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Residual inflammation and viral reservoirs: Alliance against an HIV cure

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Abstract

Purpose of review—HIV persists in cellular and anatomical reservoirs during antiretroviral therapy (ART). Viral persistence is ensured by a variety of mechanisms including ongoing viral replication and proliferation of latently infected cells. In this review, we summarize recent findings establishing a link between the unresolved levels of inflammation observed in virally suppressed individuals on ART and the mechanisms responsible for HIV persistence.

Recent findings—Residual levels of viral replication during ART are associated with persistent low levels of immune activation, suggesting that unresolved inflammation can promote the replenishment of the HIV reservoir in tissues. In addition, the recent findings that the latent HIV reservoir is maintained by continuous proliferation of latently infected cells provide another mechanism by which residual inflammation could contribute to HIV persistence.

Summary—Residual inflammation during ART is likely to be a critical parameter contributing to HIV persistence. Therefore, reducing inflammation may be an efficient way to interfere with the maintenance of the HIV reservoir in virally suppressed individuals on ART.

Keywords

HIV Reservoir; Immune activation; Immune checkpoint blockers; Proliferation

Introduction

ART dramatically inhibits HIV replication but does not eradicate HIV. The virus persists in cellular and anatomical reservoirs for the lifetime of the individuals receiving ART [1–3]. Two major mechanisms contribute to HIV persistence during ART. First, HIV may still replicate at low levels in anatomical reservoirs in which antiretroviral drugs (ARVs) may not diffuse [4]. Second, the establishment of a small pool of long-lived latently infected cells

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Conflict of interest

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early in infection, provides the virus with a cellular niche that ensures its maintenance for decades during ART [5, 6].

Several studies have clearly shown that the magnitude of the viral reservoir is strongly associated with the residual levels of immune activation that persists during ART, suggesting that HIV persistence and residual inflammation are interdependent [6–8]. The unresolved inflammation observed in the majority of individuals on ART may contribute to the maintenance of a stable reservoir for HIV by promoting the two aforementioned mechanisms of persistence. Interfering with these mechanisms is now proposed as a strategy to reduce the size of the viral reservoir, a pre-requisite to HIV remission in individuals receiving ART.

Inflammation and the active viral reservoir

Residual levels of viral replication may continuously replenish the latent reservoir during ART [9–13]. Several anatomical compartments such as the gut mucosa, genital tract, lymph nodes and the central nervous system have been shown to be enriched in HIV-infected cells [14–21]. Indeed, the concentrations of ARVs in some of these tissues were found to be lower compared to their levels in peripheral blood, even in suppressed individuals [4, 22, 23], which may allow persistent replication in lymphatic tissues. A recent study of mass spectrometry imaging for quantifying ARVs distribution into tissues showed that the drug tissue distribution was heterogeneous and could vary greatly between tissues within an individual [24]. In this setting, the high CD4⁺ T cell density in these anatomical sanctuaries combined with lower sensitivity to ART inhibition may favor cell-to-cell HIV transmission [25]. Moreover, residual HIV replication may induce activation of resident cells, which could become more permissive to HIV infection [26], contributing to slow, but continuous, replenishment of viral reservoirs. Despite this conceivable local tissue inflammation, HIV infects abortively resting non-permissive cells that represent >95% of the CD4⁺ T cell population in lymphoid tissues [27]. Subsequently they die due to an innate immune response against cytosolic viral DNA culminating with pyroptosis, a highly inflammatory form of programmed cell death [28, 29]. Therefore, dying CD4⁺ T cells release inflammatory signals that could re-activate more latently infected cells and attract more uninfected cells to die and to sustain inflammation creating a pathogenic vicious cycle.

