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Immune Activation and HIV Persistence: Considerations for Novel Therapeutic Interventions

Hiroyu Hatano¹

¹Department of Medicine, University of California San Francisco, San Francisco, CA, 94143, USA

Abstract

Purpose of review—One of the potential barriers to current HIV cure strategies is the persistence of elevated levels of immune activation despite otherwise effective antiretroviral therapy (ART). The purpose of this review is to examine the relationship between immune activation and HIV persistence, and to review novel therapeutic interventions that are currently being pursued to target immune activation in treated HIV disease.

Recent findings—Multiple groups have consistently observed that elevated levels of inflammation, immune activation, and immune dysfunction persist in ART-treated individuals, despite successful suppression of plasma viremia. Increased immune activation may lead to viral persistence through multiple mechanisms. Several novel interventions aimed at decreasing persistent immune activation are being pursued and include studies aimed at decreasing low-level viral replication, approaches aimed at decreasing microbial translocation, interventions to treat co-infections, and therapies that directly target immune activation.

Summary—There appears to be a clear and consistent relationship between immune activation and viral persistence in treated HIV disease. Whether this relationship is causal or mediated through other mechanisms is still unknown. Small-scale, pathogenesis-oriented interventional studies are necessary to further evaluate this relationship and the effect of potential interventions.

Keywords

HIV; immune activation; T cell activation; inflammation; viral persistence

INTRODUCTION

Multiple studies have shown that HIV-infected individuals have elevated levels of immune activation during untreated disease and that these levels do not normalize even with long-term treatment with otherwise effective antiretroviral therapy (ART) [1–5]. In fact, increased levels of both soluble biomarkers of inflammation and markers of T cell activation have been shown to be associated with and predictive of increased morbidity and mortality in treated HIV infection [6–12]. Immune activation is likely to be a significant contributor in both the initial establishment of and the subsequent maintenance of the viral reservoir and is therefore a potential barrier to current HIV cure strategies [13–15]. However, it is still not

known whether the relationship between immune activation and HIV persistence is causal or mediated through other mechanisms, and whether the relationship is unidirectional or bidirectional. For example, residual low-level viral replication in the setting of ART may lead to persistently elevated levels of immune activation, as suggested by a subset of recent intensification studies [16–19]. Conversely, increased immune activation may lead to viral persistence through multiple mechanisms, including increased viral production, increased number of target cells [20], homeostatic proliferation [13], and the upregulation of negative regulators such as programmed cell death protein 1 (PD-1) [13, 14].

In this paper, I will review several novel therapeutic approaches that are currently being developed with the goal of decreasing persistent immune activation in treated HIV disease. These include strategies to decrease ongoing low-level viral replication, therapies to decrease microbial translocation, treatment of co-infections, interventions aimed at reversing lymphoid fibrosis, and therapies that target immune activation directly (Table 1).

INTERVENTIONS TO DECREASE ONGOING VIRAL REPLICATION

One of the major controversies in HIV research is whether low-level viral replication persists in the setting of long-term ART. All of the recent intensification studies have shown that treatment intensification in ART-suppressed individuals does not decrease ultrasensitive plasma HIV RNA levels, suggesting that current therapies may be fully effective in suppressing viral replication [16, 17, 21–24]. However, some studies which have used other measures of HIV persistence and/or assessed persistence in lymphoid tissues where the majority of the virus resides have demonstrated that intensification can inhibit low-level viral replication. These studies have detected an early increase in 2-long terminal repeat (2-LTR) circles [16], or a decrease in levels of cell-associated HIV RNA in gut-associated lymphoid tissue (GALT) [17]. Moreover, some of these intensification studies have observed a decrease in immune activation levels with intensification in at least a proportion of ART-suppressed individuals [16–19], suggesting that residual low-level viral replication may be a contributor towards persistently elevated levels of immune activation.

