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Inflammation, Immune Activation, and Antiretroviral Therapy in HIV

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Abstract

Purpose of Review—This review focuses on the differential effects of contemporary antiretrovirals on systemic inflammation as heightened immune activation is linked to important co-morbidities and mortality with HIV infection.

Recent Findings—Antiretroviral therapy (ART) reduces dramatically systemic inflammation and immune activation, but not to levels synchronous with HIV-uninfected populations. In one ART initiation trial, integrase inhibitors appear to reduce inflammation to a greater degree than non-nucleoside reverse transcriptase inhibitors (NNRTIs); however, it is not clear that there are beneficial effects on inflammation resulting from treatment with integrase inhibitors compared to PIs, between PIs and NNRTIs, between specific nucleoside reverse transcriptase inhibitors, or with maraviroc in ART-naïve patients. In ART switch studies, changing to an integrase inhibitor from a PI-, NNRTI-, or enfuvirtide-containing regimen has resulted in improvement in several markers of inflammation.

Summary—Additional research is needed to conclusively state whether there are clear differences in effects of specific antiretrovirals on inflammation and immune activation in HIV.

Keywords

Antiretroviral therapy; Inflammation; Immune activation; HIV infection

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

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Introduction

An estimated 35 million people are living with human immunodeficiency virus (HIV) type 1, and approximately 2 million new infections are reported each year. Increased access to combination antiretroviral therapy (ART) has improved dramatically the life spans of persons living with HIV infection, reducing viral replication, and sparing the massive depletion of the immune system that has been associated with acquired immunodeficiency syndrome (AIDS), opportunistic infections, and death. Worldwide, there are an estimated 10 million HIV-infected people currently receiving ART, and based on World Health Organization and UNAIDS 90-90-90 targets and guidelines, this number will hopefully increase.

Despite reductions in risk of death with ART, HIV-infected persons continue to have increased morbidity and mortality compared to the general population, often due to non-AIDS-related events [1–3]. These include cardiovascular disease (CVD), insulin resistance and type II diabetes, osteoporosis, neurocognitive dysfunction, cancer, and frailty among others [4–9]. Taking CVD as an example, while HIV-infected persons have a disproportionately high prevalence of traditional CVD risk factors, including low levels of high-density lipoprotein (HDL) cholesterol and increased rates of smoking [10–12] and certain antiretrovirals [13–15] have been associated with higher risk of myocardial infarction (MI), there is growing appreciation that heightened systemic inflammation and persistent immune activation, specifically monocyte activation, play important roles in the pathogenesis of atherosclerosis in HIV-infected persons [16••, 17–23]. In the Multicenter AIDS Cohort Study (MACS) for every standard deviation increase in log interleukin-6 (IL-6) and log intercellular adhesion molecule-1 (ICAM-1), there were 30 and 60% increases, respectively, in the prevalence of coronary stenosis ≥50% in HIV-infected men [16••]. Additionally, increased levels of soluble tumor necrosis factor-α receptors I and II (sTNF-RI and sTNF-RII) were associated with coronary stenosis ≥70% and higher levels of IL-6, sTNF-RI, and II were associated with greater coronary artery calcium scores. The monocyte activation marker soluble CD163 (sCD163) has been linked with arterial inflammation in HIV-infected persons on ART [19]. Further, monocytes from HIV-infected persons have impaired cholesterol efflux and increased foam cell formation after transendothelial migration in vitro, a process which is blocked by antibodies directed against the receptor for tumor necrosis factor-α (TNF-α) [24]. Based on these findings, many recent studies in HIV-infected persons have focused on targeting heightened immune activation [25–27].

While levels do not reach those measured in HIV-uninfected populations [28–31], indices of immune activation and inflammation, as well as the mediators that contribute to their levels, often improve with ART [32]. Reducing viremia below the limits of detection for standard clinical assays (<40 copies [cps]/mL), regardless of the timing of ART initiation in the course of HIV-infection, has been associated with declines in immune activation [33••, 34]. Whether or not various ART combinations affect immune activation and inflammation to similar degrees has not been adequately explored. Given that HIV-infected individuals are living longer than ever before, choosing the most convenient ART, with the lowest risk for long-term toxicities, is of high priority to HIV care providers and patients alike.

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Understanding the effects of different ART combinations on residual immune activation and systemic inflammation is the focus of this review.

