

The changing virulence of HIV

Trends in HIV virulence have been studied since the beginning of the epidemic. Early studies examined direct clinical events, but the introduction of combination antiretroviral therapy (ART) necessitated the shift to studies of prognostic markers measured before initiation of treatment. Commonly used markers are the set-point viral load, CD4 T-cell count at seroconversion, and rate of CD4 cell decline, which are typically regressed against seroconversion dates to assess trends. Increasing set-point viral loads or decreasing CD4 cell counts can be interpreted as increasing virulence, and (for increasing set-point viral load) increasing HIV transmissibility.^{1,2}

In *The Lancet HIV*, Pantazis and colleagues³ examined trends in set-point viral load 1 year after seroconversion, CD4 cell count at seroconversion, and individual CD4 cell decline in CASCADE, which is a collaboration of 28 cohorts of mostly European individuals with estimated dates of HIV seroconversion. Overall, the trends are consistent with increasing HIV virulence and transmissibility; the authors estimated that from 1979 to 2008, median set-point viral load increased by about 0.4 log₁₀ viral RNA copies per mL (from 4.05 to 4.5 log₁₀ copies per mL), and CD4 cell counts at seroconversion decreased by about 200 cells per µL (from about 770 to about 570 cells per µL). Notably, trends in all three markers plateaued beginning around 2002, after which HIV virulence seems to decrease.

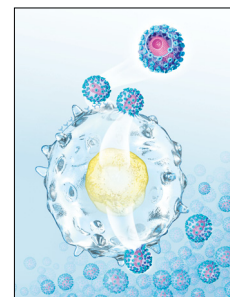
The analysis included 15 875 HIV-infected individuals, contributing a total of 110 168 CD4 cell counts and 88 205 HIV plasma viral load measurements, making this study by far the largest of its kind to date. The individuals represented about 62% of CASCADE, excluding children, individuals without CD4 or viral load data before AIDS or ART initiation, individuals who seroconverted after 2008 (due to insufficient follow-up time to estimate marker values), and the two African cohorts in CASCADE. CD4 cell count slopes and viral load trajectories were calculated for each individual, with point estimates for set-point viral load and CD4 cell count subsequently used for tests of association with seroconversion date. Potential confounders included age at seroconversion, sex, transmission risk group, ethnic origin, year entered into the cohort, and method of seroconversion ascertainment. Sensitivity analyses of potential confounders (viral load assay; censoring because of

AIDS, death, or ART initiation; risk subgroups; length of intervals between HIV tests) revealed similar trends.

No consensus exists on whether HIV virulence has changed, and reports from among more than 30 published studies have shown stable,^{4,5} increasing,^{6,7} and decreasing virulence.^{8,9} Perhaps the results from the analysis by Pantazis and colleagues³ will generate such consensus. First, the study was substantially larger than the next largest of its kind (2174 individuals in the US Military HIV Natural History Study¹⁰), and included 26 unique HIV cohorts from western Europe, Australia, and Canada. Trends estimated from a large combined database such as this are likely to be less biased than individual cohorts or study populations. Second, when Pantazis and colleagues³ assumed a strictly linear relation between seroconversion date and set-point viral load, the estimated trend was 0.016 log₁₀ copies per mL per year (95% CI 0.013–0.019; p<0.0001). This trend is consistent with the summary estimate from a recent meta-analysis of HIV prognostic markers,¹¹ 0.013 log₁₀ copies per mL per year (95% CI –0.001 to 0.027; p=0.07).

If the observed set-point viral load and CD4 cell count trends are an accurate and unbiased reflection of HIV virulence changes, what is the most likely biological explanation? Pantazis and colleagues³ offer the possibility for adaptive viral evolution toward an optimum level of virulence that balances transmission with mortality.¹² The apparent plateau in virulence starting in 2002 is consistent with adaptive evolution of HIV virulence in the early stages of an epidemic.^{13,14} Alternatively, widespread use of combination ART might modify the optimum virulence, either by shortening the available timeframe for transmission and thus selecting more virulent viruses, or through the preferential early treatment of individuals with high set-point viral load (likely to be symptomatic) and thus selecting for decreased virulence.