Persistent immune activation and inflammation lead to collagen deposition in the lymphoid tissue and to a progressive disruption of the lymph node architecture [30, 31]. This restricts T cell access to the survival factor IL-7 on the fibroblastic reticular cell network and results in apoptosis and depletion of T cells [32]. Despite this fact, significant accumulation of follicular helper CD4⁺ T cells (T_{fh}) has been described in the germinal centrals during HIV [33] or SIV-pathogenic infection [34, 35]. Indeed, T_{fh} are 30–40 times more likely to be productively infected than extra follicular CD4⁺ T cells in untreated individuals [34, 36–39], and significant differences still exist after ART-initiation [37]. The paucity of SIV-specific CD8⁺ T cells in follicles may protect infected T_{fh} cells from being killed [35] as shown in elite controllers rhesus monkey. This suggests that potent SIV-specific CD8⁺ T cells can effectively clear productive infection from extra-follicular sites, but their relative exclusion

from B cell follicles limits elimination of infected Tfh [40]. Therefore, these cells may constitute privileged latent reservoirs in ART-treated individuals.

Different ART intensification strategies could reduce residual viral replication through the addition of ARVs with higher tissue penetration (i.e. raltegravir) or an anti-inflammatory activity (i.e. Maraviroc). Several raltegravir intensification studies showed changes in markers of persistent viral replication (2-LTR circles, unspliced RNA in CD4⁺ T cells or replication competent viruses), concomitantly with a reduction in immune activation [11, 12, 41–44]. However, other studies (with different sample size, intensification periods, methodology and sampling frequencies) did not confirm these results [45–48]. Interestingly, CD8⁺ T-cell activation, specifically CD38 expression on memory cells, is modulated by raltegravir intensification [11, 12, 41, 42, 44, 49–51] and discontinuation [42]. Conversely, the effects on CD4⁺ T-cell activation are more limited, although systemic redistribution of CD45RA⁻ CD4⁺ T cells in raltegravir intensified subjects reflects resolution of local tissue inflammation [42, 49]. Both observations suggest that persistent immune activation in CD8⁺ T cells during suppressive-ART is driven, at least in part, by residual viral infection as a result of incompletely suppressive ART. Furthermore, raltegravir reduces immune activation by increasing the level of viral suppression in a reversible manner. Elite controllers display higher levels of systemic immune activation than uninfected subjects [52], which is decreased by ART [53]. These findings provide indirect, but compelling, evidence of residual viral replication in these individuals.

Several intensification studies using maraviroc, an antagonist of the HIV co-receptor CCR5, have been executed with contradictory results [54–56]. Since maraviroc may exert an anti-inflammatory activity through its ability to inhibit CCR5-mediated chemotaxis and by lowering the threshold for cellular activation, it could reduce the number of activated cells in which residual replication could occur (i.e. gut). Despite this, several authors did not observe a decrease of immune activation [55, 56], but rather an increase, specially in the rectal mucosa [54]. Moreover, it had limited effects on reducing the replication competent reservoir [55]. Likewise, autologous CD4 T cells from HIV-infected subjects were rendered permanently CCR5-dysfunctional by a zinc-finger nuclease (SB-728-T) *ex vivo* to induce acquired-genetic resistance to HIV infection. The infusion of modified-cell increased durably the levels of circulating CD4 T cells concomitantly with a decrease in HIV DNA [57]. However it is still unclear if the beneficial effect observed is related to the CCR5-genetic modification or to the sustained expansion of HIV-resistant T cell with a memory stem cell-like phenotype [58]

HIV replication disrupts the intestinal epithelial barrier, causing persistent depletion of mucosal CD4⁺ T cell [15]. This loss of CD4⁺ T cells is marked by a significant depletion of T helper 17 (Th17) cells [59], which are involved in intestinal epithelial barrier homeostasis as well as in mucosal defense. The disruption of the mucosal integrity promotes the leakage of luminal microbial products to the circulation, stimulating innate immune cells through the TLR pathways, thus contributing to the pro-inflammatory cytokine milieu and systemic immune activation even during suppressive ART [60]. Despite the restoration of Th17 during ART, the functionality of these cells might still be impaired, delaying the normalization of immune activation and microbial translocation [61, 62]. In addition, the

sigmoid provirus reservoir in ART-treated subjects is associated with persistently elevated microbial translocation and with impaired restoration of Th17 populations [61]. Early initiation of ART is able to preserve Th17 number and function and fully reversed any initial HIV-related immune activation [63]. Recently, Micci *et al.* demonstrated the beneficial role of IL-21 in the restoration of CD4⁺ T cells in the rectal mucosa of virally suppressed SIV infected macaques, which was associated with reduced markers of viral persistence [64].

