



## **Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents**

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## Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression (Last updated April 8, 2015; last reviewed April 8, 2015)

### Panel's Summary and Recommendations

- Morbidity and mortality from several AIDS and non-AIDS conditions are increased in HIV-infected individuals despite antiretroviral therapy (ART)-mediated viral suppression, and are predicted by persistently low CD4 T lymphocyte (CD4) cell counts and/or persistent immune activation.
- ART intensification by adding antiretroviral (ARV) drugs to a suppressive ART regimen does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended (**AI**).
- In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended (**BIII**).
- No interventions designed to increase CD4 cell counts and/or decrease immune activation are recommended at this time (in particular, interleukin-2 is **not recommended [AI]**) because none has been proven to decrease morbidity or mortality during ART-mediated viral suppression.
- Monitoring markers of immune activation and inflammation is not recommended because no immunologically targeted intervention has proven to improve the health of individuals with abnormally high biomarker levels, and many markers that predict morbidity and mortality fluctuate widely in individuals (**AII**).
- Because there are no proven interventions to improve CD4 cell recovery and/or inflammation, efforts should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and exercise; treating hypertension, hyperlipidemia) (**AII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**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

Despite marked improvements in antiretroviral treatment (ART), morbidity and mortality in HIV-infected individuals continues 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 II diabetes, thromboembolic disease, liver disease, renal disease, neurocognitive dysfunction, and frailty.<sup>1</sup> Although health-related behaviors and toxicities of antiretroviral (ARV) drugs may also contribute to the increased risk of illness and death, poor CD4 T lymphocyte (CD4) cell recovery, persistent immune activation, and inflammation likely also contribute to the risk.

### **Poor CD4 Cell Recovery**

As long as ART-mediated viral suppression is maintained, peripheral blood CD4 cell counts in most HIV-infected individuals 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 recently HIV-infected individuals 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, HIV-infected individuals with 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 to >500 cells/mm<sup>3</sup>.<sup>16</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 (e.g., cancer chemotherapy, interferon, zidovudine,<sup>17</sup> or the combination of tenofovir disoproxil fumarate (TDF) and didanosine (ddI).<sup>18,19</sup> If possible, these drugs should be substituted for or discontinued. Untreated coinfections (e.g., HCV, HIV-2) and serious medical conditions (e.g., malignancy) should also be considered as possible causes of CD4 lymphopenia, particularly in individuals with consistently declining CD4 cell counts (and percentages) and/or in those with CD4 counts consistently below 100 cells/mm<sup>3</sup>. In many cases, no obvious cause for suboptimal immunologic response can be identified.

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 ART 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**). In individuals maintaining viral suppression, switching ARV drug classes in a suppressive regimen also does not consistently improve CD4 cell recovery and is not recommended (**BIII**).<sup>26</sup> Two large clinical trials, powered to assess impact on clinical endpoints (AIDS and death), evaluated the role of interleukin-2, an immune-based therapy, in improving CD4 cell recovery. Interleukin-2 adjunctive therapy resulted in CD4 cell count increases but with no observable clinical benefit. Therefore, interleukin-2 is **not recommended (AI)**.<sup>27</sup> Other immune-based therapies that increase CD4 cell counts (e.g., growth hormone, interleukin-7) are under investigation. However, none of the therapies have been evaluated in clinical endpoint trials; therefore, whether any of these approaches will offer clinical benefit is unclear. Currently, such immune-based therapies should not be used except in the context of a clinical trial.

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

Although poor CD4 cell recovery likely contributes to morbidity and mortality during ART-mediated viral suppression, there is increasing focus on persistent immune activation and inflammation as potentially independent mediators of risk. HIV infection results in heightened systemic immune activation and inflammation, effects that are evident during acute infection, persist throughout chronic untreated infection, and 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 HIV-infected individuals 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, 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> 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>31,32</sup> Even in individuals with CD4 counts >500 cells/mm<sup>3</sup>, there is evidence that immune activation and inflammation contribute to morbidity and mortality.<sup>33</sup> Thus, innate immune activation and inflammation are potentially important targets for future interventions.

Although the drivers of persistent immune activation during ART are not completely understood, HIV persistence, coinfections, and microbial translocation likely play important roles.<sup>28</sup> Interventions to reduce each of these presumed drivers are currently being investigated. Importantly, adding ARV drugs to an already

suppressive ART regimen (ART intensification) does not consistently improve immune activation.<sup>20-23,25</sup> Although some studies have suggested that switching an ART regimen to one with a more favorable lipid profile may improve some markers of immune activation and inflammation,<sup>34,35</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 commonly used medications with anti-inflammatory properties (e.g., statins, aspirin) are being studied, and preliminary evidence suggests that some may reduce immune activation in treated HIV infection.<sup>36,37</sup> However, because no intervention specifically targeting immune activation or inflammation has been studied in a clinical outcomes trial in treated HIV infection, no interventions to reduce immune activation are recommended at this time.

In the absence of proven interventions, there is currently no clear rationale to 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 HIV-infected individuals. 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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