5-tropic SIVmac239. CCR7 downregulation and CCR5 upregulation are key phenotypic markers of T$_{TrM}$ and T$_{EM}$ differentiation and therefore constitute prime HIV/SIV targets. In contrast, CD4$^+$ T$_N$ and T$_{CM}$ are CCR7$^+$ and CCR5$^-$, making them inefficient targets for CCR5-tropic HIV and SIV. Regeneration of depleted CD4$^+$ T$_{EM}$ compartments is dependent on continuous recruitment of new cells from their CD4$^+$ T$_{CM}$ precursors.

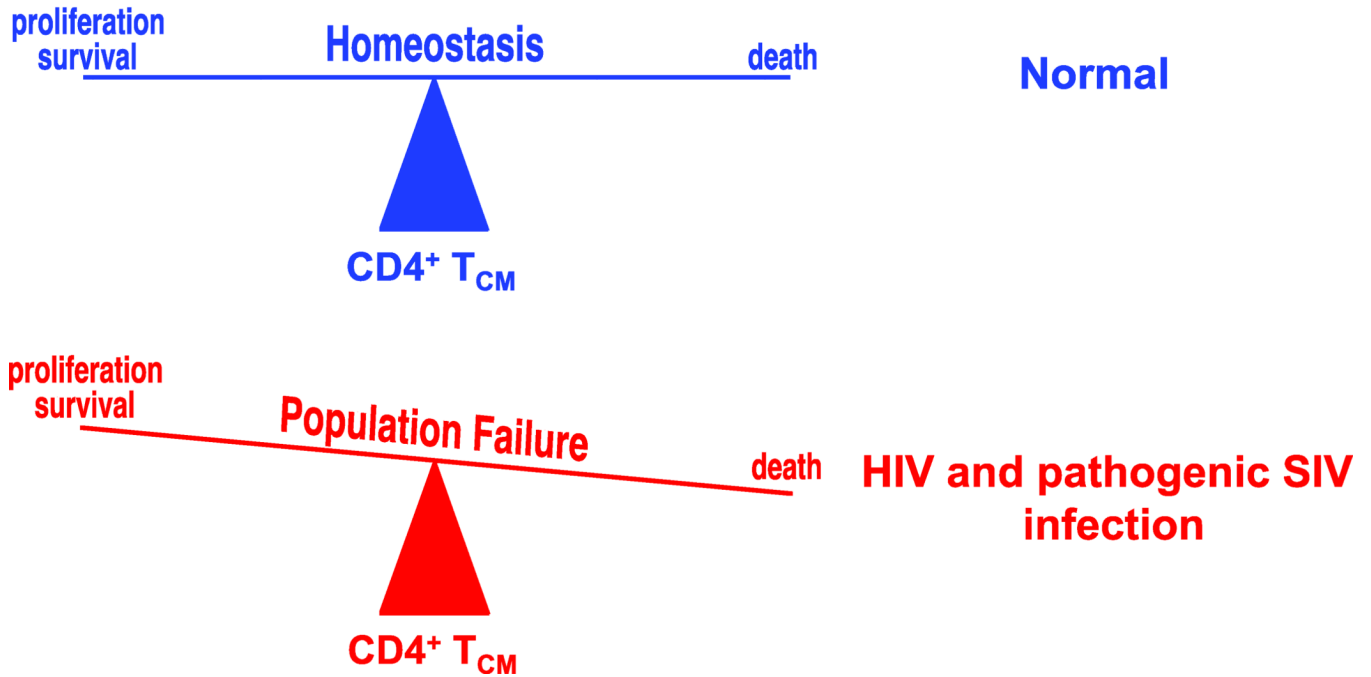# CD4+ T$_{CM}$ population dynamics

Fig. 2. CD4$^+$ TCM homeostasis is dysregulated in progressive HIV/SIV infection
In normal (healthy uninfected) individuals, proliferating cells are predominantly long-lived, while effector site CD4$^+$ T$_{EM}$ populations are stable and maintained at levels required for effective immune function. In progressive HIV/SIV infection, immune activation drives a high turnover process that produces short-lived cells. As the regenerative CD4$^+$ T$_{CM}$ cell population slowly diminishes over time, it precipitates the decline in production and influx of new CD4$^+$ T$_{EM}$ cells below a crucial threshold required to keep OIs at bay. Thus, progressive failure of CD4$^+$ T$_{CM}$ homeostasis and its consequent inability to produce new T$_{EM}$ cells plays a major role in setting the tempo of disease progression and the timing to overt immunodeficiency and AIDS.
