High Viremia in HIV-1 Subtype C Infection and Spread of the Epidemic

To the Editor—We read with interest the article by Campbell et al that described viral loads in human immunodeficiency virus type 1 (HIV-1) subtype C infection [1]. These studies show that the C subtype and non-C subtypes do not differ significantly in terms of their viral set points following seroconversion. These observations contradict the findings of Novitsky et al [2], who showed that a substantial proportion of HIV-1 subtype C–infected individuals maintained a high viral set point and proposed that the extended viremia may have contributed to the spread of HIV-1 subtype C [2]. In our opinion, there are multiple factors associated with the rapid spread of HIV-1 subtype C in the world, particularly in South Africa and India [3,4].

First, there is emerging evidence that a major determinant of the spread of HIV-1 subtype C probably lies in its genome. Studies have shown that HIV-1 subtype C strains have a third nuclear factor–κB (NF-κB) site, whereas most non-C strains, including the commonly studied subtype B viral strains, have merely 2 NF-κB sites [5]. A recent study has shown that HIV-1 subtype C strains with an additional fourth NF-κB in its long terminal repeats are expanding and replacing the subtype C viruses containing 3 NF-κB sites [6]. Individuals infected with a virus harboring 4 NF-κB sites had a higher viral load than individuals with virus containing only 3 NF-κB sites, although there was no significant difference in their CD4⁺ T-cell counts. These observations may lead one to infer that the biological advantage conferred by the addition of a fourth NF-κB site may provide HIV-1 subtype C viruses an added infectiousness, suggested by the high viral load, but not necessarily added virulence. These Darwinian evolutionary characteristics may be conducive to viral survival and spread within a population. This may also be true in the case of addition of a third NF-κB site, compared with the 2 sites in subtype B viruses.

Second, the lower penetration of antiretroviral therapy in resource-limited geographic areas where subtype C is predominant may be an important reason for uncontrolled viremia in a large percentage of the untreated population. We recently reported that a large proportion of ART-naive children and adolescents with perinatally acquired HIV-1 subtype C infection had high viremia (HIV-1 RNA load, >5 log₁₀ copies/mL) despite having maintained an acceptable clinical

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profile (ie, they were asymptomatic) and immunological profile (ie, their CD4+ T-cell count was >350 cells/mm³) [7]. Prevailing high viremia in the untreated population may also facilitate transmission kinetics and spread of HIV-1 subtype C in these areas. Finally, host genetic factors such as HLA types may also play an important role in determining viral control [8, 9]. A whole-genome association study showed that when expressed by the host, the rs2395029 polymorphism in the HCP5 gene (which encodes HLA complex P5) and the HLA-C gene can mediate HIV restriction, thus moderating the spread of HIV in the community [10].

In summary, studies conducted by our group and others indicate that there are likely to be multiple factors, including viral and host immunogenetics, as well as clinical and geographical disease-management strategies, that play pivotal roles in determining viral control. A public health approach involving studies in basic, translational, and clinical science are warranted to understand the pathobiology of the HIV-1 subtype C strain and its therapeutic and preventive management.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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