Effect of ART Classes and Specific Antiretrovirals on Markers of Inflammation and Immune Activation from ART Initiation Trials

There are several studies comparing the effects of specific antiretrovirals and antiretroviral combinations in ART-naïve individuals initiating their first ART regimen. In the AIDS Clinical Trials Group (ACTG) study, A5248, peripheral blood mononuclear cells (PBMCs) were obtained from a subset of participants before and after initiation of open-label raltegravir (RAL) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and compared with PBMCs from healthy controls [35••]. After ART initiation, heightened monocyte activation, i.e., high frequency and density of HLA-DR and CD86 expression, as well as decreased chemokine receptors, CCR2 and CX3CR1, tended to normalize, with levels approaching those measured in HIV-uninfected controls. In a randomized clinical trial of elvitegravir/cobicistat/tenofovir DF/emtricitabine (EVG/c/TDF/FTC) vs efavirenz/ tenofovir DF/emtricitabine (EFV/TDF/FTC) in ART-naïve, HIV-infected adults [36], changes in plasma markers of systemic [high-sensitivity C-reactive protein (hsCRP), IL-6, sTNF-RI] and vascular inflammation [lipoprotein-associated phospholipase A2 (Lp-PLA2)] and monocyte activation [soluble CD14 (sCD14) and sCD163] were compared from a random sample of participants with HIV-1 RNA <50 cps/mL at week 48 [37••]. Most markers tended to decrease in both groups; however, initiation of the integrase inhibitor-based regimen was associated with greater declines in hsCRP, sCD14, and Lp-PLA2. Changes in IL-6, sTNF-RI, and sCD163 were similar between treatment arms. In ACTG 5260s, ART-naïve participants were randomized to receive TDF/FTC plus open-label RAL, atazanavir/ritonavir (ATV/r), or darunavir/ritonavir (DRV/r) [38]. Changes in soluble markers of inflammation and monocyte activation, as well as cellular markers of monocyte and T cell activation, and the coagulation marker D-dimer were evaluated from participants with HIV-1 RNA <50 cps/mL at week 24 [39••]. In this study, hsCRP decreased with ATV/r and RAL by 96 weeks; IL-6 decreased with only RAL; D-dimer decreased with ATV/r and DRV/r; markers of T cell activation and sCD163, but not sCD14 or inflammatory monocyte subsets, decreased in all randomization groups. The authors concluded that there was no consistent evidence that reduction in inflammation and immune activation was different between RAL- or protease inhibitor (PI)-based regimens. It is plausible that the integrase inhibitor class may decrease inflammation and immune activation more than other antiretroviral classes, as integrase inhibitors are more lipid friendly [38, 40] and may concentrate at higher levels in enterocytes [41], which is important because HIV infection results in massive depletion of immune cells within the GI tract and the resultant microbial translocation may be an important driver of immune activation in HIV. While integrase inhibitors appear to reduce inflammation to a greater degree than non-nucleoside reverse transcriptase inhibitors (NNRTIs) based on one study, it is not clear that there is a beneficial effect on inflammation resulting from treatment with integrase inhibitors compared to treatment with PIs in ART-naïve patients, and additional studies are needed. Specifically comparing the effect of the now widely prescribed integrase inhibitor dolutegravir with NNRTIs and PIs on inflammation and immune activation should be of top priority given lack of data presently with this drug.

