Has Human Immunodeficiency Virus Become More Virulent?

Maria Dorrucci1 and Andrew Phillips2

1Istituto Superiore di Sanita’, Dipartimento di Malattie Infettive, Parassitarie ed Immunomediate, Rome, Italy; and 2 Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London, United Kingdom

(See the article by Crum-Cianflone et al. on pages 1285–92)

The possibility that the ability of HIV to lead to CD4 cell depletion could change over the course of the epidemic has been the subject of several studies [1–11]. In this issue of Clinical Infectious Diseases, Crum-Cianflone et al. [12] report results that suggest that the mean post-seroconversion CD4 cell count among HIV seroconverters has significantly decreased over the course of the HIV epidemic in the United States. Their large incident (i.e., with known seroconversion date) cohort of military personnel studied since 1985 provides an excellent source of data for evaluating temporal changes of this important indicator of early CD4 cell count depletion. Ascertainment of HIV seroconversion through regular testing of all military personnel and early CD4 cell count assessments in all infected persons means that important variables that could affect the observed CD4 cell count trend over time have been taken into account.

Studies that examine temporal trends of post-seroconversion CD4 cell counts need to verify that the observed results are not attributable to variation in the length of the seroconversion windows (i.e., time from last negative HIV test result to first positive HIV test result). For instance, the trend of decrease in the early CD4 cell counts observed by Crum-Cianflone et al. [12] could have been attributable to the fact that more-recent seroconverters had their first CD4 cell counts measured a longer time after seroconversion than did earlier seroconverters [1]. CD4 cell counts can fluctuate markedly during acute and early infection [13, 14] and, in particular, can decrease during primary HIV infection, then increase thereafter [13], then decrease further in the first 12–18 months after seroconversion [15]. Crum-Cianflone and colleagues took this important issue (i.e., the possibility of different lag times) into account by adjusting for length of the possible seroconversion window and repeating their analyses considering only those with a seroconversion window of ≤2 years and excluding patients with CD4 cell counts measured during the acute illness [12]. Residual confounding could have resulted, because the length of seroconversion window and time to initial CD4 cell count measurement both appeared to be shorter during recent years; however, these changes would have been expected to result in an increase in the initial CD4 cell count over the years and cannot explain the results of the Crum-Cianflone et al. study [12], which demonstrate the opposite trend.

The study of temporal changes in CD4 cell count and/or viral load may be approached in other ways. For example, it would be helpful to examine trends in CD4 cell count and/or viral load by considering approaches other than initial CD4 cell count assessment, as in the study by Crum-Cianflone et al. [12]; later time points could be taken into account, rather than the time near seroconversion, when CD4 cell counts might fluctuate less [2]. Estimating the individual rate of CD4 cell decrease by including repeated assessments of CD4 cell counts would be another approach, although the estimate of the CD4 slope would obviously have to be based on measurements made prior to any antiretroviral treatment initiation; this would be difficult, especially since the introduction of HAART. This is because, in this case, the estimates of CD4 cell count slopes could be affected by when individuals initiate HAART, which depends on guidelines that have changed over time as well as the varying individual severity of the disease. Models would have to adjust for potential informative censoring [16].

Several studies have been performed that examine whether there have been changes in HIV virulence over time. In observational studies, results have been in-
consistent: to date, all 3 possibilities of a stable, decreasing, and increasing virulence have been suggested [1–11]. The majority of studies have considered proxies of HIV virulence, such as the first CD4 cell count after seroconversion and/or the first HIV load measurement. Virologic studies have also shown conflicting results by assessed the in vitro replicative capacity of primary HIV isolates as a proxy for virulence. A study from Belgium [17] found that HIV replicative capacity in historical strains was significantly greater than that in recent strains, suggesting that HIV replicative fitness may have decreased since the start of the pandemic; however, an Amsterdam cohort study [18] determined that HIV replicative fitness was higher in isolates from individuals infected more recently than in those infected earlier, suggesting the opposite conclusion. As pointed out elsewhere [19], however, it is unclear whether simple immunological or virological proxies for virulence can be expected to adequately capture the whole complexity of HIV virulence and host susceptibility.

The question underlying the study by Crum-Cianfalone et al. [12] is: Is there any biological hypothesis for a change in virulence for HIV? Changes in virulence during an epidemic are possible among pathogens, but this is not known in the case of HIV [17]. In the absence of evidence to the contrary, it is generally assumed in models of HIV progression and transmission used to estimate the number of infected people and treatment need that there have not been changes in the rate with which HIV leads to AIDS. However, it cannot be excluded that HIV may evolve to be a more or less benign strain over a longer period of time. There is some evidence that some infectious agents may adapt to human hosts, becoming less virulent, but there are also some reasons to think the opposite. It cannot be excluded that HIV may become more virulent as an effect of antiretroviral therapy that may select more aggressive strains, but there is little evidence for this currently, and generally, antiretroviral therapy is successful in reducing replication, such that risk of transmission itself is low. The increased circulation of more-aggressive HIV subtypes could also explain the results of studies that show increased virulence over time. In this case, however, the apparent increased virulence would not be the consequence of a selection process but only an effect of a greater representation of more-virulent subtypes (possibly subtype D [20]) that are more prevalent in certain geographic areas. It has been hypothesized that increases in the ability of HIV to deplete CD4 cells increases over time and drives HIV progression [21–23], and there is some direct in vivo evidence from studies of viral rebound after treatment interruption that, among those with a low CD4 cell counts, HIV replicative capacity is greater than that in those with high CD4 cell counts [24]. It is also known that strains of virus that use the CXCR4 co-receptor tend to appear at some point during infection in many people, and this is associated with increased CD4 cell depletion [25–27]. It could be that, as the epidemic progresses, infected individuals are, on average, more advanced in their infection, which leads to a greater capacity of HIV to deplete CD4 cell counts over time. However, it would seem that there is a bottleneck at transmission, in that only certain strains can be efficiently transmitted [28], and this would perhaps limit the extent to which HIV could become more virulent over time at a population level [18]. Studies performed in the future may examine whether there are decreasing trends in post-seroconversion CD4 cell counts; although the study by Crum-Cianfalone et al. [12] suggests that the trend may have plateaued, such that a shift toward still lower CD4 cell counts at seroconversion in future years is perhaps unlikely.

Acknowledgments

Potential conflicts of interest. M.D. and A.P.: no conflicts.

References


