HIV-1 Subtype as a Determinant of Disease Progression

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(See the article by Kiwanuka et al. on pages 707–13.)

Although the average time from infection with HIV type 1 (HIV-1) to the development of AIDS is ~1 decade, the rate of disease progression varies considerably among infected persons. Numerous factors, including plasma HIV-1 RNA level, CD4 cell count, degree of immune activation, age, socioeconomic status, and host genetics, contribute to determining the rate of progression in the individual patient [1]. Intrinsic viral properties, such as coreceptor use and replication capacity, may also influence progression rates. Data have been accumulating to suggest that viral subtype is another contributing factor [2–4]. The report by Kiwanuka et al. [5] in this issue of the journal provides compelling evidence that infection with HIV-1 subtype A (HIV-1A) progresses more slowly than infection with HIV-1 subtype D (HIV-1D) or with recombinant or multiple HIV-1 subtypes.

As summarized in the report by Kiwanuka and colleagues, HIV is classified into types (HIV-1 or HIV type 2), groups (HIV-1 M, N, and O), and subtypes (or clades) on the basis of genetic relatedness. At present, 9 subtypes are recognized (A–D, F–H, J, and K), along with several circulating recombinant forms, which contain sequences from >1 subtype. Because the different HIV-1 subtypes are not uniformly dispersed, comparisons of virulence and transmissibility are hampered by potential confounders, such as ethnic, socioeconomic, and other epidemiological factors. The cocirculation of HIV-1A, HIV-1D, and several intersubtype recombinants in the Rakai district of Uganda provides an opportunity to compare rates of disease progression associated with these different subtypes within a similar population.

In the current report, Kiwanuka et al. [5] compared rates of progression among HIV-1 seroconverters who were followed as part of the Rakai Health Sciences Program. Subjects identified during 1997–2002 were followed through 2004, when antiretroviral therapy became available in Rakai district. The HIV-1 subtype was determined by a multiregion hybridization assay in which gag, pol, vpu, env, and gp41 amplicons from plasma HIV-1 RNA were tested in a second-round PCR with subtype-specific Taqman probes. This approach allowed the authors to categorize samples as comprising a single subtype, mixtures of ≥2 subtypes, or intersubtype recombinants. The primary end point was the time to achievement of a CD4 cell count of ≥250 cells/mm³ or death due to AIDS.

Of the 350 seroconverters enrolled, nearly 60% were infected with HIV-1D, 15% with HIV-1A, 21% with recombinant subtypes, and 4% with multiple subtypes. Progression to a CD4 cell count of ≥250 cells/mm³ was significantly less common among subjects infected with HIV-1A (20%), compared with subjects infected with HIV-1D (40%), recombinant forms (40%), or multiple subtypes (53%) (P = .03). Death from AIDS was also less common among subjects infected with HIV-1A. These differences were reflected in the longer time to AIDS onset for HIV-1A–infected subjects (8.05 years), compared with those infected with HIV-1D (6.49 years), recombinant forms (5.57 years), or multiple subtypes (5.80 years). In multivariable models that controlled for virus load, age, and sex, subjects infected with multiple subtypes, HIV-1D, or intersubtype recombinants were 4.40, 2.13, and 2.16 times, respectively, more likely to progress to AIDS, compared with those infected with HIV-1A. Similarly, subjects infected with non-A subtypes had an approximately 6–8-fold greater risk of death from AIDS.

Previous studies involving cohorts of persons with seroprevalent infection also found that the risk of disease progression is greater for persons with HIV-1D infection than for those with HIV-1A infection [3, 4]. Although seroprevalent cohorts can provide important information about late events, such as death after AIDS, they potentially suffer from survival bias (i.e., subjects with rapid progression tend to be
excluded from analysis) [6]. In addition, because the timing of HIV-1 infection is rarely known, it is difficult to control for duration of infection in analyses of sero-prevalent cohorts. Thus, the use of a cohort of persons with seroincident infection is a particular strength of the study by Kiwanuka and colleagues. An important unanswered question is the biological basis for the apparent lower virulence of HIV-1A. A possible clue comes from data suggesting that emergence of CXCR4-using (X4) variants is less common in HIV-1A infection, compared with HIV-1D infection. In a study of rural HIV-1 infection in southwest Uganda, investigators found that X4 and dual-tropic variants were more common in HIV-1D infection, but the differences were not statistically significant, and the cross-sectional design precluded analyzing the effect of coreceptor use on the risk of disease progression [7]. Preliminary data from the Rakai investigators found a similar excess of X4 viruses among HIV-1D–infected subjects [8]. Longitudinal studies involving predominantly subjects infected with HIV-1 subtype B (HIV-1B) showed a significantly greater risk of disease progression among those infected with CXCR4-using virus [9, 10]. It will be important to explore the relationship between emergence of CXCR4-using virus and subsequent disease progression in the Rakai cohort of seroconverters. The finding that HIV-1A infection progresses less rapidly than HIV-1D infection raises the question of whether other HIV-1 subtypes also are associated with different rates of disease progression. It would be interesting to compare progression rates in Brazil, where HIV-1B and HIV-1 subtype F cocirculate along with B-F recombinants, and in Thailand, where HIV-1B and the circulating recombinant form CRF01_AE predominate. Comparison of progression rates for infections due to HIV-1B and HIV-1 subtype C (HIV-1C), which cocirculate in China, would be of particular interest given that HIV-1C accounts for the largest number of infections worldwide, although differences observed in Chinese populations might not apply to populations on the Indian subcontinent or in southern Africa, where most HIV-1C infections are found. Although the current report highlights the importance of viral characteristics in determining the rate of HIV-1 disease progression, a growing body of data point to the importance of host genetic factors, as well. Among the most important factors are polymorphisms in the genes encoding the chemokine coreceptors and their ligands [11] and in the genes encoding human leukocyte antigens [12]. Variation in the killer immunoglobulin-like receptor genes also affects the course of HIV-1 disease [13]. These receptors are found on natural killer (NK) cells and regulate NK activity by recognition of certain HLA class I molecules on the surface of target cells. It seems likely that these genetic factors exert their effect on disease progression by modifying the innate and adaptive host immune responses to HIV-1 infection. A comprehensive effort to examine the interplay of viral, immune, and host genetic factors in the control of HIV-1 replication is currently underway through the International HIV Controller Consortium [14]. Similar efforts should be undertaken in diverse human populations infected with a variety of HIV-1 subtypes in order to understand fully the complex interplay of virus and host in AIDS pathogenesis.

References