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Immune activation and HIV persistence: Implications for curative approaches to HIV infection

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Summary

Despite complete or near-complete suppression of human immunodeficiency virus (HIV) replication with combination antiretroviral therapy, both HIV and chronic inflammation/immune dysfunction persist indefinitely. Untangling the association between the virus and the host immune environment during therapy might lead to novel interventions aimed at either curing the infection or preventing the development of inflammation-associated end-organ disease. Chronic inflammation and immune dysfunction might lead to HIV persistence by causing virus production, generating new target cells, enabling infecting of activated and resting target cells, altering the migration patterns of susceptible target cells, increasing the proliferation of infected cells, and preventing normal HIV-specific clearance mechanisms from function. Chronic HIV production or replication might contribute to persistent inflammation and immune dysfunction. The rapidly evolving data on these issues strongly suggest that a vicious cycle might exist in which HIV persistence causes inflammation that in turn contributes to HIV persistence.

Keywords

AIDS; immunodeficiency diseases; dell activation; cell differentiation; cell proliferation; inflammation

Introduction

With the recent optimization of antiretroviral drugs, most motivated human immunodeficiency virus (HIV)-infected patients with access to therapy can achieve durable and perhaps life-long viral suppression. Although these drugs improve quality of life, prevent acquired immunodeficiency syndrome (AIDS), and reduce overall mortality, they do not fully restore health. Treatment-mediated immune reconstitution is often incomplete, even after many years of viral suppression (1–3). Inflammation and T-cell activation remain elevated, and $CD4^+$ T-cell counts often fail to achieve normal levels (4–8). Limited immune reconstitution is particularly notable in mucosal lymphoid tissues (9–14) and may result in a diminished capacity of the adaptive immune system to function effectively (15, 16). As

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compared to age-matched uninfected adults, treated HIV-infected adults have higher risk of developing a number of non-AIDS-related non-immunological diseases, including cardiovascular disease, cancer, kidney disease, liver disease, neurologic disease, and bone diseases (17). Some (but not all) studies have argued that the life-span of the typical long-term treated adult is not normalized by effective combination antiretroviral therapy. Chronic immune dysfunction, immune activation, and inflammation predict and likely contribute to this excess risk of morbidity and mortality (18–23). Defining the mechanisms for persistent inflammation during combination antiretroviral therapy is key question for the field.

Many factors contribute to persistent inflammation and immune dysfunction during therapy in HIV-infected individuals. Deposition of collagen in lymphoid organs during untreated disease causes irreversible tissue fibrosis, which likely contributes to failed T-cell homeostasis (12, 24), persistent immunodeficiency, excess levels of various pathogens such as cytomegalovirus (CMV) (25), destruction of mucosal surfaces (26), and persistent inflammation all likely contribute to ongoing dysfunction. HIV-associated mucosal immune dysfunction and loss of immunoregulatory mucosal cells such as interleukin-17 (IL-17)-producing cells also likely persists during therapy, leading to failed control of microbial translocation and consequent persistent inflammation (27–30). Although less well-studied, traditional risk factors such as central obesity, treatment-mediated effects on metabolism leading to the metabolic syndrome, and substance abuse likely also contribute to inflammation during combination antiretroviral therapy.

One of the more controversial areas in HIV medicine pertains to the association between persistent HIV infection and chronic inflammation during long-term effective antiretroviral therapy (where effective is defined as having maintained undetectable plasma HIV RNA levels using conventional assays for several years)(31). As outlined in detail below, a positive correlation exists between measures of immune activation (particularly those based on $CD4^+$ T-cell phenotype) and HIV persistence (as measured in cells and tissues) among long-term treated adults. Whether immune activation is a cause, a consequence, or both a cause and a consequence of HIV persistence is unknown. Understanding the mechanisms for this association could lead to the optimization of strategies aimed at curing HIV infection and/or at reducing inflammation-associated disease. In this review, we summarize what is known about immune activation and HIV persistence during antiretroviral therapy and describe ongoing studies in humans and non-human primates that examine how the virus and immune system interact once treatment-mediated control of HIV replication is achieved.

Pathogenesis of HIV-associated immune activation

The central role of immune activation in HIV disease progression was noted in the earliest observations of the clinical disease (32) (Fig. 1). In the 1990s, Janis Giorgi and her colleagues (33) performed seminal work which argued that HIV-associated alterations in T-cell phenotype (as defined by expression of ‘activation’ markers such as CD38 and HLA-DR) predicted disease progression independently of other factors. After the resolution of primary infection, an apparently steady-state level or ‘set-point’ of T-cell activation is achieved; this level predicts the rate of $CD4^+$ T-cell decline (34). Importantly, as the level of T-cell activation is strongly and consistently correlated with level of HIV replication during untreated disease, defining with precision the independent effects of T-cell activation on outcome has been challenging (35). Perhaps the strongest evidence that the inflammatory response to the virus is a critical determinant of pathogenesis comes from study of natural host for the simian version of the virus (SIV). Although SIV replication is high in these animals, immune activation/inflammation and disease progression are both limited. Preservation of central memory $CD4^+$ T cells due to low CCR5 expression, rapid downregulation of type interferon I response post-infection, preservation of lymphoid

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tissues, maintenance of mucosal barrier integrity, and lower tissue burden of virus are consistent correlates of protection in these models (36–38). Indeed, all of these factors can be a cause or effect (or both) of chronic immune activation and disease progression in untreated HIV infection and thus likely underlie lack of disease progression in natural hosts.

In untreated HIV disease, there is a striking and consistent association between activation of T cells and plasma HIV RNA levels. In some studies, the association between viremia and T-cell activation is more consistent in $CD8^+$ T cells than in $CD4^+$ T cells, while the peripheral $CD4^+$ T-cell count is a more consistent predictor of $CD4^+$ T-cell activation (39–42). These latter observations have been used to argue that viremia drives $CD8^+$ T-cell activation directly, while homeostatic signals associated with low $CD4^+$ T-cell counts upregulate certain markers on circulating $CD4^+$ T cells.

