

Is the Rate of CD4 Cell Decline Changing Over Time in Antiretroviral-Naïve Patients?

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Dear Editor,

CD4+ CELL COUNTS are used to determine risk for HIV disease progression, eligibility for antiretroviral therapy (ART), and immunologic response to ART. A recent Brazilian study suggested that CD4 cell counts are declining more rapidly among recently infected patients than in the pre-combination ART era.¹ Rates of CD4 cell decline were compared in a well-characterized clinical cohort from the Hospital das Clínicas (HCFMUSP) in São Paulo, Brazil, in patients diagnosed in the pre-ART era (<1998) and those diagnosed after ART became widely available in Brazil (≥1998).^{2,3} We examined 81 ART-naïve patients at HCFMUSP with known dates of HIV diagnosis between 1988 and 2012 who presented with ≥500 CD4 cells/μL. Our primary outcome variable was time from cohort entry until the date of first CD4 count ≤350 cells/μL or of first clinical stage 3 or 4 presentations (WHO). Predictor variables included gender, age, transmission category, CD4 cell count at diagnosis, years of HIV follow up since diagnosis, and chemokine co-receptor type (CXCR4 or CCR5). We dichotomized year of diagnosis into <1998 and ≥1998. We calculated median survival from baseline and 95% confidence intervals (CI) using the Kaplan-Meier method and tested for equality of survivor functions using the log rank statistic. We used the Cox proportional regression model to estimate the hazard ratio (HR) of the association between the predictor variables and outcome (CD4 count ≤350 cells/μL). We also fitted generalized estimating equations (GEE) to build a linear model considering the within-individual correlation structure of repeated CD4 and using the robust variance estimator method. We stratified the GEE model for <1998 and ≥1998 and report the crude and adjusted regression coefficients as rates of CD4 change over time.

Out of 81 eligible cases; 32 entered care ≤1998 and 49 afterwards. There were no differences between the groups in age, gender, transmission category, baseline CD4 count,

baseline plasma viral load, length of time followed, or CXCR4 tropism. There was a statistically significant association between the period of diagnosis and time to T CD4+ cells decline to ≤350 cells/mm³ (log rank $p < 0.001$). Before 1998, the mean time to a CD4 count of 350 cells/μL was 2.43 (95% CI 1.70–3.15) years and from 1998 and later 7.03 (95% CI 5.63–8.42) years (Fig. 1). This adjusted hazard ratio was 0.17 (95% CI 0.08–0.32), corresponding to a decline of 56.68 cells/μL/year before 1998 and 49.74 cells/μL/year in 1998 and later. Having CXCR4 tropic HIV (HR, 3.1, 95% CI, 1.2–7.8) was statistically associated with progression to CD4 count ≤350 cells/μL. Despite the clinical impression that treatment-naïve patients are progressing more rapidly in the ART era, we found that CD4 cell counts were, in fact, declining less rapidly in 1998 and later than before 1998. We also found that CXCR4 tropic viruses were associated with faster progression disease, as have other authors,^{1,4} but the differential presence of CXCR4 tropic viruses did not explain the changes we observed. Our study was limited by its small sample and irregularly sampled CD4 cell measurements, especially before 1998. Larger and more regularly sampled cohorts may have different results. Nonetheless, our findings are compelling and suggest slower CD4 cell declines in treatment-naïve patients in the era of effective ART. The mechanism for this is not clear. Additional studies will facilitate the identification of factors that may underlie this trend.

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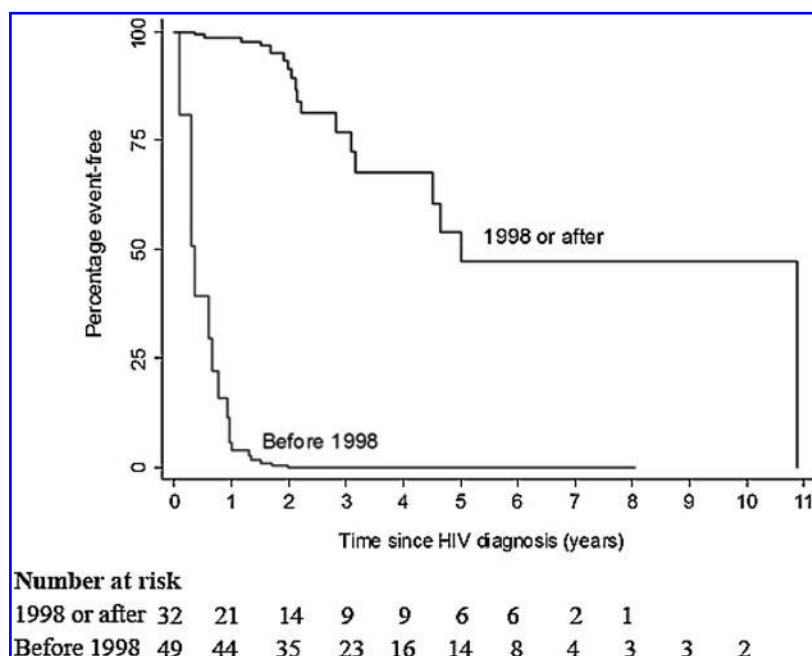


FIG. 1. Survival curves to CD4 less than 350 by ART era (before and after 1998) adjusted for covariates (age, gender, HIV follow-up time, and CD4 at baseline).

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Author Disclosure Statement

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