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Are HIV-Positive Persons Progressing Faster After Diagnosis Over the Epidemic?

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To the Editors:

Recently, two large studies found that documented HIV seroconverters are presenting with significantly lower initial CD4 cell counts during the epidemic^{1,2}. Trends in the initial CD4 counts may be important for healthcare planning since they are key markers for immune competence and initiation of highly active antiretroviral therapy (HAART)³. To further understand these trends, we examined the time to CD4 counts <500 cells/mm³ after adjusting for the initial CD4 count.

We evaluated documented HIV-1 seroconverters from 1986–2007 as part of the U.S. Military HIV Natural History Study (NHS)⁴. Active duty members are HIV negative upon service entry and undergo testing every 1–5 years, resulting in narrowly defined seroconversion windows. Participants were racially diverse and from various geographic areas within the U.S.

For this analysis, participants had documented seroconverting windows of ≤4 years (mean 1.4, standard deviation (SD) 0.8 years). We excluded those who initiated antiretroviral therapy

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before the first documented CD4 count (n=96), those without a documented CD4 count (n=365) or a CD4 <500 cells/mm³ at diagnosis (n=1060).

Participants were evaluated at HIV diagnosis and at six-month intervals; clinical data, including CD4 counts, were recorded. Subjects were censored at the earliest time of last observed CD4 count, three consecutive missed study visits, death, initiation of HAART, or after four years of follow-up.

The primary variable of interest was the period of HIV diagnosis. The study period was *a priori* divided into 1986–1990, 1991–1995, 1996–2001, and 2002–2007, similar to our previous work². Time zero was the date of documented HIV seropositivity. Kaplan-Meier curves and Cox proportional hazard models were utilized to estimate the hazard ratios (HR) to the first CD4 <500 cells/mm³ for each time period. Models were stratified by clinical site and adjusted for age, gender, ethnicity, body mass index, seroconverting window, time from HIV diagnosis to initial CD4 count, initial CD4 count and HIV RNA level at diagnosis, and time-updated duration of single or dual-agent ART. Models were repeated among participants with narrow seroconverting dates (window ≤12 months). Analyses were conducted using SAS (version 9, Cary, NC).

We evaluated 1,085 documented HIV seroconverters with a mean age of 28 (SD 7) years; 95% were male; 48% were Caucasian and 41% were African American. The overall mean post-seroconversion CD4 cell count was 720 (SD 204) cells/mm³ and were 765, 707, 682, and 712 cells/mm³ for the four time periods, respectively (p<0.0001).

In the adjusted multivariate models of time to CD4 count <500 cells/mm³, the HR of a CD4 count <500 cells/mm³ increased during the epidemic: 1.14 (95% confidence interval (CI), 0.92–1.41) for those seroconverting during 1991–1995, 1.12 (0.78–1.60) for 1996–2001, and 1.29 (0.91–1.82) for 2002–2007, compared to 1986–1990.

The analyses were repeated among participants with seroconverting windows of ≤12 months (n=402). The HRs for the time periods were 1.09 (95% CI, 0.73–1.62), 1.88 (0.97–3.64), and 1.83 (0.95–3.51), respectively (Figure 1). We performed additional analyses using a delayed entry approach (time zero was the estimated seroconversion date, but participants were not at risk until the HIV diagnosis date); similar results were noted.

In addition, analyses were repeated among participants with seroconverting windows of ≤12 months utilizing other calendar period cut-offs reflective of the literature¹, the delayed entry approach, and similar censoring (but at two years, not four), stratification and adjusting variables (except for time-updated antiretroviral therapy). We found that compared to seroconverters in 1986–1990, HRs for time to CD4 count <500 cells/mm³ were 1.05 (95% CI, 0.63–1.75) for 1991–1994, 1.67 (95% CI, 0.74–3.74) for 1995–1998, 2.61 (95% CI, 1.08–6.27) for 1999–2002, and 2.08 (95% CI, 0.91–4.77) for 2003–2007.

In summary, our study found that recent documented HIV seroconverters have trends for a faster time to progression to a CD4 count <500 cells/mm³ after initial diagnosis than those diagnosed earlier in the epidemic. Although most HRs were not statistically significant, likely due to our sample size, they do show potentially important trends. Previous studies have suggested that HIV patients are presenting with lower initial post-seroconversion CD4 counts over the epidemic^{1,2}. Our data extends the existing literature by examining the risk of CD4 count decline after HIV seroconversion.

Our results are concurrent to those from a European cohort, which showed that both the initial and follow-up CD4 counts are lower and declining faster, respectively, over the epidemic¹. Our findings suggest that similar trends are also occurring in the U.S. The reasons for the faster

progression of HIV are unclear, but some have suggested that HIV may have become more pathogenic^{1,2,5}; further studies are needed.

Our findings have potentially important healthcare implications since HIV patients appear to be progressing to a CD4 count <500 cells/mm³ faster over time, and recent treatment guidelines now suggest initiation of HAART at this CD4 level³. Data on potential changes in HIV progression over time are important components of healthcare planning. Based on these data, we advocate future studies examining CD4 trends over time among HIV seroconverters to detect further changes in disease progression.

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Figure 1.

Hazard Ratios for a CD4 count <500 cells/mm³ from the Adjusted Multivariate Models among Documented HIV Seroconverters with a Window of ≤ 12 Months