The expression of many of the negative regulators of T-cell activation such as programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) is also strongly correlated with viremia (43–50), while in other studies the frequency of forkhead box protein 3 $(FoxP3)^+$ and T-regulatory (Treg) cells are correlated with viremia (28, 29, 50, 51). As is common in these types of studies, it is impossible to define whether HIV replication drives an immunoregulatory response or whether the immune-suppressive effects of these responses causes increased viremia, perhaps by preventing an effective HIV-specific immune response. Untreated HIV infection is also associated with activation and dysregulation of B cells (52–58). B-cell dysfunction prevents optimal antibody production in both primary and secondary immune responses, leading to compromised responses to infection and vaccination (52, 54, 57, 59). Furthermore, innate cells such as natural killer (NK) cells, dendritic cells, macrophages, and other key regulators of immune function are also affected by HIV infection and may underlie the high plasma levels of proinflammatory cytokines and biomarkers observed during infection (60). Indeed, monocytes and macrophages have been shown to be hyper-activated and have reduced propensity for phagocytosing pathogens such as bacteria, further promoting microbial translocation and activation (58, 61, 62). Altered dendritic cell subsets have also been observed during HIV infection, including abnormal plasmacytoid and myeloid dendritic cells, and (in some studies) loss of mucosal $CD103^+$ dendritic cells (27, 63, 64). NK cells are also dysfunctional with both altered cytokine production and homing to tissues observed in HIV-infected individuals (64–66).

A major driver of immune activation and dysfunction during HIV infection is damage to the mucosal barriers and lymphoid structures (Fig. 1). Densely populated CCR5-expressing $CD4^+$ T cells in the gastrointestinal tract are likely the preferred infection targets of HIV/SIV during early stages of the infection (9, 11, 13, 67–71). HIV/SIV-associated breaches in the tight epithelial barrier of the gastrointestinal tract allows microbial products to translocate across the barrier, resulting in local and systemic activation (27, 61, 72–75). This local activation in the GI tract contributes to increased numbers of inflammatory cells such as plasmacytoid dendritic cells (pDCs), neutrophils, and monocytes and decreased numbers of cells that are essential for mucosal regulation, including IL-17 and IL-22-producing lymphocytes and $CD103^+$ dendritic cells (27, 63, 64, 76–78). The loss of IL-17 and IL-22-producing $CD4^+$ T cells may be particularly problematic, as these cells regulate epithelial homeostasis and thus loss of these subsets likely directly contributes to breakdown of the mucosal barrier (27, 30, 79–85).

In addition to direct infection, a major mechanism underlying lack of reconstitution of $CD4^+$ T cells activation-induced collagen deposition in lymphoid tissues (12, 24) (Fig. 1). Thus, the vicious cycle of HIV replication and immune activation induces and maintains mucosal immune dysfunction during HIV infection, which further drives systemic activation.

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Inflammation and immune activation during combination antiretroviral therapy

The level of T-cell activation declines rapidly and durably during combination antiretroviral therapy but rarely achieves a normal steady state (5, 86). Although the frequency of HLA-DR and CD38-expressing T cells is a strong predictor of disease progression in untreated disease, the clinical implications of these cells during treated disease remains largely undefined, although some studies have suggested they retain some prognostic significance (20, 87). The immunologic profile of circulating T cells during effective antiretroviral therapy is also often characterized by lower than normal expression levels of CD28, elevated levels of CD57 and elevated levels of PD-1, a profile that is consistent with T-cell 'senescence' and dysfunction (87–91).

Data on B-cell and innate cell activation during combination antiretroviral therapy is not as complete as in untreated infection. While partial functional restoration may occur during treatment, these immune cells are still clearly dysfunctional compared to uninfected individuals. Indeed, NK cells remain activated despite virus suppression by combination antiretroviral therapy, and defective antibody-dependent cell-mediated cytotoxicity (ADCC) signaling by NK cells persists during treatment (92). Monocyte dysfunctions also persist despite treatment, whereby monocytes maintain decreased phagocytosis and resemble those isolated from elderly individuals, even in very young patients (93). Furthermore, sCD163, a marker of monocyte activation, remains elevated despite combination antiretroviral therapy and is associated with increased risk for atherosclerosis (94, 95). During treatment, the numbers and function of pDCs and mDCs remain altered as well, and plasma factors have been demonstrated to contribute to dsyfunctionality despite long-term combination antiretroviral therapy (96, 97). Finally, it has been demonstrated that even during long-term combination antiretroviral therapy treatment, innate responses to other pathogens, such as malaria, remain dysfunctional (98).

There has been a recent shift in clinical research from studies focused on T-cell phenotype to studies focused on plasma biomarkers of inflammation. This shift occurred in part because the number of clinical events in HIV-infected patients has declined, making it difficult for those cohorts which store peripheral blood mononuclear cells (PBMCs) to define with adequate power the role of T-cell activation and/or dysfunction during therapy in predicting subsequent morbidity and mortality. Also, the biology of chronic inflammation during treated disease is almost certainly unique from that in untreated disease. Many of the biomarkers that seem to be most strongly associated with disease progression in the modern era reflect innate immune activation [e.g. IL-1, IL-6, tumor necrosis factor (TNF), C-reactive protein](18, 19, 99). Markers specific to monocyte activation and/or microbial translocation (e.g. soluble CD14, CD163) and the coagulation cascade (D-dimers, fibrinogen) are also consistent correlates or predictors of disease (18, 19, 94, 99–108). Long-term effective combination antiretroviral therapy reduces many of these markers, but the treatment effect is less consistent than that observed with T-cell activation outcomes, suggesting factors other than HIV replication contribute to those pathways associated with these biomarkers (109–111).

Mechanisms for HIV persistence during antiretroviral therapy

Several non-mutually exclusive mechanisms underlie HIV persistence in adults who have received suppressive combination antiretroviral therapy for extended periods of time. The best characterized and potentially the most paramount mechanism for persistence is the generation and maintenance of a 'silent' provirus in resting memory CD4+ T cells (112–114). The memory $CD4^+$ T-cell compartment where HIV largely resides is heterogeneous. Using markers such as CD45RA (a tyrosine phosphatase), CCR7 (a lymph node homing receptor), and CD27 (a member of the TNF superfamily critical for the long term

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maintenance of immunological memory)(115, 116), it has been possible to demonstrate that HIV primarily persists in three memory T-cell subsets endowed with distinct functional and survival capacities, namely central memory (T_{CM})($CD45RA^{-}CCR7^{+}CD27^{+}$), transitional memory ($T_{TM}$)($CD45RA^{-}CCR7^{-}CD27^{+}$) and effector memory ($T_{EM}$) ($CD45RA^{-}CCR7^{-}CD27^{-}$) $CD4^{+}$ T cells (117).