Many co-infections non-specifically activate the host immune system and several organisms can directly facilitate HIV replication [65, 66]. Persistent and intermittent CMV replication causes bystander activation [67], thereby potentially generating more activated CD4⁺ T cells for HIV replication. Even asymptomatic shedding of CMV in the genital tract from HIV-infected individuals has been associated with increased T-cell activation and proliferation in blood and increased levels of total HIV DNA in both ART-naïve [68, 69] and ART-suppressed individuals [70]. Importantly, valganciclovir, an agent with potent activity against CMV and most other herpesviruses, in combination with ART has been shown to significantly reduce CD8⁺ T-cell activation and this effect persisted even after stopping the drug [71]. Larger studies will be needed to determine the clinical benefit of treatment of CMV and its effect on HIV persistence.

Inflammation and the latent reservoir

As previously mentioned, inflammation is associated with T-cell activation and proliferation during HIV infection, even during ART. The frequency of CD4⁺ T cells harbouring integrated HIV DNA is associated with the frequency of proliferating CD4⁺ T cells (measured by Ki67) in individual receiving ART [6]. The direct relationship between T-cell proliferation and HIV persistence has recently been reported in two seminal studies. Maldarelli *et al.* and Wagner *et al.* identified specific HIV integration sites linked to clonal expansion of HIV-infected cells [72, 73]. Integrations of proviruses were frequently found into genes associated with cancers or cell cycle regulation, promoting the persistence of HIV-infected cells through proliferation and increased survival. The limited number of subjects extensively analyzed in these two studies did not allow assessing the contribution of ongoing T-cell activation, homeostatic proliferation or antigen-induced expansion to HIV persistence. The replication capacity of the clonally expanded provirus is still under debate. In their study combining integration sites analysis with viral sequencing, Cohn *et al.* did not identify functional viral sequences in the clonally expanded proviruses [74].

Interestingly, two studies reinforced the concept of proliferation as a mechanism of viral persistence in memory CD4⁺ T cells in blood and lymphoid tissues during ART [75, 76]. In-depth longitudinal phylogenetic analysis of plasma and cell-associated viruses revealed that a majority of viral sequences are identical, suggesting that HIV persists through cell proliferation rather than through ongoing replication in these individuals. Further investigations will be needed to establish how inflammation would favor one or the other mechanism. Additionally, effector memory CD4⁺ T cells more frequently harbor proviruses with identical sequences than less differentiated CD4⁺ T-cell subsets, indicating that clonal expansion of HIV-infected cells is a characteristic of differentiated cells. Higher frequencies of these differentiated cells were observed in virally suppressed individuals with persistent

lymphopenia [77] suggesting that homeostatic proliferation may drive HIV persistence in this group of subjects. IL-7 is a major contributor to CD4⁺ T cell proliferation *in vivo* [78]. IL-7 administration has been reported to increase the size HIV reservoir pool by induction of CD4⁺ T-cell proliferation without increasing genetic diversity of the proviral population [79]. This study clearly demonstrates the contribution of IL-7-induced proliferation to the maintenance of latently infected cells during ART.

Overall, it remains difficult to determine whether the clonally expanded reservoir is the result of homeostatic or antigen-induced proliferation. While, the restricted number of highly expanded clone supports antigenic expansions of a restricted number of clonotypes, the association between CD4⁺ T-cell depletion, IL-7 levels and reservoir persistence strongly support a role for homeostatic proliferation in that process.