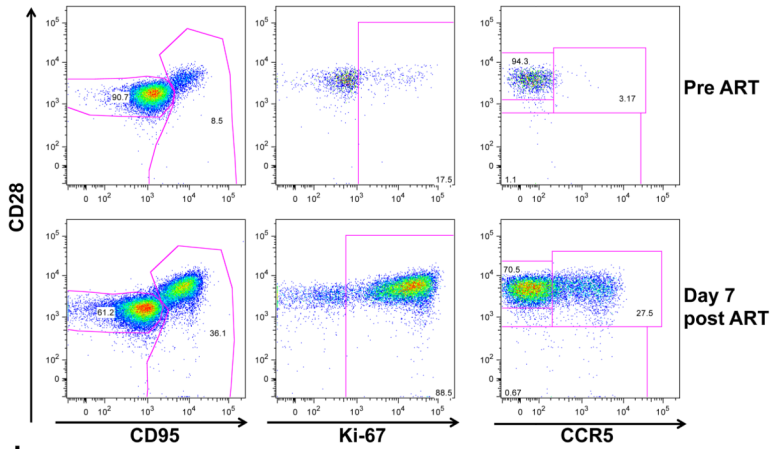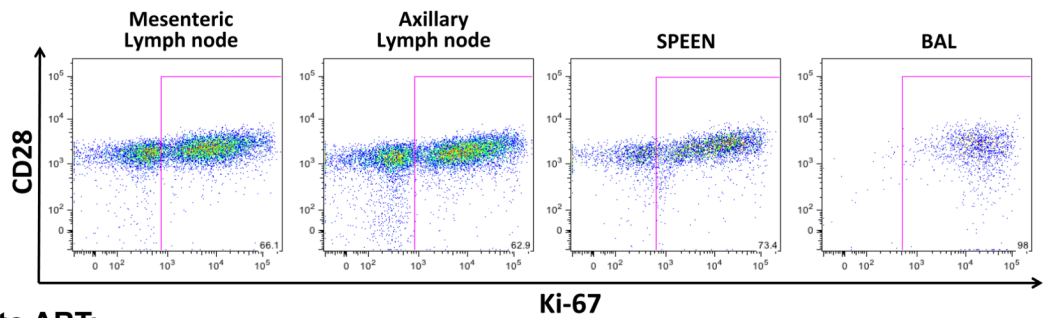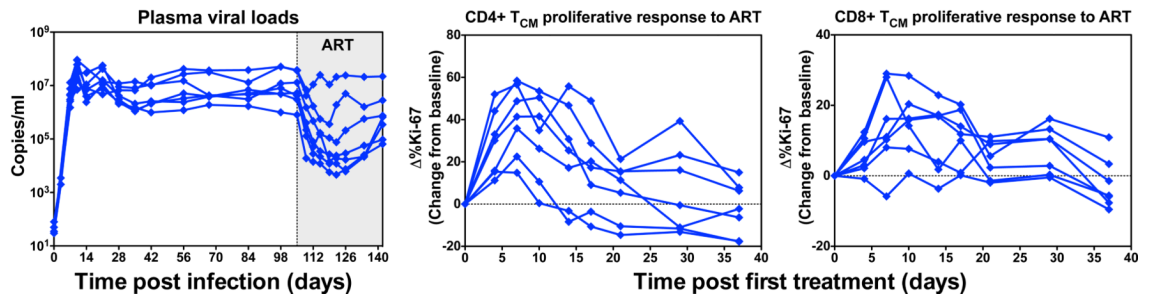
(a) CD4+ T cell gated:

(b) CD4+ memory T cell gated:

(c) Response to ART:

Fig. 3. CD4$^+$ memory T-cell regenerative capacity can be restored with ART even at end-stage disease

At end-stage disease, the total CD4$^+$ memory T-cell proliferative response declines below a crucial threshold that typically signals the failure of the CD4$^+$ T$_{CM}$ regenerative potential and subsequent effector site CD4$^+$ T$_{EM}$ population collapse. (A) Administration of ART leads to a robust proliferative burst in CD4$^+$ T$_{CM}$ cells in the peripheral blood of an RM at end-stage disease. (B) This proliferative response is also observed in secondary lymphoid tissues (spleen, axillary and mesenteric lymph nodes) and results in the influx of new CD4$^+$ T$_{EM}$ cells into extra-lymphoid effector sites (such as the BAL). (C) Administration of partially suppressive ART to chronically SIVmac239-infected RMs induces proliferative responses in both CD4$^+$ T$_{CM}$ and CD8$^+$ T$_{CM}$ cells in the peripheral blood.