The distinct T-cell subsets which harbor HIV have unique functional and phenotypic properties, suggesting that cellular reservoirs might support viral persistence through different mechanisms. For instance, the drastic differences in the activation status of T_{CM} and T_{EM} cells (115, 117) suggest that the former may represent an ideal reservoir for latent HIV, whereas the latter may be more prone to support residual levels of viral replication in the face of combination antiretroviral therapy. In one study, approximately 85% of the circulating cells harboring integrated HIV DNA displayed a T_{CM} or a T_{TM} phenotype, with T_{EM} representing only 15% of the pool of latently infected cells. The distribution of virus in mucosal T-cell subsets is less well-characterized. The rate at which these unique cell populations decay during therapy is unknown, but the total resting memory cell reservoir decays slowly, with an estimated half-life in chronically infected adults of 40 to 44 months, indicating that more than 70 years of intensive therapy would be required for its eradication (118).

Other reservoirs for HIV persistence have been described, but their contribution after many years of effective antiretroviral therapy is less certain. Naive $CD4^{+}$ T cells, macrophage/monocytes, astrocytes, and microglial cells are possible reservoirs (31). Most of these cellular and tissues reservoirs which persist during therapy are assumed to have been generated prior to treatment. As outlined in detail below, there are some emerging data that suggest that the suppression of viral replication by combination antiretroviral therapy may be incomplete in some if not most individuals. Theoretically, low-level replication allows the continuous replenishment of a small pool of infected cells (119).

Association between immune activation and HIV persistence during therapy

The association between HIV burden and immune activation during effective therapy remains controversial. Progress in untangling this association has been limited by the lack of well-validated measures of viral load during effective therapy. HIV RNA can often be detected in the plasma of individuals receiving antiretroviral therapy, but the levels are very low (i.e. 0.1 to 5 copies RNA/mL) and near the limit of quantification for even the most sensitive assays. HIV can often be more easily detected in cells residing in lymphoid and mucosal tissues, but such tissues are hard to access, and it is unclear as to whether one should measure the frequency of virus in all cells, in all $CD4^{+}$ T cells, or in all resting memory $CD4^{+}$ T cells.

Despite these limitations, a number of consistent trends have emerged. There appears to be no consistent association between T-cell activation (as defined by CD38 and HLA-DR expression) and the level of HIV RNA in plasma during effective therapy. Although some small studies have suggested a positive correlation (120), the vast majority of studies have found no association (89, 121–125). These observations suggest that T-cell activation is unlikely to be major determinant of plasma HIV RNA levels and that whatever process causes release of HIV RNA into plasma is not related to a quantifiable level of activated T cells circulating in blood; also, these observations suggest that HIV production is probably only a minor determinant of the level of residual T-cell activation that is observed during treatment.

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In contrast to the largely negative associations between T-cell activation and viremia in treated disease, there is a consistent association between T-cell activation and level of cell-associated HIV DNA or HIV RNA (89). This effect may be even more apparent in tissues, where the majority of the virus resides (126–129). Other markers of T-cell activation and dysfunction that remain elevated despite long-term effective therapy include PD-1 and CTLA-4 (89, 130). A positive correlation between PD-1-expressing $CD4^+$ T cells and frequency of infected cells has also been noted in a few studies (89, 117).

Immune activation as a cause of HIV persistence during therapy

The mechanism for the consistent association between T-cell activation and cell-associated HIV burden during therapy is not known. Indeed, it is not clear if higher levels of T-cell activation cause higher levels of HIV burden or whether higher viral burdens cause higher levels of immune activation. As outlined in this and the following sections, it is likely that the both pathways are active during treated disease, and that a 'vicious cycle' might exist during treatment that results in maintenance of both immune activation and HIV persistence (Fig. 2).

Inflammation and target cell generation

Theoretically, persistently high levels of $CD4^+$ T-cell activation during combination antiretroviral therapy may contribute to HIV persistence by continuously providing a pool of cellular targets for the virus to infect (131–133)(Figs 2 and 3). The recent observation that $CD8^+$ T-cell activation during effective therapy predicts subsequent episodes of low-level detectable viremia is generally consistent with this possibility (125). In one early study of long-term treated adults, higher levels of HIV DNA were found in activated compared to resting $CD4^+$ T cells; phylogenetic analyses suggested ongoing rounds of *de novo* infection events between these distinct populations (134). Similarly, it has been argued that the continuous production of HIV antigens from any cell source may lead to the generation of activated HIV-specific $CD4^+$ T cells, which are being continually primed to migrate to foci of virus production, thereby providing the virus with a potential source of target cells. Although experimental data from such a model is lacking during treated disease, there are data from untreated individuals, which support this possibility (135, 136).

While resting $CD4^+$ T cells are resistant to *in vitro* infection by HIV compared to activated $CD4^+$ T cells, resting memory $CD4^+$ T cells with integrated HIV DNA can be stimulated *ex vivo* and presumably *in vivo* to produce infectious virions (137–140). Multiple inflammatory stimuli can cause production of virus from resting cells, including many known to be elevated during treated HIV disease such as IL-2, TNF, IL-6, IL-12 and IL-18 (141–144). Furthermore, exposure to a combination of certain chemokines (i.e. CCL19 and CCL21) renders resting $CD4^+$ T cells susceptible to infection and the establishment of latency *ex vivo* (144, 145). Many of these pro-inflammatory stimuli are known to remain elevated during treated HIV disease. While the role of these cytokines and chemokines in promoting infection and generation of latency *in vivo* is unknown, the increased permissibility to HIV infection that occurs on exposure to these cytokines/chemokines indicates that an inflammatory environment in the host might make $CD4^+$ T cells more susceptible to infection(146).