The inflammatory environment not only promotes T-cell proliferation but also stimulates a compensatory response aimed at breaking the inflammatory vicious circle. Immune checkpoint molecules (ICs) are key players in this arsenal of regulatory factors by modulating the duration and magnitude of immune responses. PD-1, the archetype immune checkpoint, is highly expressed on CD4⁺ and CD8⁺ T cells during HIV infection and its expression is not fully normalized by ART [80]. During ART, PD-1 expression is related to CD4⁺ T cell homeostasis as suggested by its association with CD4⁺ T cell count [80] and its up regulation by γ -c-cytokines such as IL-7 [81]. In addition, the expression of PD-1 on CD4⁺ T cells is associated with virological markers of HIV persistence suggesting a connection between PD-1 and HIV persistence [6, 7]. Therefore, PD-1 may regulate the interplay between T cell proliferation and HIV persistence. PD-1 and two additional ICs, LAG-3 and TIGIT, were identified as markers of HIV infected CD4⁺ T cells during ART, suggesting a direct role for ICs in HIV persistence [82]. Future studies will be needed to better characterize the relationship between ICs and HIV persistence in tissues, as the expression of these molecules is tightly regulated by the microenvironment. For instance, CTLA-4 is mainly expressed by CD4⁺ T cells in gastrointestinal tissues and remains elevated during ART [83]. It is currently difficult to determine if the association between ICs and HIV persistence reflects a cause or a consequence. The impact of the blockade of these pathways by IC blockers (ICBs) on HIV persistence will certainly be informative.

T regulatory CD4⁺ T cells (Tregs) are a key modulator of the inflammatory pathways. The suppressive capacity of Tregs is influenced by several factors, such as IL-2, inhibitory cytokines (IL-10, TGF- β , or IL-35) and ICs such as CTLA-4 and LAG-3 [84, 85]. In lymphopenic ART individuals, the frequency of Tregs is associated with markers of activation [86] and Tregs may act as a preferential reservoir for HIV during ART [87].

A complex balance between pro-inflammatory cytokines and anti-inflammatory cytokines determine the magnitude and the duration of inflammation. Recently, IL-37, an anti-inflammatory cytokine, has been found to be up regulated during HIV infection but not normalized by ART [88]. An association between IL-37 transcripts and HIV DNA suggests a relationship between HIV persistence and the anti-inflammatory response. Further investigations are needed to fully characterize the role of anti-inflammatory cytokines such as IL-10 and TGF- β in HIV persistence during ART.

Clinical interventions: breaking the vicious circle

Since residual inflammation during ART is likely to be a critical parameter contributing to HIV persistence, its reduction may efficiently interfere with the maintenance of the HIV reservoir.

During ART, persistent low levels of viral transcription occurring in latently infected cells can generate transcripts [89, 90] and maybe proteins [91] that are likely to contribute to the unresolved inflammation observed in suppressed individuals. Current ARVs do not inhibit viral transcription from an integrated viral genome and do not prevent reactivation from latency nor the inflammation that results from this phenomenon. Recently, Mousseau *et al.* identified a novel Tat-inhibitor (didehydro-cortistatin, dCA) that has the ability to prevent reactivation of viral transcription after potent cell stimulation [92]. In addition to its direct beneficial effect through inhibition of residual viral replication, treatment with dCA may also decrease the production of incomplete viral products that stimulate the innate and adaptive immune responses, thereby reducing inflammation, which would in turn decrease the proliferation of latently infected cells. Therefore, one can hypothesize that dCA may have beneficial effects on both the active and latent reservoirs. This promising novel approach is still at its development stage and the clinical potential and toxicity of dCA are currently unknown. Nonetheless, this innovative approach appears to be unique as it may significantly impact inflammation by targeting the virus, a possible cause of inflammation, rather than its consequence.

While anti-inflammatory therapeutic strategies have been used with the aim of restoring the CD4 compartment or reducing HIV co-morbidities [93], their impact on HIV persistence is a relatively novel area of research. Whether a decrease in the levels of residual inflammation and fibrosis can significantly reduce HIV persistence is currently explored *in vivo* by administering agents with specific anti-inflammatory and anti-fibrotic actions such as the angiotensin II blocker losartan to ART-suppressed individuals (NCT01852942). Telmisartan, which has a similar mechanism of action, is currently used in a phase I clinical study in acute HIV infection to determine if biological markers of immune activation in the blood and cerebrospinal fluid can be reduced to limit the spread of HIV reservoirs early in infection (NCT02170246).

