Are All HIV Type 1 Strains Created Equal?

Thomas B. Campbell
Division of Infectious Diseases, Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado

(See the article by Vasan et al. on pages 843–52)

Although most would agree that HIV-1 genetic diversity is an important consideration for the design of vaccines to prevent or attenuate HIV-1 infection, there is debate regarding whether circulating strains of HIV-1 differ in their ability to be transmitted from person to person, the course of disease after initial infection is established, or their response to treatment with antiretrovirals. Because data are sparse, opinions differ, and, in general, current guidelines for health care and treatment policies do not take into account potential differences in biological properties that could result from viral biological diversity.

The global spread of HIV-1 has been characterized by rapid genetic diversification as the virus has adapted to replicate in human hosts. Evidence suggests that cross-species transmission of chimpanzee simian immunodeficiency virus to humans has occurred more than once, giving rise to at least 3 distinct groups of HIV-1 called M, N, and O [1–4]. Despite the establishment of infections in humans by the ancestral M, N, and O viruses in similar periods of time, only group M has spread globally. Group N and O remain localized in western equatorial Africa, where they cause a small fraction of cases of HIV-1 infection, and they are rare in other parts of the world. This inequality in the global distribution of HIV-1 groups suggests that there are intergroup biological differences [5], a hypothesis that is supported by the observation of differences in group O and M virus replication fitness and inherent drug susceptibility [6].

The potential biological consequences of the global diversity of group M has also been the subject of a number of investigations that have sometimes provided conflicting results regarding differences in transmission, response to treatment, and disease pathogenesis among the many distinct group M subtypes. Certainly, the rapid spread of subtype C (but not other subtypes) throughout southern Africa and the Indian subcontinent suggests that there are inherent differences in the transmissibility of subtype C in heterosexual populations. The fact that genital track viral loads are greater in pregnant women in Kenya infected with subtype C, compared with viral loads of subtypes A or D, supports this hypothesis [7]. Likewise, in Tanzania, mothers infected with subtype A, C, or intersubtype recombinant viruses are more likely to transmit virus to their babies than are mothers infected with subtype D, and subtype C infection is associated with a higher risk of in utero transmission [8, 9]. However, in another study, the risk of mother-to-child transmission was not associated with subtype, despite the study’s use of a similar sample size of HIV-infected African women [10]. In Thailand, subtype E infection is associated with a higher plasma viremia [11] and a greater probability of transmission of HIV-1 among injection drug users than is subtype B [12]. Thus, existing data, although limited and sometimes contradictory, do provide evidence that intrinsic differences in the transmissibility of group M subtypes exist.

Most of what is known about the use of antiretroviral agents to treat HIV-1 infection comes from experiences in North America, Europe, and Australia, where group M subtype B predominates. Because the use of antiretroviral therapy has been limited in areas of the world where there is greater HIV-1 genetic diversity, little is known about the factors that affect response to antiretroviral therapy in persons infected with non–subtype B HIV-1. Most available data suggest that the response to initial antiretroviral therapy is similar among people infected with various group M subtypes. Although interpretation and generalization of many existing studies are limited by nonrandomized designs and small numbers of participants infected with non–subtype B HIV-1, there are some hints that subtle differences exist in the frequency and pathways to the evolution of antiretroviral drug resistance in different HIV-1 group M subtypes. Examples include the findings that natural resistance to nonnucleoside...

In this edition of Clinical Infectious Diseases, Vasan et al. [16] report that the rate of disease progression differs among pregnant African women infected with diverse HIV-1 subtypes. This work is unique because it correlates group M subtype with relevant clinical events (e.g., death and the World Health Organization stage 4 of disease) and CD4+ lymphocyte counts in a population infected with relatively equal proportions of subtypes A, C, D, and intersubtype recombinant viruses. As the authors point out, their study is the first to have this degree of genetic diversity in a sample size that provides sufficient power to detect associations between disease progression and subtype. The important finding of this study is that subtype D was associated with more-rapid disease progression in Tanzania than were the other subtypes that are prevalent throughout Africa. This finding provides further evidence that intragroup M biological differences exist and that these differences are important factors to consider when formulating approaches to the treatment of HIV-1 infection around the world.

The study by Vasan et al. [16] has limitations, including a patient population with unknown dates of HIV-1 seroconversion and a homogenous population (i.e., pregnant women) that is a subset of the larger HIV-infected population. Despite the limitations, which are discussed extensively by the authors, this study remains an important step towards a better understanding of the public health implications of diverse HIV-1 subtypes. As discussed above, previous studies have demonstrated that subtype D more easily develops resistance to nonnucleoside reverse-transcriptase inhibitors. Now there is evidence that subtype D may also be more virulent than previously thought. The associations of subtype D with more-rapid disease progression, combined with differences in the evolution of drug resistance, provide evidence that existing paradigms for the initiation of antiretroviral treatment and composition of antiretroviral regimens, which have been derived largely from experience with subtype B infection, may not be completely applicable for patients in Africa. Hopefully, future studies will be forthcoming to provide better insight into the molecular mechanisms for differences in group M subtype virulence, transmissibility, and drug resistance and regarding whether intersubtype biological differences require different approaches to clinical management of HIV infection in diverse areas of the world.

Acknowledgments

Financial support. US Public Health Service (AI32770).

Potential conflicts of interest. T.B.C.: no conflicts.

References