Many of the activated T cells during untreated and perhaps treated HIV infection target herpes viruses. CMV-specific $CD4^+$ and $CD8^+$ T-cell responses, for example, are much higher in HIV-infected adults than age-matched uninfected adults (147). If these cells are preferentially activated, then they may be more likely to become infected and hence enriched for HIV during untreated and eventually treated disease. In one recent survey of

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untreated men presenting with early HIV infection, the presence of detectable CMV in semen or PBMCs was associated with higher HIV DNA content in PBMCs (148).

Although many have argued that activation-induced production of virus from latently infected cells might lead to their destruction and ultimately a cure (149–152), this hypothesis is dependent on HIV-producing cells dying through some clearance mechanisms and on all susceptible target cells being protected by antiretroviral therapy. Both of these assumptions are now being challenged (153).

Inflammation and migration of target cells to sites of HIV spread

HIV/SIV spread to new target cells is likely localized, with virions only able to infect cells which are nearby (154) (Figs 2 and 3). This is likely to be particularly true when other factors such as strong immunity (as seen in elite controllers) or antiretroviral therapy place additional constraints on HIV replication. Indeed, it has been argued that any residual replication of HIV during potent antiretroviral therapy will be via direct cell-to-cell contact, which allows such high concentrations of spreading virions that standard concentrations of antiretroviral drugs in cells fail to inhibit replication (155). The finding that raltegravir intensification reduced HIV levels and inflammation in lymphoid tissue-rich ileum but not in blood is consistent with this emerging model of HIV persistence (127).

HIV-associated damage to the mucosal barrier causes localized inflammation in gastrointestinal tract tissues (27, 61, 74). This inflammation drives migration of T cells to mucosal tissues, where the higher concentration of activated target cells should make HIV replication more efficient (49, 156, 157). The concentration of highly-susceptible gut-homing activated$\alpha_4\beta_7^{high}$ $CD4^+$ T cells in mucosal surfaces likely contribute to development of an optimal environment for cell-to-cell spread (158, 159). Reduced penetration of certain antiretroviral drugs into these tissues might also allow localized rounds of HIV replication (160, 161). In addition, although the translocation of microbial products from a ‘leaky gut’ is reduced during antiretroviral therapy (26), abnormally high levels of bacterial products often persist and may contribute to HIV persistence by inducing production of pro-inflammatory cytokines known to enhance cell cycling and/or HIV replication (such as IL-1 and IFN)(129, 162). This may result in increased levels of residual viral replication and in the cycling of infected cells, thereby promoting viral spread and possibly persistence. Tissue-based studies of lymphoid tissue-rich areas of the gut will be needed to define the precise role of localized inflammatory environment in lymphoid structures of the gut as a cause of persistence.

Reeves and colleagues (163) have recently found that interferon-α-producing plasmacytoid dendritic cells (pDCs) accumulate in the gut mucosa during untreated SIV disease and that the level of viremia correlated with frequency of these cells (as defined by expression of retention integrinα4β7). They argued that pDC activation in mucosa might cause trafficking and retention of CCR5-expressing $CD4^+$ T cells to foci of localized inflammation (perhaps by secretion of MIP-1β and other chemokines), thereby enabling more efficient transmission of virus. Similarly, Favre and colleagues (28, 29) have found that activation of mDCs results in upregulation of indoleamine 2,3-dioxygenase (IDO) and a shift in local T-cell populations, with loss of Th17 cells (which protect against microbial translocation and regulate epithelial cell regeneration) and increased Treg cells (which have complex effects, including potentially blunting local clearance mechanisms for HIV and other pathogens). Activation of this complex pathway appears to contribute to ongoing microbial translocation, which in turn activates dendritic cells, resulting in ongoing cycles of localized inflammation. Consistent with these various observations, Chege and colleagues (68) observed persistent loss of duodenal Th17 cells during effective antiretroviral therapy. The loss of these cells was associated with higher levels of microbial translocation (as expected),

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while higher levels of microbial translocation (as defined by plasma lipopolysaccharide levels) was associated with higher levels of HIV DNA in gut. The observed correlation between markers of microbial translocation, T-cell activation, and HIV DNA levels in the gut of treated individuals is largely consistent with this model (126, 129). The critical role of location in driving the impact of inflammation on HIV persistence is well illustrated by recent studies of T-follicular helper cells (Tfh cells). These cells largely reside in the germinal centers of lymph nodes, are defined phenotypically by the expression of CXCR5, PD-1, and Bcl-6, produce high levels of IL-21, and regulate antibody development by nearby B cells. The chronic inflammatory response to SIV infection appears to drive the expansion and activation of these cells in lymph nodes (164). In untreated SIV and HIV disease, the frequency of activated Tfh cells appears to be expanded (165), and these cells appear to be enriched for HIV DNA (as compared to other $CD4^+$ T-cell populations)(57, 166, 167). The degree to which this process persists during long-term effective antiretroviral therapy is not known.

The theoretical model that inflammation-associated release of chemokines could lead to migration of $CD4^+$ T cells to these foci of inflammation was the rationale for at least one of the maraviroc intensification studies (168). Other interventions aimed specifically at addressing these mucosa-based pathways are in development, including the potential use of IDO inhibitors and inhibitors of the interferon-α pathway(169).

Inflammation and the immunoregulatory response

Successful integration of HIV DNA into genomes of resting memory T cells occurs very early during acute infection (170–172). Acute HIV infection is associated with a potent inflammatory response marked by the production of excess amounts of a number of pro-inflammatory cytokines, including interferon-α, interferon-γ, TNF, IL-6, IL-8, IL-15, and CXCL10 (173, 174). This inflammatory response causes a potent and sustained immunoregulatory response, with the production of cytokines such as IL-10 observed very early during acute infection (173). Treg cell numbers and responses also occur, which along with other cells release strong anti-inflammatory cytokines such as transforming growth factor-β (TGF-β). These immunoregulatory responses to chronic inflammation persist during untreated chronic infection and even during long-term effective antiretroviral therapy (175–177).

