EDITORIAL COMMENTARY

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

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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 be 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

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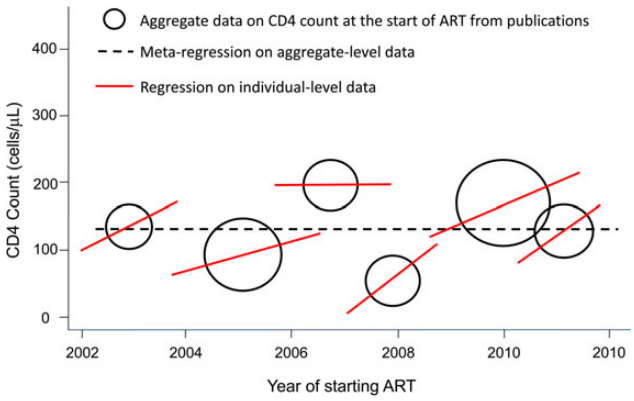

Figure 1. Ecological bias: hypothetical example of aggregate and individual level CD4 cell count data at the start of antiretroviral therapy (ART). In 5 of 6 programs, the CD4 cell count at the start of ART increased over calendar time (solid regression lines), yet the regression line fit to the aggregated data indicates that there was no change (broken regression line).

time, all but 1 [13] report either calendar year increases in median CD4 cell count [14–17], reductions in the proportion of patients presenting with low CD4 cell counts [18], or both [19, 20]; these 7 studies account for around two-thirds (65%) of the data included in the meta-analysis. Furthermore, 2 recent analyses of large cohort collaborations reported improvements in immune status at the start of ART, for both adults [21] and children [22]. The analysis in adults was based on individual-level data from almost 400 000 patients and showed that in low- and middle-income countries the increase was from about 90 cells/μL in 2002 to about 150 cells/μL in 2009 [21]. The annual increase varied within country income groups and was greater among women than men. For example, among lower middle-income countries, the annual change in median CD4 cell counts ranged from –2 cells/μL among Nigerian men to 13 cells/μL among women in Côte d'Ivoire [21]. More recent data from the IeDEA collaborative cohort from 2013 show that among the 19 countries from sub-Saharan Africa, the median CD4 count at the start of ART was >200 cells/μL in 17 countries, >250 cells/μL, in 9 countries, and >300 cells/μL in 2 countries [23].

In light of these data, an appropriate conclusion to draw from the available data is that there have been program-level increases in CD4 at start of ART over time in most but not all programs, and that the magnitude of this increase has been variable. This finding is consistent with operational research demonstrating that some clinics and programs function better than others. Reasons for this include human resource constraints, geographic differences in distance to services, and differing engagement strategies [21].

Thus, although progress has been made, the findings of all the studies draw attention to the fact that the CD4 cell count at start of ART initiation in sub-Saharan Africa remains far too low. The current consensus definitions of late presenters in Europe—a CD4 cell count of <350 cells/μL or an AIDS diagnosis within 6 months of HIV diagnosis—is associated with a >13-fold increased risk of AIDS or death [24]. According to this definition, even the latest estimates for 2013 indicate that the majority of patients starting ART in sub-Saharan Africa are late presenters.

The meta-analysis [10] also highlights important declines in CD4 status around 100 cells/mm^3 between engagement in care and initiation of treatment, despite the fact that average CD4 at engagement in care warrants immediate initiation of ART. A 100 cell/mm^3 difference represents a period of approximately one year, a period of depletion linked to both decreased future life expectancy and increased risk of transmission. There are important issues that need to be evaluated between engagement in care and initiation of ART, such as management of coinfections to reduce the likelihood of immune response inflammatory syndrome and patient readiness.

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.

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