# Immune Activation and Inflammation Among People With HIV Receiving Antiretroviral Therapy

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| Key Considerations and Recommendations |
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| • HIV-related immune activation and systemic inflammation, despite viral suppression with antiretroviral therapy, are associated with increased risk for cardiovascular disease and metabolic complications, as well as a broad spectrum of comorbidities.<br>• Switching or adding antiretroviral (ARV) drugs solely to reduce immune activation or inflammation **is not recommended,** except in a clinical trial **(AII).**<br>• The use of immunomodulatory or anti-inflammatory therapy to reduce HIV-related immune activation or inflammation **is not recommended,** except in a clinical trial **(AII).**<br>• Routine monitoring of markers of immune activation or inflammation (e.g. high-sensitivity C-reactive protein [CRP] or interleukin-6 [IL-6]) to inform the clinical management of HIV **is not recommended (BII).** |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Weak*<br>***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion* |

## The Influence of Immune Activation and Inflammation on Disease Risk in People With HIV

Compared to people without HIV, people with HIV have demonstrated higher overall immune cell activation and higher levels of systemic inflammation (as measured by biomarkers such as interleukin-6 [IL-6]) and acute phase reactants (e.g., high-sensitivity C-reactive protein [hsCRP]).

Although immune activation declines with suppressive antiretroviral therapy (ART), it often persists at elevated levels in virologically suppressed people with HIV.[1,2] Extensive literature over the past decades has demonstrated a link between HIV-related systemic inflammation and an increased risk of age-related comorbidities, as well as mortality from non-AIDS conditions.[3-16] Specifically, blood markers of systemic inflammation among people with HIV have been associated with increased risk for a wide range of chronic conditions, including atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus, obesity, cancer, osteopenia/osteoporosis, and chronic obstructive pulmonary disease.[8-18] Even in individuals with CD4 T lymphocyte (CD4) cell counts >500 cells/mm$^3$, immune activation and inflammation are associated with increased morbidity and mortality from age-related comorbidities.[19,20]

## Antiretroviral Therapy as a Strategy to Reduce Inflammation

Early HIV diagnosis combined with prompt ART initiation can effectively achieve a lower level of persistent immune activation. Most inflammatory markers decline during the first several months of ART and may achieve a stable "setpoint" within 1 to 2 years.[21,22] In observational studies, people with HIV who initiated ART during acute HIV infection appeared to achieve a lower immune activation setpoint during ART-mediated viral suppression than those who started ART at later disease stages.[23] These data reinforce the recommendation to start ART as soon as possible after HIV diagnosis, regardless of CD4 count (see Initiation of Antiretroviral Therapy).

Currently, data do not support intensifying or modifying ART as a strategy to reduce immune activation after viral suppression is already achieved. For example, adding antiretroviral (ARV) drugs to an already suppressive regimen (or ART intensification) does not consistently improve immune activation.[24-28] Although some studies have suggested that switching an ARV regimen to one with a more favorable lipid profile may improve some markers of immune activation and inflammation, these studies have limitations, and results are not consistent across markers or among studies.[29-31] Thus, adding or switching ARVs solely to reduce immune activation or inflammation **is not recommended,** except in a clinical trial **(AII).**

## Adjunct Treatments to Reduce Immune Activation and Inflammation

Treatment strategies targeting immune activation and inflammation have been a focus of ongoing investigation. In this context, research strategies to mitigate inflammation among people with HIV on suppressive ART have typically taken one of three approaches: (1) target the root drivers of immune activation specific to HIV disease, (2) downregulate inflammatory pathways broadly, or (3) leverage anti-inflammatory properties of medications targeting traditional risk factors.

The HIV-related mechanisms driving immune activation have been posited to include viral persistence, permanent injury impairing immune recovery (i.e., due to lymphatic tissue fibrosis), presence of copathogens, as well as dysbiosis and microbial translocation.[32-36] Among these mechanisms, investigational approaches have targeted HIV reactivation from latently infected cells, fibrotic pathways, the gut microbiome, and cytomegalovirus coinfection.[27,37-41] However, thus far, none of these strategies have improved clinical outcomes. Therefore, these interventions should be pursued only in the context of clinical trials.

Data have emerged demonstrating the potential clinical benefit of broadly anti-inflammatory and immunosuppressive strategies among people without HIV who are at high risk for ASCVD events. The CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) studied canakinumab, a human monoclonal antibody targeting cytokine interleukin-1b, a driver of the IL-6 signaling pathway, as a secondary prevention strategy among people with known ASCVD who do not have HIV. CANTOS demonstrated a treatment effect for reducing inflammation, as well as cardiovascular events and cancer death, in the general population.[42] In people with HIV, canakinumab and tocilizumab, inhibitors of the receptor for IL-6, have been shown to reduce blood levels of markers of inflammation and immune activation.[43,44] However, it is unclear whether the potential risks of these immunomodulatory therapies, including the increased sepsis risk seen in the CANTOS trial,[42] outweigh their possible benefits for people with HIV, particularly with long-term use. Therefore, the clinical use of immunomodulatory or anti-inflammatory therapy solely to reduce HIV-associated immune activation or inflammation **is not recommended** among people with HIV, except in a clinical trial **(AII).**

Finally, beyond the well-established clinical benefit for reducing ASCVD events, hydroxymethylglutaryl coenzyme A (or HMG-CoA) reductase inhibitors, also known as statins, have been shown to improve biomarker levels of inflammation (e.g., hsCRP) and immune activation in the general population.[45,46] In this context, data from REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) have demonstrated a reduction in cardiovascular events with pitavastatin use among people with HIV (see Statin Therapy in People With HIV). Other commonly used medications with anti-inflammatory properties—such as aspirin, angiotensin-converting enzyme inhibitors, methotrexate, and angiotensin receptor blockers—have failed to consistently reduce biomarkers of immune activation and/or inflammation in people with HIV in randomized controlled trials.[39,47-50]

## Monitoring Inflammation

As evidence is insufficient to inform differential screening practices or clinical management strategies (e.g., for ASCVD) based solely on the level of individual blood biomarkers, there is no clear rationale to routinely monitor levels of immune activation and inflammation in people with HIV. Thus, routine monitoring of markers of immune activation or inflammation (e.g., hsCRP, IL-6) to inform the clinical management of HIV **is not currently recommended (BII).**

## References


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