These anti-inflammatory responses may contribute to establishment and maintenance of latent infection. IL-10 might inhibit T-cell activation, allowing resting cells containing integrated DNA to persist indefinitely (178). Upregulation of negative regulators of T-cell activation, which are aimed at containing the inflammatory response and preventing tissue damage, may act to prevent recently infected cells from dying, leading to persistence. The observation that PD-1-expressing $CD4^+$ cells are enriched for HIV and associated with reservoir size is consistent with this hypothesis (89, 117). Inflammation-associated upregulation of Treg cells and local release of TGF-β may initiate a cascade of events in lymphoid tissues resulting in collagen deposition, lymphoid fibrosis, and irreversible immune dysfunction (179, 180), leading to a chronic inflammatory state and persistent HIV through multiple mechanisms outlined in this review.

Inflammation and dysfunction of adaptive and innate immune responses

Not all HIV-mediated immune responses are harmful. $CD8^+$ T-cell responses are the quintessential immune cell that protects from virus replication. Although HIV-specific cytotoxic activities are decreased or dysfunctional during chronic untreated disease, a small subset of individuals appear to effectively control their virus in the absence of therapy due to the generation and preservation of effective immunity (44, 181–184). Polyfunctional $CD8^+$

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T-cell responses and proliferation capacity are consistent correlates of virus control (185, 186). Certain 'protective' class I HLA alleles such as B5701 are highly enriched in controllers, providing strong evidence for positive role of active CTL activation in virus control (186–189), although HLA may be mediating its effect via other mechanisms, including directing the activity of NK cells and other immune responses (190, 191).

$CD4^+$ T-helper cell responses are also vital to adaptive immunity against infections. Although less well characterized than $CD8^+$ T-cell responses, HIV-specific $CD4^+$ T-cell function and proliferation seems to predict virus control in the absence of therapy (133, 192). This beneficial effect may be mediated through direct killing/control of the virus, or indirectly through enhanced $CD8^+$ T-cell and B-cell activities (53, 54, 57, 193). More recently, chronic activation and HIV/SIV infection of $CD4^+$ Tfh in lymphoid tissues has been recently demonstrated to result in dysfunctional B-cell responses (57, 194, 195).

Although the influence of the adaptive immune response on HIV replication in the absence of combination antiretroviral therapy has been extensively studied, surprising few studies have focused on the impact of these responses during therapy. In the early combination antiretroviral therapy era, a substantial proportion of treated patients failed to achieve complete viral suppression. Many of these 'virologic failures' were able to maintain partial suppression of viral replication for months to years, even as high-level drug resistance emerged. Strong HIV-specific $CD8^+$ and $CD4^+$ T cells were often present in such individuals, with levels that were in comparable to those observed in elite controllers, suggesting that the adaptive immune response could contribute to virus control virus when used with combination antiretroviral therapy (196–198).

There has as of yet been no comprehensive assessment of the role of HIV-specific immunity in determining the size of the reservoir during combination antiretroviral therapy. In one cross-sectional analysis of individuals of long-term treated adults with undetectable viremia who were enrolled in a treatment intensification study, strong HIV-specific $CD8^+$ and $CD4^+$ T cells (as defined by the co-expression of IL-2 and interferon-γ) in the rectal mucosa was associated with lower frequency of infected cells (122). T-cell vaccine-mediated reduction in frequency of infected cells in one study also argues that effective adaptive immunity during therapy may affect the size of the reservoir (199), perhaps because a greater than expected proportion of 'resting' cells make low levels of HIV proteins (200).

Another consequence of chronic inflammation that is likely to contribute to HIV persistence is the deleterious impact that immune activation has on HIV-specific T-cell responses (Figs 2 and 3). Indeed, it is well described that chronic exposure to antigens leads to T-cell exhaustion (43, 45, 47). Although HIV-specific $CD8^+$ T cells that persist after prolonged combination antiretroviral therapy may regain some function (201, 202), it is clear that their frequency is extremely low and that they may not migrate or persist in the compartments in which HIV replication still occurs (203). In a recent study, Shan and colleagues (153) demonstrated that HIV-specific cytotoxic T lymphocytes (CTLs) from the blood of virally suppressed subjects are inefficient at eliminating $CD4^+$ T cells in which HIV replication occurs. Of note, the killing capacity of these cells may be restored after *in vitro* stimulation with HIV peptides (204). This observation suggests that the extremely low frequency of HIV-specific $CD8^+$ T cells after prolonged therapy is unable to control residual levels of HIV replication and that, assuming the problem of virus epitope escape can be surmounted, strategies aiming at increasing these frequencies (through vaccination for example) may be needed to eliminate or at least control the small pool of productively infected $CD4^+$ T cells that persists during combination antiretroviral therapy.

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The inflammatory environment of treated HIV infection stimulates a compensatory response aimed at blunting any inflammation-associated harm. For example, HIV-associated inflammation causes increased numbers of Treg cells(205). During HIV infection, Tregs are dysfunctional and accumulate in high numbers, particularly compared to T-cell subsets such as Th17 cells (28, 29, 206). The increased levels of Tregs may, in turn, suppress the capacity of the adaptive immune system to clear virus.

Another potential driver of HIV latency may be inappropriate antigen presentation and innate immune cell function due to immune activation. As discussed above, several antigen-presenting cells, including monocytes/macrophages, B cells, and dendritic cells, are dysregulated, hyper-activated, and exhausted during HIV infection (55, 56, 62, 63, 108, 207, 208). Given that antigen-presenting cells are responsible for inducing antigen-specific responses in T cells via major histocompatibility complex (MHC):T-cell receptor (TCR) interactions, dysfunctionality of these cells may lead to inappropriate activation and exhaustion of T cells.

Another innate immune system factor that may affect HIV persistence is the relationship between restriction factors and innate immune activation. Recent studies have demonstrated that restriction factors (e.g. TRIM5α and APOBEC3G) play a role in the innate immune response to HIV and may alter the viral replication life cycle in this process (209–212). Thus, restriction factor inhibition of complete HIV replication may result in non-productively or latently infected cells, which may later be inducible to re-establish productive HIV replication. While preliminary evidence exists for the mechanisms described here, these are hypothetical ideas for how immune activation may induce and maintain HIV persistence and latency, and further studies are required.