In a recent study by our group, we examined whether low-level viral replication persists during ART and whether this low-level viral replication contributes to persistent immune activation and dysfunction [25]. We conducted a randomized, double-blind, placebo-controlled study of raltegravir intensification in ART-suppressed individuals and assessed whether intensification led to an increase in 2-LTR circles. Intensification did not decrease levels of ultrasensitive plasma HIV RNA (as detected by a single copy assay), cell-associated HIV RNA, proviral HIV DNA, or CD4+ or CD8+ T cell activation (CD38+HLA-DR+) [24]. However, intensification did lead to a rapid increase in 2-LTR circles in the raltegravir group, suggesting the presence of ongoing low-level viral replication in these individuals. We also observed a significant decrease in levels of D-dimer (a measure of clot formation and degradation) in the raltegravir group, suggesting that low-level viral replication contributes to the persistent alterations in the coagulation pathway that have been documented in HIV-infected individuals [10–12]. Finally, amongst the subjects who had an increase in 2-LTR circles, we found that intensification led to a significant decrease in immune activation levels (defined as %CD38+HLA-DR+ CD8+ T cells). These data are

consistent with results from a study by Buzon et al., who previously found that raltegravir intensification led to an early increase in 2-LTR circles, and that the raltegravir subjects who had an increase in 2-LTR circles had higher levels of immune activation at baseline which then decreased with intensification [16]. Collectively, these data suggest that low-level viral replication persists in a proportion of patients even after long-term suppressive ART, and that low-level viral replication should be considered as a potentially modifiable factor in future strategies aimed decreasing immune activation and cure.

INTERVENTIONS TO DECREASE MICROBIAL TRANSLOCATION

Seminal work by several groups has shown that during primary infection HIV rapidly kills most CD4⁺ T cells in the gastrointestinal tract [26, 27]. The loss of mucosal Th17 CD4⁺ cells (which maintain gut epithelial barrier integrity) leads to microbial translocation [28, 29], which then leads to chronic systemic immune activation [30, 31] and may in fact also contribute to downstream clinical events [32]. Several interventions targeted at blocking microbial translocation are currently being investigated [33], including the use of prebiotics and probiotics. The gut microbiota is thought to be an important barrier to colonization by pathogenic bacteria [34] and modulates the innate and adaptive immune system [35, 36]. Because there is an overrepresentation of pathogenic bacteria and an underrepresentation of beneficial bacteria in HIV infection [37, 38], prebiotics and probiotics can be used to modify this imbalance. In a recent randomized, double-blind, placebo-controlled study, untreated HIV-infected individuals received a prebiotic oligosaccharide mixture for 12 weeks [39]. Microbiota composition improved substantially and there was a significant reduction in levels of soluble CD14 (sCD14), which is released by monocyte/macrophages in response to lipopolysaccharide (and hence may be a measure of microbial translocation), and has been found to be predictive of mortality in HIV infection [8]. In a separate study by Klatt et al., SIV-infected pigtail macaques were treated with a combination of prebiotics/probiotics/ART vs. ART alone for 5 months [40]. In this study only subtle changes were observed in microbiota composition and there were no significant changes in measures of immune activation or microbial translocation. However, animals who received combination treatment with prebiotics/probiotics/ART had increased colonic CD4⁺ reconstitution, increased frequency/functionality of antigen presenting cells in the colon, and decreased lymphoid fibrosis in the colon. Collectively, these two studies suggest that supplementing ART with prebiotics/probiotics may improve gut immunity; additional studies in ART-suppressed HIV-infected patients are necessary to confirm this.

Other ongoing studies aimed at decreasing microbial translocation that are in various stages of maturity include the administration of rifaximin (a minimally absorbed oral antibiotic with a broad spectrum of bactericidal activity that is concentrated in the gastrointestinal tract, AIDS Clinical Trials Group [ACTG] 5286), sevelamer (an oral phosphate binder used in dialysis patients that binds bacterial endotoxin in the gut, ACTG 5296), mesalamine (an oral anti-inflammatory drug used to treat patients with inflammatory bowel disease that acts locally on the gut tissue to decrease inflammation, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01090102) NCT01090102), and chloroquine (which inhibits toll-like receptor signaling [41], ACTG 5258). Results of these studies will undoubtedly help us to understand the contribution of microbial translocation to elevated immune activation levels in treated HIV infection.

