Inadequate CD4 Recovery Linked to More Clinical Events

People whose CD4 T-cell count remains below 200 or even 350 are more prone to AIDS-related events and non-AIDS infections.

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People with HIV who do not experience full recovery of their CD4 T-cell count after starting antiretroviral treatment remain susceptible to both AIDS-defining clinical events and non-AIDS infections compared to those with adequate CD4 recovery, according to a new analysis published in the Journal of Infection.

Effective antiretroviral therapy (ART) halts HIV replication and allows CD4 cells to recover, but around 15% to 20% of people who start treatment with a very low count never reach a normal level (500 or higher). Those with a CD4 count below 200 (the threshold for an AIDS diagnosis) remain susceptible to opportunistic illnesses, but even those with higher subnormal levels are at greater risk for adverse health outcomes.

While the link between a persistently low CD4 count and greater morbidity is not surprising, this systematic review and meta-analysis underscores the importance of starting antiretroviral therapy promptly and staying on treatment to maintain an undetectable viral load, as it can be easier to preserve immune function that to reverse advanced immune deficiency later.

Tangwei Mou, of the First Affiliated Hospital of Kunming Medical University in China, and colleagues performed a comprehensive search of the EMBASE, PubMed, Web of Science and Cochrane Library databases, looking for studies on antiretroviral therapy, CD4 counts and AIDS-defining and non-AIDS clinical events.

They identified 15 relevant studies, with a combined patient population of 188,945 individuals, conducted after the advent of effective combination ART and published between 1999 and 2020. Most were from the United States and Canada (7) or Europe and the United Kingdom (6); there was one study each from Latin America and Asia. A majority were retrospective cohort studies.

The meta-analysis showed a significant inverse correlation between CD4 counts and morbidity, including both AIDS-defining events clinical events and non-AIDS infections. In particular, people with a CD4 count below 200 after starting treatment had a seven-fold higher risk for AIDS-defining events compared with those whose CD4 count reached 500 or higher. Those with a count of 200 to

350 still had a 63% elevated risk.

Looking at non-AIDS infections, people with a CD4 count below 200 had nearly a three-fold higher risk, while those in the 200-350 range had a 50% higher risk compared to those with a normal count. In contrast, however, people with a low CD4 count did not have a significantly higher risk for noninfectious non-AIDS clinical events.

These findings “emphasize the critical importance of maintaining CD4 cell counts above specific thresholds to mitigate the risk” of AIDS-defining events and non-AIDS infections, the study authors concluded. “This understanding can assist clinicians in making more informed decisions regarding treatment intensification or modification for patients with inadequate CD4 T-cell recovery.” They also suggest more frequent monitoring for people with a CD4 count below 200.

Furthermore, they note, the lack of an association between CD4 counts and noninfectious non-AIDS events “highlights the need for comprehensive care that addresses other risk factors beyond immunological recovery.”

Indeed, a growing body of research shows that people with HIV—even those on effective treatment with a high CD4 count—are more prone to non-AIDS comorbidities such as heart disease and kidney disease. Many experts think this is because even very low-level residual virus can trigger persistent immune activation and chronic inflammation.

Unfortunately, studies have shown that ART intensification, or adding more antiretroviral drugs to an already suppresses regimen, does not improve CD4 cell recovery or reduce immune activation, and it is not recommended in federal treatment guidelines. Various immune-boosting strategies (such as interleukin-2) have also been tested, but these are not recommended outside of clinical trials “because no current interventions have been proven to decrease morbidity or mortality during ART-mediated viral suppression.”

Instead, the guidelines recommend efforts that “focus on addressing modifiable risk factors for chronic disease,” such as smoking cessation, a healthy diet regular exercise and managing high blood pressure and elevated cholesterol.

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