

## Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression

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Key Considerations and Recommendations
<ul style="list-style-type: none"><li>• Persistently low CD4 T lymphocyte (CD4) cell counts and immune activation are each associated with increased AIDS- and non-AIDS-related morbidity and mortality among individuals with antiretroviral therapy (ART)-mediated viral suppression.</li><li>• Adding antiretroviral (ARV) drugs to a suppressive ARV regimen (ART intensification) does not improve CD4 cell recovery or reduce immune activation and, therefore, <b>is not recommended (AI)</b>.</li><li>• In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce all relevant markers of immune activation and <b>is not recommended (BIII)</b>.</li><li>• Interleukin-2 <b>is not recommended (AI)</b> to increase CD4 cell counts and/or decrease immune activation, because clinical trial data demonstrated no clinical benefit.</li><li>• Other interventions designed to increase CD4 cell counts and/or decrease immune activation <b>are not recommended</b> outside of a clinical trial, because no current interventions have been proven to decrease morbidity or mortality during ART-mediated viral suppression <b>(AII)</b>.</li><li>• Efforts to decrease morbidity and mortality during ART-mediated viral suppression should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and regular exercise; treating hypertension and hyperlipidemia).</li><li>• Monitoring markers of immune activation and inflammation is not recommended, because no intervention targeting immune pathways has proven to improve the health of individuals with HIV, and many blood markers that predict morbidity and mortality fluctuate within individuals <b>(AII)</b>.</li></ul>
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = <b>Weak</b></p> <p><b>Rating of Evidence:</b> 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</p>

Despite marked improvements in antiretroviral treatment (ART), morbidity and mortality in individuals with HIV continue to be greater than in the general population, particularly when ART is delayed until advanced disease stages. These morbidities include cardiovascular disease, many non-AIDS cancers, non-AIDS infections, chronic obstructive pulmonary disease, osteoporosis, type 2 diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and the frailty phenotype.<sup>1</sup> Although health-related behaviors and toxicities of antiretroviral (ARV) drugs are important factors, immune characteristics, such as a poor CD4 T lymphocyte (CD4) cell recovery and persistent immune activation and inflammation, likely also contribute to the disease risk among persons with HIV.

### **Poor CD4 Cell Recovery**

As long as ART-mediated viral suppression is maintained, peripheral blood CD4 cell counts in most individuals with HIV will continue to increase for at least a decade. The rate of CD4 cell recovery is typically most rapid in the first 3 months of suppressive ART, followed by more gradual increases over time.<sup>2-4</sup> If ART-mediated viral suppression is maintained, most individuals will eventually

recover CD4 counts in the normal range (>500 cells/mm<sup>3</sup>); however, approximately 15% to 20% of individuals who initiate ART at very low CD4 counts (<200 cells/mm<sup>3</sup>) may plateau at abnormally low CD4 cell counts.<sup>3-5</sup> Early initiation of ART in individuals with recent HIV diagnoses likely provides the best opportunity for maximal CD4 cell recovery.<sup>6</sup>

Persistently low CD4 cell counts despite ART-mediated viral suppression are associated with increased risk of morbidity and mortality. For example, individuals with HIV who have CD4 counts <200 cells/mm<sup>3</sup>, despite at least 3 years of suppressive ART, had a 2.6-fold greater risk of mortality than those with higher CD4 cell counts.<sup>7</sup> Lower CD4 cell counts during ART-mediated viral suppression are associated with an increased risk of non-AIDS morbidity and mortality,<sup>8-11</sup> including cardiovascular disease,<sup>12</sup> osteoporosis and fractures,<sup>13</sup> liver disease,<sup>14</sup> and infection-related cancers.<sup>15</sup> The prognostic importance of higher CD4 cell counts likely spans all ranges of CD4 cell counts, though incremental benefits are harder to discern once CD4 counts increase<sup>16</sup> to >500 cells/mm<sup>3</sup>.