INTERVENTIONS TO TREAT CO-INFECTIONS

Many HIV-infected patients are also co-infected with other chronic viral infections such as cytomegalovirus (CMV), and it has been hypothesized that treatment of these co-infections may reduce systemic immune activation levels in HIV-infected individuals. In a recent randomized, placebo-controlled study by Hunt et al., ART-treated HIV-infected and CMV-seropositive individuals with CD4+ T cell counts < 350 cells/mm³ were randomized to receive valganciclovir vs. placebo for 8 weeks [42]. The valganciclovir group had a significant decrease in immune activation levels (defined as %CD38+HLA-DR+ CD8+ T cells). Additional strategies that allow for chronic treatment of common co-infections in HIV-infected individuals should be developed.

INTERVENTIONS TO DECREASE LYMPHOID FIBROSIS

Multiple studies by Haase, Schacker, Estes and their colleagues, as well as others, have shown that: (1) lymphoid architecture is damaged early in HIV infection due to immune activation and collagen deposition, a process which may be initiated in part by the anti-inflammatory T regulatory release of transforming growth factor beta-1 (TGF- β 1) during acute infection; (2) lymphoid fibrosis persists during suppressive ART [43]; (3) lymphoid fibrosis disrupts T cell homeostasis, as defined in part by the capacity of the immune system to reconstitute normal CD4+ T cell counts during ART [44–46]; and (4) lymphoid fibrosis prevents effective interaction between antigen presenting cells and HIV-specific T cells [47, 48]. In the context of suppressive ART, we have found that individuals who have lower levels of immune activation [14] and stronger mucosal HIV-specific responses in GALT [23] have lower levels of the latent reservoir. Collectively, these data suggest that lymphoid fibrosis is both a cause and consequence of immune activation, and that lymphoid fibrosis leads to suboptimal adaptive immune responses and is therefore a potentially modifiable barrier to cure.

One strategy that is currently being pursued by our group is the administration of an angiotensin converting enzyme (ACE) inhibitor in ART-suppressed, HIV-infected individuals ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01535235) NCT01535235). A central source of HIV-associated lymphoid fibrosis is thought to be excess production of TGF- β 1 [49]. Angiotensin converting enzyme (ACE) is located in multiple organs and converts angiotensin I (AT1) to angiotensin II (AT2). AT2 is proinflammatory and induces fibrosis by increasing levels of TGF- β 1 [50]. ACE inhibitors have consistently exhibited benefit in a number of clinical settings, but emerging data from multiple animal and human studies indicate that this class of drugs may also have anti-fibrotic properties [51, 52]. In this pilot study, we will assess whether the addition of an ACE inhibitor (lisinopril) to standard ART decreases immune activation, reverses fibrosis in lymphoid tissues, and whether this leads to more effective HIV-specific host immune responses and an accelerated clearance of the latent reservoir. A recently published randomized, double-blind, placebo-controlled study by Baker et al. suggests that a relatively low and short course of lisinopril may indeed decrease levels of immune activation in treated HIV [53]. Studies evaluating the use of other antifibrotic agents such as angiotensin receptor blockers (ACTG 5317) are currently in development.

INTERVENTIONS THAT DIRECTLY TARGET IMMUNE ACTIVATION

Several studies that directly target immune activation in HIV infection have been reported. In a recent randomized, open-label study, untreated HIV-infected individuals were randomized to receive a cyclooxygenase type 2 (COX-2) inhibitor (celecoxib) for 12 weeks [54]. Administration of the COX-2 inhibitor decreased levels of immune activation (defined as CD38 density on CD8+ T cells) as well as PD-1 density on CD8+ T cells. In another recent randomized, double-blind, placebo-controlled study, untreated HIV-infected individuals were randomized to receive high-dose atorvastatin (80 mg daily) vs. placebo for 8 weeks [55]. The atorvastatin group had a significant reduction in immune activation levels (defined as %CD38+HLA-DR+ CD8+ T cells); interestingly, reductions in immune activation did not correlate with reductions in levels of low-density lipoprotein cholesterol. Both of the above approaches should be duplicated in studies in ART-suppressed patients (ACTG 5275).