The public health implication of increasing HIV virulence, manifested by higher set-point viral load and lower CD4 cell count at seroconversion, is that infectiousness is increasing since the beginning of the epidemic. This observation supports the implementation of more frequent testing among people at risk and earlier ART initiation, and the need for an HIV vaccine¹⁵ or other interventions to reduce set-point viral load and the viral reservoir.



Henning Dalhoff/Science Photo Library

Published Online
November 18, 2014
[http://dx.doi.org/10.1016/S2352-3018\(14\)00004-6](http://dx.doi.org/10.1016/S2352-3018(14)00004-6)
See [Articles](#) page e119

For more on CASCADE see
<http://www.ctu.mrc.ac.uk/cascade>

*Joshua Herbeck, Connie Celum

International Clinical Research Center, Department of Global Health, University of Washington, Seattle, WA 98104, USA
herbeck@uw.edu

We declare no competing interests.

- 1 Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *New Engl J Med* 2000; **342**: 921–29.
- 2 Lingappa JR, Hughes JP, Wang RS, et al. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. *PLoS One* 2010; **5**: e12598.
- 3 Pantazis N, Porter K, Costagliola D, et al, on behalf of CASCADE Collaboration in EuroCoord. Temporal trends in prognostic markers of HIV-1 virulence and transmissibility: an observational cohort study. *Lancet HIV* 2014; published online Nov 18. [http://dx.doi.org/10.1016/S2352-3018\(14\)00002-2](http://dx.doi.org/10.1016/S2352-3018(14)00002-2).
- 4 Müller V, Ledergerber B, Perrin L, et al. Stable virulence levels in the HIV epidemic of Switzerland over two decades. *AIDS* 2006; **20**: 889–94.
- 5 Herbeck JT, Gottlieb GS, Li X, et al. Lack of evidence for changing virulence of HIV-1 in North America. *PLoS One* 2008; **3**: e1525.
- 6 Dorrucchi M, Phillips A, Longo B, Rezza G. Changes over time in post-seroconversion CD4 cell counts in the Italian HIV-Seroconversion Study: 1985–2002. *AIDS* 2005; **19**: 331–35.
- 7 Gras L, Jurriaans S, Bakker M, et al. Viral load levels measured at set-point have risen over the last decade of the HIV epidemic in the Netherlands. *PLoS One* 2009; **4**: e7365.
- 8 Keet IPM, Veugelers PJ, Koot M, et al. Temporal trends of the natural history of HIV-1 infection following seroconversion between 1984 and 1993. *AIDS* 1996; **10**: 1601–02.
- 9 Muñoz A, Xu J. Models for the incubation of AIDS and variations according to age and period. *Stat Med* 1996; **15**: 2459–73.
- 10 Crum-Cianflone N, Eberly L, Zhang Y, et al. Is HIV becoming more virulent? Initial CD4 cell counts among HIV seroconverters during the course of the HIV epidemic: 1985–2007. *Clin Infect Dis* 2009; **48**: 1285–92.
- 11 Herbeck JT, Muller V, Maust BS, et al. Is the virulence of HIV changing? A meta-analysis of trends in prognostic markers of HIV disease progression and transmission. *AIDS* 2012; **26**: 193–205.
- 12 Fraser C, Hollingsworth TD, Chapman R, de Wolf F, Hanage WP. Variation in HIV-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis. *Proc Natl Acad Sci USA* 2007; **104**: 17441–46.
- 13 Herbeck JT, Mittler JE, Gottlieb GS, Mullins JL. An HIV epidemic model based on viral load dynamics: value in assessing empirical trends in HIV virulence and community viral load. *PLoS Comput Biol* 2014; **10**: e1003673.
- 14 Shirreff G, Pellis L, Laeyendecker O, Fraser C. Transmission selects for HIV-1 strains of intermediate virulence: a modelling approach. *PLoS Comput Biol* 2011; **7**: e1002185.
- 15 Gupta SB, Jacobson LP, Margolick JB, et al. Estimating the benefit of an HIV-1 vaccine that reduces viral load set point. *J Infect Dis* 2007; **195**: 546–50.