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Markers of inflammation and immune activation have been evaluated in trials comparing NNRTIs with PIs as well. In a randomized, open-label trial of EFV or lopinavir/ritonavir (LPV/r) in combination with zidovudine/lamivudine (AZT/3TC), sTNF-RI, and sTNF-RII decreased significantly over 24 weeks; however, sTNF-RI tended to increase to baseline levels by week 96, whereas decreases in sTNF-RII were maintained. There were no between-group differences in the changes observed [42]. Similarly, in the SUPPORT trial, a 96-week, open-label, randomized, multicenter study comparing fosamprenavir/ritonavir (FPV/r) and EFV both in combination with abacavir/lamivudine (ABC/3TC) and changes from baseline levels in hsCRP, IL-6, soluble vascular cell adhesion molecule-1 (sVCAM-1), D-dimer, fibrinogen, and plasminogen were evaluated [43]. Most markers tended to decrease without differences between groups, although hsCRP levels increased at week 4, then returned to baseline for those participants in the FPV/r group, whereas hsCRP levels remained elevated in the EFV group through 96 weeks. In ACTG A5224s, a substudy of A5202, where ART-naïve, HIV-infected participants were randomized to ABC/3TC or TDF/FTC with EFV or ATV/r in a factorial design, changes in markers of inflammation over 24 and 96 weeks were evaluated [44]. Most markers, including sTNF-RI and sTNF-RII, TNF-α, IL-6, and adhesion molecules (sVCAM-1 and sICAM-1), decreased significantly by week 96, without significant differences between arms. In a 2-year observational study, IL-6, interferon γ-inducible protein-10 (IP-10), and monokine induced by interferon γ (MIG) decreased significantly, essentially to normal levels, whereas sCD14 did not change in treatment-naïve participants initiating ABC/3TC or TDF/FTC with EFV, LPV/r, or ATV/r [45]. Last, in the Adolescent Trials Network (ATN) study 061, among young adults achieving HIV-1 RNA <100 cps/mL by week 24 after initiating TDF/FTC and ATV/r, levels of CD8+ T cell activation, measured by CD38 and HLA DR expression, decreased over 48 weeks but remained higher than levels in the comparison group of uninfected young adults not on ART [46••]. Levels of sCD14 and sCD163 did not decrease following ART initiation in this study. Taken collectively, PIs and NNRTIs appear to reduce indices of systemic inflammation similarly, with the exception of hsCRP, where the results are mixed. Further, sCD14 and sCD163 do not consistently decrease with initiation of ART combinations containing NNRTIs or PIs.

Differences in specific nucleoside reverse transcriptase inhibitors (NRTIs) in the ART-naïve population have been evaluated as well, and most recent literature has focused on differences between ABC and TDF given the association of ABC with MI in some studies [14, 15]. Results from studies comparing changes in inflammation and immune activation between these two antiretrovirals have been mixed. In ACTG A5224s described earlier, hsCRP decreased less in those on ABC/3TC than among TDF/FTC recipients, and at 96 weeks, hsCRP was significantly higher than baseline for the ABC/3TC plus EFV group [44]. In an observational study of ART-naïve, HIV-infected persons initiating either ABC/3TC or TDF/FTC both with EFV, decreases in IL-6, TNF-α, sVCAM-1, sICAM-1, E-, and P-selectin were comparable after 48 weeks between the two groups; hsCRP did not change [47], whereas in a small study evaluating ART-naïve, HIV-infected adults initiating EFV, AZT, and 3TC, with or without ABC, there were lesser decreases in sTNFR-II and sVCAM-1 in the ABC-treated individuals than in participants not receiving ABC [48]. In these studies, differences in changes in inflammation markers were small and of

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questionable clinical significance. Changes in soluble markers of inflammation and monocyte activation were compared in a subset of participants randomized to TDF vs tenofovir alafenamide (TAF), both in combination with EVG/c and FTC, and declines were equivalent between groups [49]. In this study, there were significant declines from baseline for sTNF-RI, sCD163, and D-dimer by week 12, and IL-6 by week 24, in the combined sample. Contemporary NRTIs appear to result in similar decreases in measures of inflammation, with the exception of hsCRP where levels do not appear to improve with time on ART.

Change in Inflammation and Immune Activation in ART Switch Studies

As access and availability to ART are improving, and as more information is generated about the differential effects of ART on immune activation and inflammation, HIV-infected persons and clinicians are facing decisions about the potential benefits of switching ART regimens. In the SPIRAL study ($N = 233$), switch to a RAL-based from a PI-based regimen led to improvements in levels of hsCRP, IL-6, TNF-α, and D-dimer; these changes could only partially be attributed to improvements in lipoprotein levels in the RAL arm [50]. Similarly, in the ANRS 138 trial, switch to RAL from an enfuvirtide-based regimen led to improvements in all inflammatory markers tested, including IL-6, hsCRP, and D-dimer [51], a finding which was likely due, at least in part, to regression of injection site reactions associated with enfuvirtide. Last, in a small study ($N = 37$) where woman who were virologically suppressed on their current PI- or NNRTI-based ART were randomized to immediate or delayed switch to RAL, levels of sCD14, but not IL-6, hsCRP, or sCD163, decreased significantly in both the immediate and delayed switch groups; the decline in sCD14 was statistically different between the RAL and combined PI/NNRTI groups at week 24 [52]. These results are contrary to what has been seen in ART initiation studies where such significant differences between the integrase inhibitor class and other ART classes have not been as apparent.