Sekaly, Chomont, and colleagues have recently generated a testable model that links HIV-associated immune activation/dysfunction and HIV persistence. In order to control inflammation and prevent inflammation-associated harm, T cells upregulate a number of “negative regulators”, including PD-1, CTLA-4 and Tim-3 [56]. When engaged by their ligands (which are also upregulated in sites of inflammation), these negative regulators prevent activation-associated T cell death, inhibit T cell function, and may inhibit T cell expansion and regeneration [57, 58]. As activated T cells are more likely to become infected, the expression of these negative regulators may be a marker of an infected cell. Consistent with this model, Chomont et al. found that PD-1 expressing CD4+ T cells are enriched for HIV compared to non-PD-1 expressing CD4+ T cells during ART [13], and we have found a consistent association between the frequency of PD-1 expressing cells and the size of the reservoir [14]. Our group has also found a striking association between PD-1 expressing and CD4+ T cell counts during ART, suggesting that immune activation-mediated upregulation of PD-1 may contribute to suboptimal CD4+ T cell gains during ART [14]. Finally, in both non-human primate studies and in early human oncology studies, inhibition of the PD-1 pathways have led to improved T cell function, improved vaccine responsiveness, and perhaps clinical resolution of some cancers [59–62]. Studies aimed at reversing PD-1 in ART-suppressed HIV-infected individuals are currently in development (ACTG 5301).

CONCLUSION

One of the potential barriers to current HIV cure strategies is the persistence of elevated levels of immune activation despite otherwise effective antiretroviral therapy. There appears to be a clear and consistent relationship between immune activation and viral persistence in treated HIV disease. Whether this relationship is causal or mediated through other mechanisms is still unknown. Several novel interventions aimed at decreasing persistent immune activation are being pursued and include studies aimed at decreasing low-level viral replication, approaches aimed at decreasing microbial translocation, interventions to treat co-infections, and therapies that directly target immune activation. Small-scale, pathogenesis-oriented interventional studies in well-characterized, ART-suppressed, HIV-

infected individuals are necessary to further evaluate this relationship and the effect of potential interventions. It is likely that a combination approach will be necessary to perturb HIV-associated immune activation.

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** of outstanding interest

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KEY POINTS

- One of the potential obstacles to current HIV cure strategies is persistently elevated levels of immune activation.
- There is a clear relationship between persistent immune activation and HIV persistence in treated HIV disease, although it is still not known whether this relationship is causal or mediated through other mechanisms.
- Several novel approaches are actively being pursued to directly or indirectly decrease persistent immune activation.
- Small-scale, pathogenesis-oriented interventional studies in well-characterized, ART-suppressed, HIV-infected individuals are necessary to further evaluate the relationship between immune activation and viral persistence, and the effect of potential interventions.

Table 1

Select Ongoing Studies that Target Persistent Immune Activation in Treated HIV Disease

Study	Purpose
ACTG 5286	To determine whether administration of rifaximin (a minimally absorbed oral antibiotic with a broad spectrum of bactericidal activity that is concentrated in the gastrointestinal tract) leads to decreased immune activation in treated HIV-infected patients.
NCT01090102	To determine whether administration of mesalamine (an oral anti-inflammatory drug used to treat patients with inflammatory bowel disease that acts locally on the gut tissue to decrease inflammation) leads to decreased immune activation in treated HIV-infected patients.
NCT01535235	To determine whether administration of lisinopril (an angiotensin converting enzyme [ACE] inhibitor) decreases immune activation, reverses lymphoid fibrosis, improves HIV-specific host immune responses, and accelerates clearance of the latent reservoir in treated HIV-infected patients.
ACTG 5275	To determine whether administration of atorvastatin (a “statin” drug used to lower cholesterol levels) leads to decreased immune activation in treated HIV-infected patients.

ACTG, AIDS Clinical Trials Group; NCT, National Clinical Trial. Source: ClinicalTrials.gov.