Immunosuppressant are also considered as adjunct therapy to ART to reduce inflammation, which may impede HIV persistence. Sirolimus (rapamycin) inhibits a key regulatory kinase that controls cell-cycle progression (mTOR). Stock *et al.* explored the impact of sirolimus following kidney transplantation [94]. Sirolimus use was associated with lower post-transplant HIV DNA levels, suggesting that immunosuppressant may affect the level of HIV persistence during effective therapy. Of note, this effect was not observed in virally suppressed individuals who received cyclosporine [95]. The precise mechanism by which sirolimus exerts this beneficial effect is still unknown and will be evaluated in an ongoing clinical trial (NCT02440789). Everolimus, another mTOR inhibitor, will also be evaluated for its capacity to interfere with HIV persistence in virally suppressed individuals after kidney or liver transplant (NCT02429869).

Janus kinase (JAK) inhibitors, another class of anti-inflammatory molecules indicated for the treatment rheumatoid arthritis, myelofibrosis and other type of cancers, may also have an impact on inflammation and HIV persistence during ART. Gavegnano *et al.* reported that ruxolitinib and tofacitinib, two inhibitors with selectivity for subtypes JAK1/2 can potentially inhibit viral reactivation *in vitro* [96]. This suggests that in addition to their direct anti-inflammatory effects, these molecules may also directly act on the virus life cycle, and like dCA, may prevent residual levels of viral production from the reservoir. The effect of ruxolitinib on residual inflammation and HIV persistence is currently evaluated *in vivo* (NCT02475655).

The aforementioned anti-inflammatory strategies were designed to reduce viral persistence during ART. However, a transient increase in the level of immune activation may also reflect an efficient reactivation of the latent reservoir, as desired outcome in shock and kill curative strategies. Indeed, recent data from a clinical trial using the HDACi panobinostat indicate that innate immune factors, such as natural killer cells, plasmacytoid dendritic cells, and the expression patterns of interferon-stimulated genes, are associated with a decline in the HIV reservoir measured by viral DNA [97]. This suggests that innate immunity may play an important role in reducing the residual reservoir of HIV-infected cells or that innate immune functions are a sensitive sensor of viral production induced by latency reversing agents during ART.

Another example of a transient increase in the level of immune activation that may result in a decrease in the level of viral persistence is given by the manipulation of ICs. Several ICBs have been successfully used in the treatment of cancer, particularly those targeting the PD-1 and CTLA-4 receptors [98–100]. This has led to the idea of using these antibodies to restore HIV-specific function in HIV infection, which will likely be a key component of a successful eradication strategy [101]. A single case report study has evaluated the *in vivo* effects of CTLA-4 blockade (ipilimumab) on the HIV reservoir in an HIV-infected individual with metastatic melanoma [102]. Treatment with ipilimumab induced a marked increase in cell-associated unspliced HIV RNA and was associated with a subsequent decline in plasma HIV RNA. Concomitantly, increases in CD4⁺ T-cell activation as measured by HLA-DR, CD38 and CCR5 expression were noted. Whether these increases reflect a direct enhancement of T-cell function following CTLA-4 blockade or antigen-induced T-cell responses following viral reactivation remains unclear. Nonetheless, this study provides the first evidence that ICBs can be used to perturb the HIV reservoir and modify immune activation levels.

Conclusion

Viral persistence and residual inflammation are interdependent and fuel each other in a “vicious circle” that seems difficult to interrupt (Figure 1). Therapeutic strategies that will tackle residual levels of viral production will certainly help in assessing the impact of residual HIV on inflammation. Conversely, the results from several ongoing clinical studies will be critical to understand the role played by inflammation on HIV persistence. Most likely, breaking the vicious circle will require targeting both phenomena concomitantly. If the panel of anti-inflammatory molecules available is relatively large, there is currently no

drug available to prevent continuous production of viral products from the reservoir, a likely cause of residual inflammation. The development of such novel antivirals will certainly be a major weapon of the therapeutic arsenal aimed at reducing inflammation during ART.