Common γ chain cytokines and HIV persistence

IL-7-induced cycling of $CD4^+$ T cells (which is distinct from the T-cell proliferation induced by inflammatory cytokines discussed above) has also been associated with reservoir size during long-term effective therapy. In one study of long-term treated adults, the frequency of $CD4^+$ T cells expressing Ki67 (a cell cycle marker) but not the frequency of cells expressing classical activation markers such as CD25, HLA-DR, and CD71 was significantly associated with frequency of $CD4^+$ T cells harboring HIV DNA (117). Subjects with low $CD4^+$ T-cell counts and higher levels of IL-7-mediated proliferation had higher levels of Ki67 expressing cells. They also had levels of HIV DNA in those cell populations which emerge from such proliferation events (i.e. transitional memory $CD4^+$ T cells)(117). In a related analysis from a separate cohort, a lower pre-treatment $CD4^+$ T-cell count nadir was associated with higher frequency of infected cells, a finding that is consistent with a model in which homeostatic proliferation of $CD4^+$ T cells contributes to HIV persistence(213).

The stability of the T_{CM} reservoir is ensured by the intrinsic capacity of these cells to survive for decades and to self-renew upon antigenic stimulation (Figs 2 and 3) (116). The survival of T_{CM} cells depends, at least in part, on the activation and phosphorylation of signal transducer and activator of transcription 5a (STAT5a) and FOXO3a. Signaling via both the TCR and γ-chain (γc) cytokine receptors (such as CD127, the receptor for IL-7) leads to FOXO3a phosphorylation and drives the survival of T_{CM} cells. The T_{TM} reservoir also appears to be maintained in part by the effect of IL-7 on homeostatic proliferation, a natural mechanism ensuring the long-term persistence of immunological memory. The importance of this mechanism for the persistence of latently infected $CD4^+$ T cells was originally predicted by a mathematical model (214) and is now supported by several studies that indicate a role for this cytokine in the maintenance of a stable pool of latently infected cells.

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The impact which IL-7 might have on the latent reservoir during effective therapy is the focus of intense interest. IL-7 is produced in lymphoid organs by stromal cells, which have yet to be fully characterized. In a recent study, fibroblastic reticular cells and lymphatic endothelial cells were identified as the major producers of IL-7 during lymph node remodeling after viral infection in mice and humans (220). Unlike many other cytokines that act on lymphocytes, IL-7 production by stromal cells is not substantially affected by extrinsic stimuli. The amount of available IL-7 protein is thought to be regulated by the rate that it is scavenged by T cells (221). In states of chronin lymphopenia (such as HIV disease), less consumption of IL-7 leads to higher levels of this cytokine. As a consequence, the remaining T cells encounter abundant IL-7, which induces expansion in the depleted niche. In HIV disease, this model of 'regulation through consumption' is supported by the strong negative correlation between $CD4^+$ T-cell counts and plasma IL-7 levels (217) and by the high frequencies of $CD4^+$ T cells undergoing cell proliferation in subjects displaying abnormally low $CD4^+$ T-cell counts, independently of their plasma viremia (42, 222).

Although the impact of such a mechanism on the pool of reservoir cells is still unclear, it is likely that IL-7 not only expands uninfected T cells but also expands T cells harboring integrated HIV DNA. *In vitro*, physiological concentrations of IL-7 induce homeostatic proliferation of latently infected cells without viral production (223), suggesting that IL-7 does not disrupt viral latency as originally proposed (224, 225) but rather induces proliferation of latently infected cells. In addition, a recent study examining the sequences of viruses recovered during viral blip episodes upon IL-7 administration showed that these viral particles reflect predominantly transient induction of virus from a pre-existing pool of productively infected cells rather than activation of silent quasispecies from stable reservoirs (226). In line with this model, incomplete T-cell recovery and elevated IL-7 levels would be predicted to cause increased levels of T-cell proliferation and with stability of the HIV reservoir in its size and genetic diversity over time (117). These findings collectively argue that T-cell division of latently infected cells in the absence of viral production is likely to be a major mechanism contributing to the restoration of the $CD4^+$ T-cell compartment and to the persistence of a pool of reservoir cells during suppressive combination antiretroviral therapy.

Other cytokines involved in the maintenance of memory $CD4^+$ T cells may contribute to HIV persistence by promoting survival and/or proliferation of latently infected cells during treatment: Several γc cytokines (IL-2, IL-7, IL-15 and IL-21) have been shown to induce the expression of PD-1 at the surface of T cells (227), a marker associated with $CD8^+$ T-cell dysfunction that identifies HIV infected cells in the $CD4^+$ T-cell compartment in treated and untreated lentiviral infections (117, 228, 229). In addition to their potential role in the establishment and maintenance viral latency, these cytokines are important immunomodulators and may contribute to the control of residual levels of viral replication during antiretroviral therapy by enhancing antiviral T-cell responses, particularly in tissue reservoirs. For instance, administration of IL-15 to SIV-infected macaques has originally been shown to induce $CD4^+$ effector memory T-cell production and tissue emigration (230). However, a recent study in which the cytokine was administered concomitantly with combination antiretroviral therapy indicates that although IL-15 is able to transiently promote the proliferation of antigen-specific $CD8^+$ T cells in the peripheral blood, it failed to boost antiretroviral treatment-induced $CD4^+$ T-cell recovery both in the blood and in peripheral tissues and delayed viral suppression (231). Taken together, these studies suggest that IL-15 may have a positive impact on antiviral T-cell responses when viremia is fully suppressed by combination antiretroviral therapy, whereas the administration of the cytokine may have no impact or even a deleterious effect when residual levels of viral replication persist. These IL-15 studies emphasize the difficulty to predict the beneficial of deleterious effect of a γc cytokine-based therapy during combination antiretroviral therapy and suggest

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that the degree of viral suppression may be a critical parameter to monitor before initiating such therapies.

Impact of immune-based therapeutics on HIV persistence

The consistent observation that immune activation and measures of HIV persistence are positively correlated is intriguing and consistent with a number of theoretical models. However, establishing causal biological pathways to explain these associations in humans will require controlled clinical trials in which the pathways are interrupted or enhanced in a precise manner, and the size of the reservoir measured. The recent development of effective antiretroviral treatment regimens for non-human primates allows this model to be used to explore the role of agents aimed at interrupting the inflammatory response on viral persistence. For example, probiotic/prebiotic supplementation of combination antiretroviral therapy decreased the frequency of cycling $CD4^+$ T cells in the colon of SIV-infected macaques; although not tested, this effect would be expected to result in reduce levels of SIV persistence (232). Many such studies in nonhuman primates are now being developed.