Individuals with poor CD4 cell recovery should be evaluated for modifiable causes of CD4 cell lymphopenia. Concomitant medications should be reviewed, with a focus on those known to decrease white blood cells or, specifically, CD4 cells. If possible, these drugs should be substituted for or discontinued. Untreated coinfections (e.g., hepatitis C virus, HIV-2) and serious medical conditions (e.g., malignancy) also should be considered as possible causes of CD4 lymphopenia, particularly in individuals with consistently declining CD4 cell counts (and percentages) and in those with CD4 counts consistently below 100 cells/mm<sup>3</sup>.

In rare cases, CD4 cell counts actually decline, despite suppressive ART in the absence of an obvious clinical cause. Severe derangements in interleukin (IL)-7-mediated naive T cell homeostasis have been reported in these individuals, although the pathophysiology is likely to be multifactorial.<sup>17-19</sup>

Despite strong evidence linking low CD4 cell counts and increased morbidity during ART-mediated viral suppression, no adjunctive therapies that increase CD4 cell count beyond levels achievable with ART alone have been proven to decrease morbidity or mortality. Adding ARV drugs to an already suppressive ARV regimen does not improve CD4 cell recovery,<sup>20-25</sup> and does not reduce morbidity or mortality. Therefore, ART intensification is not recommended as a strategy to improve CD4 cell recovery (**AI**). Similarly, for individuals who are already maintaining viral suppression, switching ARV drug classes also does not consistently improve CD4 cell recovery and is not recommended (**BIII**).<sup>26</sup>

Immune-based therapies also have been investigated as a strategy to increase CD4 cell counts (e.g., IL-2, IL-7, growth hormone). Two large clinical outcome trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of interleukin-2 for improving CD4 cell recovery. IL-2 adjunctive therapy resulted in substantial CD4 cell count increases but with no observable clinical benefit.<sup>27</sup> Therefore, IL-2 is **not recommended (AI)**. Given the lack of established clinical benefit to date, other immune-based therapies should not be used except in the context of a clinical trial.

### ***Persistent Immune Activation and Inflammation***

HIV infection results in heightened systemic immune activation and inflammation, which predict more rapid CD4 cell decline and progression to AIDS and death, independent of plasma HIV RNA levels.<sup>28</sup> Although immune activation declines with suppressive ART, it often persists at abnormal levels in many individuals with HIV maintaining long-term ART-mediated viral suppression—even

in those with CD4 cell recovery to normal levels.<sup>29, 30</sup> Immune activation and inflammatory markers (e.g., IL-6, D-dimer, high sensitivity C-reactive protein (hs-CRP) also predict mortality and non-AIDS morbidity during ART-mediated viral suppression, including cardiovascular and thromboembolic events, cancer, neurocognitive dysfunction, and frailty.<sup>28</sup> A low CD4/CD8 ratio also might reflect this inflammatory state to some degree,<sup>31</sup> although it predicts AIDS events far more strongly than non-AIDS morbidity.<sup>32</sup> Although individuals with poor CD4 cell recovery (i.e., counts persistently <350 cells/mm<sup>3</sup>) tend to have greater immune activation and inflammation than those with greater recovery,<sup>29</sup> the relationship between innate immune activation and inflammation and morbidity/mortality is largely independent of CD4 cell count.<sup>33, 34</sup> Even in individuals with CD4 counts >500 cells/mm<sup>3</sup>, immune activation and inflammation are associated with increased morbidity and mortality.<sup>35, 36</sup>

### **ART as a Strategy to Reduce Inflammation**

Early diagnosis and treatment of HIV is, potentially, an effective strategy to achieve a lower level of persistent immune activation with ART. Most inflammatory markers decline during the first several months of ART and achieve a stable “setpoint” within 1 to 2 years.<sup>37, 38</sup> 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.<sup>39, 40</sup> Indeed, those randomized to the immediate treatment arm of the START trial appeared to achieve a lower early inflammatory setpoint than those who were randomized to delayed therapy.<sup>41</sup> Longer-term follow-up of START participants is needed to determine whether such a reduced inflammatory setpoint persists and translates into reduced morbidity and mortality. Collectively, these data reinforce the recommendation to start ART as soon as possible after HIV diagnosis (see [Initiation of Antiretroviral Therapy](#)).