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Key points

1. HIV persistence and residual inflammation are interdependent mechanisms.
2. Anatomical and cellular sanctuaries (low ARV penetration in tissues and Tfh, respectively) may favor residual levels of replication in tissues during ART. The local inflammation could re-activate more latently infected cells and attract more uninfected cells into the lymphoid tissue to sustain inflammation and residual replication.
3. Homeostatic and antigen-induced proliferation of latently infected cells contribute to HIV persistence during ART.
4. Interventions aiming to block viral production/replication or to modulate immune cells could be used to break this vicious-cycle

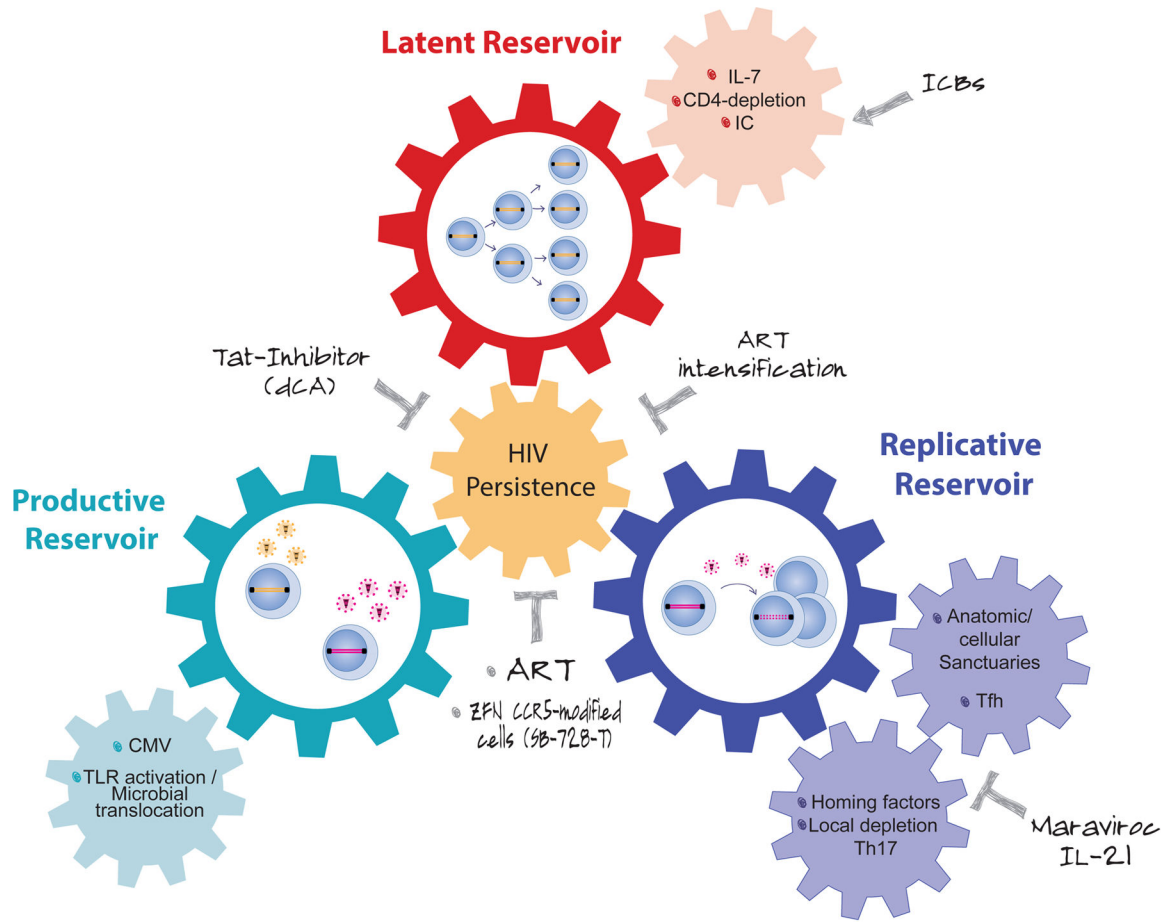


Figure 1. In HIV-infected, ART-suppressed subjects, the latent reservoir (red wheel) is maintained by continuous proliferation of latently infected cells, which can produce viral particles upon activation constituting the productive reservoir (turquoise wheel). When reactivated cells are in anatomical/cellular sanctuaries, where ART cannot diffuse efficiently, residuals levels of viral replication can occur (blue wheel), fueling continuously the latent reservoir. Increased levels of immune activation and/or inflammation promote the three mechanisms of HIV persistence (small wheels). Several therapeutic strategies designed to act directly on viral production/replication or to modulate the immune cells could be used to interrupt this vicious circle.