There are additional switch studies where changes in immune activation could be assessed. The Switching Boosted-PI to Rilpivirine in Combination with Truvada as a Single-Tablet Regimen (SPIRIT study) explored the safety and potential benefits of switching from a ritonavir-boosted PI and two NRTIs, to the single-tablet regimen of rilpivirine/emtricitabine/tenofovir DF (RPV/FTC/TDF) [53]. The primary objective of non-inferior virologic suppression at 24 weeks was met; the RPV/FTC/TDF combination also improved LDL, total cholesterol, and triglyceride levels. This improvement in lipid profiles could be explored further, measuring changes in other pro-inflammatory lipid subclasses that have been associated with inflammation and immune activation in HIV infection [54, 55••, 56]. Two recent studies explored the effects of switching to EVG/c/FTC/TDF from an NNRTI-containing regimen (STRATEGY-NNRTI) [57] or switching from a PI-containing regimen (STRATEGY-PI) [58]. The primary endpoint for both of the STRATEGY studies was the proportion of participants with viral loads less than 50 copies/mL in either of the switch groups compared to the participants maintaining their current regimens. Participants in the STRATEGY-PI study who switched their therapy had superior viral control compared to participants who maintained PI-containing ART [58]. Switching regimens in the STRATEGY-NNRTI study was non-inferior to maintaining NNRTI-containing ART with

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regard to virologic suppression [57]. These studies could also be used to investigate the effects of switching ART regimens on markers of immune activation and inflammation.

The Effect of Maraviroc on Immune Activation

Several studies have evaluated the effect of maraviroc (MVC), CCR5 inhibitor, either as an ART intensification strategy or part of an initial ART regimen. CCR5 is a chemokine receptor and a key co-receptor used by HIV-1 for infection of CD4+ T cells. Treatment with MVC-boosted ART, compared to ART alone, improved CD4+ T cell counts and reduced viral replication after 48 weeks in participants who had previously been receiving ART [59]. More recent studies have provided mixed results on improvement of CD4+ T cell counts and reduction of immune activation following administration of MVC-containing ART. Intensification of ART regimens with MVC, compared to placebo, resulted in a decrease in plasma lipopolysaccharide (LPS) levels, but increases in plasma levels of sCD14 and the CCR5 ligand MIP-1β, as well as increases in T cell activation (%CD38+ HLA-DR+) in peripheral blood and rectal tissues [60]. In the single-arm trial A5256, the addition of MVC to suppressive ART resulted in no change in HIV persistence and a reduction in CD4+ T cell activation following 24 weeks of therapy [61••]. In a 48-week placebo-controlled intensification trial, there was no difference between the MVC and placebo arms in changes in CD4+ T cell numbers, T cell activation, or the plasma markers sCD14 and sCD163; MVC treatment did increase the proportions of CCR5+ CD4+ and CD8+ T cells and increased CCR5 ligands in the plasma [62]. The mixed results generated in these MVC intensification studies should be explored further in order to determine the value of adding MVC to successful ART for the purpose of reducing residual immune activation.

Studies exploring the benefits of MVC within initial ART treatment have also yielded mixed results. In a subanalysis of the MVC vs EFV as Initial Therapy (MERIT) study, participants randomly selected to receive MVC and tended to have more rapid decreases in levels of D-dimer and CD38 expression on T cells than did participants receiving EFV, despite similar gains in CD4+ T cell counts and suppression of viremia at 48 weeks [63]. Also, HIV-infected participants receiving initial ART regimens containing MVC had greater drug penetrance in the gut and greater normalization of CCR5+ CD4+ T cells, than did participants receiving a regimen containing EFV in ART-naïve participants [64••]. The authors also reported that MVC-induced reductions in sCD14 and zonulin levels but MVC treatment also resulted in activation of mucosal naïve CD8+ T cells. Initiation of an ART regimen with MVC, compared to one with TDF, resulted in greater CD4+ T cell gains, but fewer CD8+ T cell declines, resulting in less improvement in the CD4+/CD8+ ratio in MVC-treated participants [65••]. Both arms had similar declines in markers of immune activation and inflammation. While greater penetration of MVC into gut-associated tissues may be beneficial for reducing immune activation in some settings, increasing T cell activation in the tissues and plasma levels of CCR5 ligands may outweigh the potential benefits. Further studies are warranted.