Defining the role of host environment in HIV persistence will ultimately require performance of controlled clinical trials in which long-term treated individuals receive an immune-based therapeutic and the impact of this intervention on HIV persistence quantified. Several questions remain as to the optimal design of such studies. How long should antiretroviral treatment be administered before enrolling subjects? Will response to such regimens differ in those individuals treated during acute versus chronic infection? How should HIV persistence be quantified? Which tissues (if any) need to be sampled? When should primary outcomes be measured? Will promising agents that might work in only in combinations with other modalities be allowed to move forward in combination regimens even if monotherapy studies fail to detect an effect? Finally, given that HIV is generally no longer a fatal disease in the setting of antiretroviral therapy, ethical questions will likely arise as to the benefit conferred by using potentially toxic interventions to manipulate the immune response in an attempt to cure an infected individual.

HIV persistence as cause of immune activation

As emphasized throughout this review, the directionality of any observed associations between HIV persistence and immune activation is difficult to define *in vivo*. Although the focus of this review is how immune activation might contribute to HIV persistence, HIV production/replication can cause immune activation through several mechanisms (Figs 1–3). Most of the activated $CD4^+$ T cells during untreated disease are not HIV-specific. More specifically, a higher than expected frequency of activated cells are specific for persistent herpes virus antigens (147, 233). Mechanistically, it has been proposed that HIV activates dendritic cells and that these cells are more likely to activate $CD4^+$ T cells in the presence of commonly prevalent antigens, such as those associated with Herpes simplex virus, Epstein-Barr virus, and CMV (234). The remarkably high levels of CMV-specific T cells in untreated and treated HIV infection is consistent with this model (147, 235, 236). These observations might argue that much of the latent reservoir during combination antiretroviral therapy is in herpes-specific T cells, a hypothesis which should be testable.

The strongest evidence that HIV causes immune activation during therapy comes from recent therapy intensification studies. Although some studies have failed to find an impact of intensification on T-cell activation in blood or rectal mucosa (122, 237), one study found that the addition of raltegravir reduced the frequencies of infected cells and of activated cells in ileum (which is densely populated with T cells)(127, 128). In one randomized study of raltegravir intensification, a decline in T-cell activation was more readily detectable in those individuals who exhibited a virologic response to the intervention (238, 239). Other studies

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have found an impact of raltegravir intensification on immune activation (240, 241). These data provide compelling evidence that HIV persistence during antiretroviral therapy causes immune activation, although a larger more definitive study will be needed to address remaining uncertainty on this issue.

The lack of clear temporal evolution in viral sequences during suppressive therapy reported in some studies (242, 243) as well as the failure of most clinical trials to demonstrate an appreciable effect of combination antiretroviral therapy intensification on HIV persistence (122, 244–246) suggest that persistent low levels of HIV RNA in plasma and tissues primarily reflect continuous production from stable reservoir. However, increased levels of 2-LTR circles (238) as well as a significant reduction in the amount of cell associated RNA in the gut of combination antiretroviral therapy subjects upon intensification with raltegravir (127) suggest that complete cycles of viral replication may still occur during combination antiretroviral therapy, at least in a subset of individuals. Novel therapeutic strategies aimed at abrogating these low levels of viral replication/production are clearly needed. For instance, selecting a combination of antiretroviral drugs endowed with the ability to penetrate in anatomical reservoirs such as the CNS and the gut may prove to be beneficial in reducing residual replication and inflammation in virally suppressed subjects.

Conclusion

Despite the effectiveness of combination antiretroviral therapy in suppressing virus replication, immunological abnormalities persist, even after years of suppressive therapy (5, 7, 247–249). Combination antiretroviral therapy does not always restore normal $CD4^+$ T-cell counts, and in a substantial fraction of virally suppressed subjects, levels of immune activation remain elevated compared to uninfected individuals (216, 250). The association observed between residual levels of immune activation and viral persistence suggests that these two phenomena may be reciprocally connected (216, 251). However, whether immune activation is a cause or a consequence of HIV persistence is still unclear. It is likely to be both.

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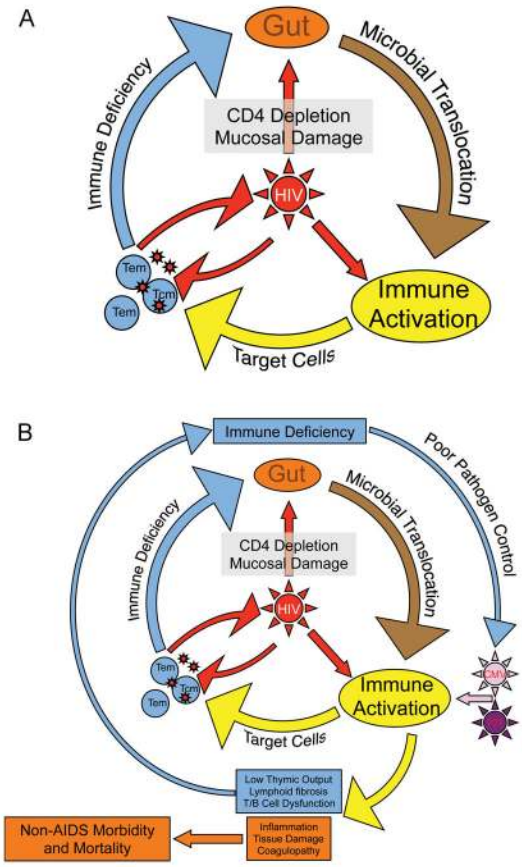

Fig. 1. HIV initiates and sustains a 'vicious cycle'

(A). Acute HIV infection causes damage to the mucosal integrity of the gastrointestinal tract, resulting in continuous local and systemic exposure to gut microbial products. HIV and these microbial products cause activation of T cells and expansion of $CD4^+$ T cells, resulting in more target cells and higher levels of HIV replication. Direct and indirect mechanisms lead to $CD4^+$ T-cell loss, broad immunodeficiency, and higher levels of both HIV and microbial translocation. (B). Chronic activation of the immune system results in direct damage to lymphoid tissues, which in turn contributes to failure to regenerate T cells and overall decrease in function of adaptive and innate immune systems. The resulting immunodeficiency results in excess pathogens (e.g. HIV, gut microbes, herpes viruses) and, as a result, yet more immune activation. This chronic inflammatory state predicts and presumably causes development of AIDS and non-AIDS conditions such as early cardiovascular disease.

