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 log_{10} 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 the rapid spread and prevalence of HIV-1 subtype C strains globally. 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.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Received 30 January 2013; accepted 5 March 2013; electronically published 10 June 2013.

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The Journal of Infectious Diseases 2013;208:866–7
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DOI: 10.1093/infdis/jit258