Immunodeficiency at Start of Antiretroviral Therapy: The Persistent Problem of Late Presentation to Care

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Keywords. antiretroviral therapy; CD4; ecological bias; immunodeficiency; late presentation.

The CD4 T-cell count at the start of antiretroviral therapy (ART) is a critical indicator in measuring how well programs are responding to human immunodeficiency virus (HIV). CD4 cell count measures at initiation of ART are strongly associated with morbidity, mortality, life expectancy, and program costs [1-5].

The first programs to start providing ART in sub-Saharan Africa were initially confronted with very sick populations: the median CD4 cell count at start of ART in these early programs was <50 cells/µL [6]. As HIV testing and program reach expanded, the CD4 count at initiation of ART increased to around 150 cells/µL by 2006-2007 [6, 7]. Since then, guidelines have evolved toward recommending ART initiation at higher CD4 counts [8], and this has been associated with further increases in CD4 at start of ART [9]. The expectation is that as guidelines change and program coverage improves, most patients will present to care and start ART earlier, and this will result in reductions in mortality, morbidity, and costs. Put simply, the job will become progressively simpler as initial efforts to expand access are rewarded by a patient population that is increasingly asymptomatic, requiring fewer clinic resources and fewer clinical visits.

The findings of a systematic review and meta-analysis of trends in CD4 at presentation and ART initiation in sub-Saharan Africa, by Siedner et al, published in this issue of Clinical Infectious Diseases may therefore come as a disappointment. This systematic review assembled a large meta-analytic dataset of studies reporting CD4 at presentation or at start of ART in sub-Saharan Africa and, surprisingly, found no evidence of change between 2002 and 2013 [10]. However, it would be wrong to take the findings as meaning that no progress has been made. Meta-analysis of published, aggregate data is not the ideal approach to analyzing trends in CD4 cell counts. In particular, such analyses will be prone to ecological bias, where misleading conclusions about individuals are derived from aggregate-level data [11]. For example, the authors included published data from 2 ART programs in Côte d’Ivoire and Malawi, which participate in the International Epidemiological Databases to Evaluate AIDS (IeDEA) [12]. They used the median CD4 count of 128 cells/µL reported in the publication [3] and assigned this value to the median of the study period (2005). These aggregated data were then included in the meta-regression analysis, which found no change in the CD4 count at start of ART. However, the data from these programs show that CD4 count in fact increased by about 10 cells per year from 2004 to 2007.

The way in which ecologic bias (also known as the ecological fallacy, aggregation bias, or cross-level bias) can influence analyses of CD4 cell count at initiation is illustrated in Figure 1. The black bubbles and the broken line represent the meta-regression of the data aggregated at the program level: no trend over time in CD4 counts is seen. The red lines show that the aggregated data hide the fact that in most ART programs the CD4 cell count increased, with the rate of increase differing between sites.

In support of this interpretation, among the largest cohort studies (>10 000 patients) included in the meta-analysis that provide information on CD4 change over...
in conclusion, to further reduce HIV-associated illness and death, a major focus of attention is needed on increasing CD4 at entry to care. As the authors of the systematic review and meta-analysis rightly conclude, renewed efforts are needed to improve the timeliness of ART initiation, including through earlier HIV testing and referral. Community-based testing approaches that include house-to-house testing [25], point-of-care CD4 testing, and peer support [26] are among the interventions that could help raise the baseline. With almost 12 million people now on ART in low- and middle-income settings, emphasis is shifting toward adapting service delivery models to support the management of HIV as a lifelong chronic disease. This requires decentralizing care such that healthier patients require less clinical investment. Although this is certainly needed and appropriate for those on ART, programs need to retain clinical capacity to respond to late presenters as a critical component of the AIDS response. Finally, monitoring of CD4 cell counts at presentation and start of ART in sub-Saharan Africa and elsewhere should be based on individual-level data, rather than aggregate data.

**Note**

*Potential conflicts of interest.* All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**