An important consideration when assessing changes in markers of immune activation and inflammation following initiation of ART regimens, and for comparing the effectiveness of one regimen to that of another, is to evaluate the pretreatment levels of activation markers.

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Reduction in markers of immune activation is likely a consequence of how effective the ART regimen is, but it is also a reflection on the immune status of the participants at baseline. For example, a population initiating ART at low CD4 counts (<200 cells/μL) will likely have increased levels of immune activation pre-ART, compared to levels in a population initiating ART with CD4+ T cell counts >500 cells/μL; therefore, the change in immune activation levels may be more dramatic in participants with more advanced disease, enhancing regimen's perceived effectiveness. Studying changes in indices of inflammation and immune activation within the context of randomized clinic trials allows for direct comparisons between groups regardless of baseline immunodeficiency; however, overall, the magnitude of change may in fact be different or not apparent depending on baseline levels of inflammation. The immune status of participants initiating ART should be considered when assessing the effectiveness of ART at reducing immune activation, especially when comparing results from multiple studies and populations.

Residual Immune Activation Despite ART

Despite tremendous advances in the effectiveness of ART and increases in patient access to ART over the last two decades [1, 66, 67], virologic suppression with ART is often not sufficient to fully ameliorate the heightened immune activation present with HIV infection, especially among those who fail to restore CD4+ T cell counts [29, 32, 34]. Continued immune activation in HIV-infected persons on ART is likely the result of several mechanisms. First, persistent HIV replication in tissue sites, such as the lymph nodes, the GI tract, or very low levels in plasma detected with assays more sensitive than those used for clinical care, may be an important driver of immune activation [68–71]. HIV viral proteins generated as a result of low-level viral replication can activate immune responses [72]. Also, inflammatory lipids may contribute to immune activation in ART-treated HIV infection. Levels of oxidized low-density lipoprotein (oxLDL) are higher in HIV-infected individuals compared to HIV-uninfected individuals, and oxLDL levels correlate with markers of monocyte activation [54]. Levels of oxidized high-density lipoprotein (oxHDL) decrease and levels of oxLDL increase, over 96 weeks of ART, and there are positive associations between oxHDL and several markers of inflammation and immune activation over time including IL-6 and sCD163 at all time points [55••]. Further evidence for the potential inflammatory contribution of lipids is provided by a study where participants switched from a PI-based regimen to an integrase inhibitor-based regimen. This switch improved both lipid profiles and markers of inflammation, and changes in both indices were weakly correlated with each other [50]. The importance of co-infections on chronic immune activation in ART-treated HIV infection should also not be overlooked, as co-infections with hepatitis B virus, hepatitis C virus, or cytomegalovirus are common with HIV infection and have been linked to heightened levels of LPS and CD8+ T cell activation, respectively [73–75]. Finally, there is significant damage to the GI tract as a result of HIV infection, specifically to the tight epithelial barrier, which allows microbial products, including LPS, to enter the lamina propria and systemic circulation [76–79]. Microbial translocation into the bowel wall is associated with ongoing immune dysfunction within the GI tract. While levels of LPS in the systemic circulation tend to decrease with ART, they often remain higher than levels in uninfected individuals [80–82]. Attempts have been made to target some of these potential contributors to chronic immune activation [83, 84]. The effectiveness of these interventions

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has been variable. Discussion of these studies and their results is outside of the scope of this review.

Conclusion

Given what is now known regarding the association of residual immune activation and important co-morbidities in aging HIV-infected persons, one could argue that it is time to start thinking of ART as anti-inflammatory therapy. Regardless of class, ART initiation consistently leads to decreases in most systemic inflammatory markers, indices of T cell, and monocyte activation albeit rarely to levels comparable to HIV-uninfected individuals. Within this context, it is important to understand differences in ability to reduce immune activation between antiretroviral classes and even individual drugs within a class. While current literature does not strongly support the use of one class of ART over another, further research is needed. For example, with current ART, body mass index in general increases. Understanding the specifics about the distribution of this weight gain and links to systemic inflammation needs to be unraveled. With increasing ART options for patients, providers should focus on not only on convenience, short-term tolerability, and potential long-term toxicity, but also what is known regarding the anti-inflammatory properties of the drugs.

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