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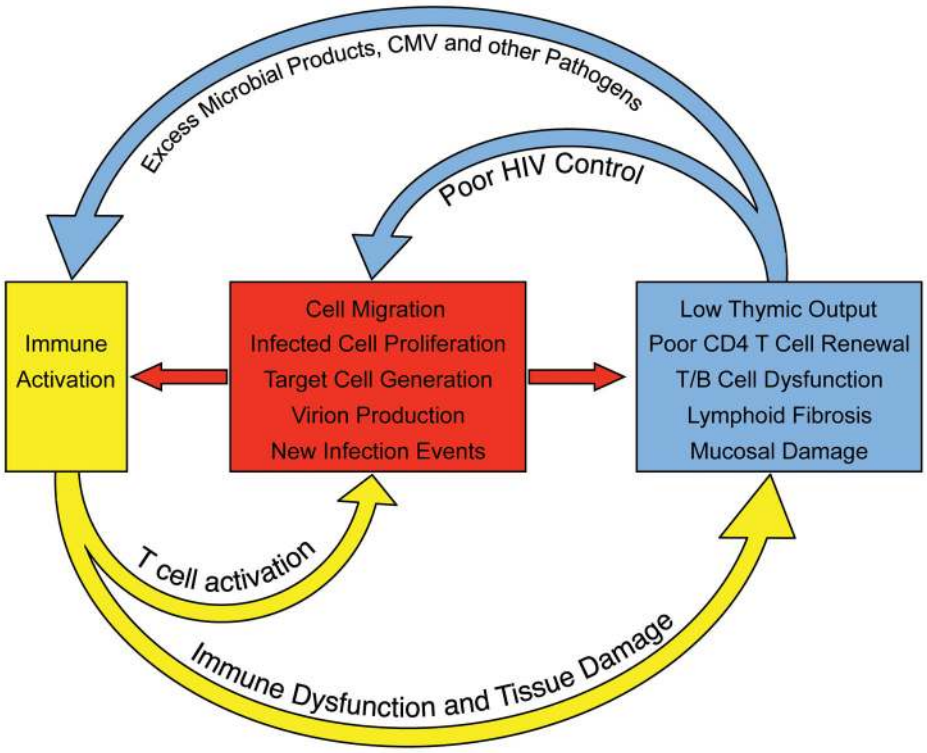

Fig. 2. Immune activation sustains HIV persistence during antiretroviral therapy

HIV-associated damage to the lymphoid system is only partially reversible. During long-term antiretroviral therapy, the residual immune dysfunction (which is due in part to loss of thymic tissue, fibrosis in germinal centers of secondary lymphoid structure, hematopoietic stem cell loss, and mucosal barrier breakdown) results in immunodeficiency, excess amounts of pathogens and chronic immune activation. The immune activation in turn leads to migration of $CD4^+$ T cells to foci of HIV replication, generation of activated and susceptible target cells, and production of virus from latently infected cells (all of which enable more efficient cell-to-cell spread of HIV and replenishment of infected cells). The inflammatory environment also leads to proliferation and maintenance of latently infected cells. The residual HIV replication/production in turn contributes to sustained tissue damage and immune activation.

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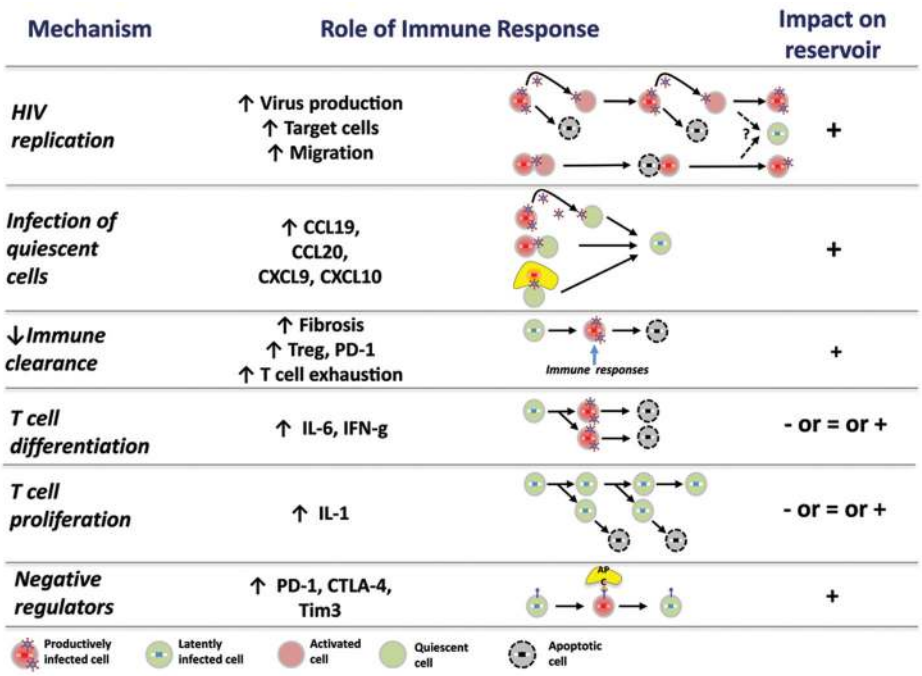

Fig. 3. Mechanisms by which immune activation causes HIV persistence

The chronic immune dysfunction of antiretroviral-treated HIV infection contributes to HIV persistence by (1) enabling HIV replication via generation of activated $CD4^+$ T cells, (2) enabling infection of resting cells, (3) reducing the capacity of the adaptive immune system to clear infected cells, (4) causing differentiation and proliferation of infected cells, and (5) increasing expression of cell-surface negative regulators, which in turn contributes to persistence of latently infected cells. Detailed knowledge regarding the mechanisms which contributes to each of these steps might lead to the development of immune-based therapeutics which could contribute to an HIV cure.