Although earlier initiation of ART appears to consistently reduce the inflammatory setpoint during ART, intensifying or modifying ART after viral suppression is already achieved does not appear to consistently reduce immune activation. For example, adding ARV drugs to an already suppressive ARV regimen (or ART intensification) does not consistently improve immune activation.<sup>20-23, 25</sup> 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,<sup>42-44</sup> these studies have limitations and results are not consistent across markers and among studies. Thus, at this time, ART modification cannot be recommended as a strategy to reduce immune activation (**BIII**).

### **Other Immune-Based Strategies**

Because persistent immune activation is associated with morbidity and mortality among people with HIV who are virologically suppressed with ART, strategies targeting immune-mediators of inflammation are under investigation. Although the efficacy of canakinumab is not yet proven in people with HIV, the CANTOS trial provided important proof of concept for the causal role of inflammation in the risk of multi-morbidity in people without HIV but with cardiovascular disease. The study demonstrated that treatment with canakinumab, a human monoclonal antibody targeting cytokine IL-1 $\beta$ , a driver of the IL-6 signaling pathway, reduced cardiovascular events and cancer death.<sup>45</sup> In people with HIV, canakinumab and the IL-6 inhibitor tocilizumab have been shown to reduce blood levels of markers of inflammation and immune activation.<sup>46, 47</sup> Nevertheless, it remains unclear whether the potential risks of these therapies, such as the increased risk of death from sepsis observed in the CANTOS trial, might outweigh any benefits in people with HIV. Therefore,

interventions targeting immune mediators of inflammation are not currently recommended for clinical use for the treatment of immune activation in people with HIV (AII).

### **Treatments Targeting Traditional Risk Factors and Inflammation**

Beyond the well-established clinical benefit for reducing cardiovascular events, HMG-CoA reductase inhibitors (or statins) have been shown to improve biomarker levels of inflammation (e.g., hsCRP) and immune activation in the general population.<sup>48-50</sup> This premise, and the data suggesting similar benefit among people with HIV, motivated the design of a large clinical trial (REPRIEVE), now fully enrolled, to determine whether pitavastatin reduces cardiovascular events in people with HIV who do not already have a clinical indication for cholesterol-lowering therapy.<sup>51</sup> Although the results will not be known for several years, in addition to identifying the primary cardiovascular outcomes, assessing the impact of pivitastatin on non-cardiovascular events (such as cancer, osteoporotic fractures, and frailty phenotypes) that may be linked to the inflammatory state also will be valuable. Similarly, it remains unclear whether statins might further increase type 2 diabetes risk, which is increased in people with HIV.<sup>52</sup> Other commonly used medications with anti-inflammatory properties—like aspirin, angiotensin-converting enzyme inhibitors, methotrexate, and angiotensin receptor blockers<sup>53</sup>—have failed to consistently reduce biomarkers of immune activation and/or inflammation in people with HIV in randomized controlled trials and,<sup>54-57</sup> as a result, clinical outcome trials specific to this population are not anticipated.

### **Treatments Targeting Putative Drivers of the Inflammatory State**

Other investigational approaches to reduce the inflammatory state in patients with viral suppression on ART have focused on the presumed root drivers of inflammation, including HIV reactivation from latently infected cells, microbial translocation, and chronic co-infections, particularly cytomegalovirus (CMV).<sup>28</sup> Thus far, the only approach targeting these root drivers that has broadly reduced systemic immune activation is treating asymptomatic CMV co-infection,<sup>58</sup> an approach that is being pursued further in a prospective larger trial ([ACTG A5383](#)). Presently, none of these strategies have been proven to be effective in clinical endpoint trials, so these interventions should be pursued only in the context of clinical trials.

### **Monitoring Inflammation**

In the absence of proven interventions, there is no clear rationale to routinely monitor levels of immune activation and inflammation in treated HIV infection. Furthermore, many of the inflammatory markers that predict morbidity and mortality fluctuate significantly in individuals with HIV. Thus, clinical monitoring with immune activation or inflammatory markers **is not currently recommended (AII)**. The focus of care to reduce chronic non-AIDS morbidity and mortality should be on maintaining ART-mediated viral suppression and addressing strategies to reduce risk factors (e.g., smoking cessation, healthy diet, and exercise) and managing chronic comorbidities, such as hypertension, hyperlipidemia, and diabetes (AII).

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