Rising prevalence of variant HIV-1 subtypes poses new diagnostic challenge

By John M. Robinson, PhD

Just as clinicians were gaining a high degree of confidence that most patients with HIV-1 infection could be treated and monitored successfully with drug therapies, they now face the troubling emergence of variant subtypes of HIV-1. According to some studies, these infections, found mainly in immigrant populations from Africa and Asia, may represent up to 10% of HIV-1 infections in certain areas of the United States and have important implications for HIV-1 diagnostics and therapy.

Variant strains of HIV-1 originating in Africa, Asia, and Latin America have been detected with greater frequency in the United States, especially New York City and other areas with immigrants from continents where non-B subtypes predominate. A study published last year in the *Journal of Acquired Immune Deficiency Syndrome* by Linqi Zhang and colleagues from the Aaron Diamond AIDS Research Center noted more than two million immigrants now reside in New York and many come from areas with high prevalence of HIV-1 infection. They are believed to be a major source for the introduction and dissemination of novel HIV-1 strains in the United States.

According to the study, “It is generally assumed that infections in the United States are exclusively with the B-clade and that this situation is going to continue into the foreseeable future. This study shows that this is unlikely to be the case and that non-B subtype strains already have a strong presence in the United States and have the potential for spreading in the future.”

Further, it has been reported that nearly three in four of all African- and Asian-born HIV patients in New York City have non-B HIV strains and, although the data is inconclusive, some believe that certain subtypes are more infectious than others and may more easily develop resistance to antiviral therapies.

Public-health officials have raised the issue of the growing genetic diversity of HIV-1, which poses significant challenges for diagnosis and treatment of new HIV infections. Optimal drug treatment requires ongoing, precise measurement of viral levels. If variant subtypes are present and significantly underquantified or undetected, therapy could be compromised.

HIV-1 is classified into groups M (major), O (outlier) and N (new). The vast majority of known infections are group M strains, but the high mutation rate and rapid evolution of the virus resulted in the emergence of different group M subtypes, designated A through K. Moreover, recombination events between different strains resulted in viruses composed of multiple viral genomic regions.

A recent study by the Centers for Disease Control and Prevention reported the estimated prevalence of non-B subtypes and circulating recombinant forms represent about 5%. A growing cause for concern is that most diagnostic test reagents for HIV have been engineered for subtype B, but due to immigration and frequent international travel, the regional balance of HIV subtypes is shifting quickly.

A compelling finding of the Zhang study is that non-B HIV subtypes already have a strong presence in the United States and will spread further. In an analysis of African-born immigrants, Charles Cartwright, from the Hennepin County Medical Center in Minneapolis, observed a significant rise in newly diagnosed individuals in his institution (4% in 1996 to almost 20% in 2004. Less than 5% of these individuals were infected with subtype B, with the predominant subtypes observed being C, A, CRF02_AG and D).

In addition to variant group M subtypes, HIV-1 group O infections also are being watched carefully. Group O, or outlier HIV infections, are found mainly in west central Africa but a small number of cases have been documented in the United States. We have known about group O since the mid-1990s when west Africans and anyone traveling there were deferred from donating blood. It is not unreasonable, therefore, to expect that continued immigration and international travel will bring more group O infections to patient populations across the Atlantic.

Based on several studies, current molecular-based diagnostic tests vary in their ability to detect and reliably quantify HIV-1 group O and have been found to underquantify certain group M

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non-B strains. Continuing diversification and redistribution of HIV-1 requires that viral-load tests be regularly evaluated to assess their reliability and quantification accuracy. In his Journal of Medical Virology article, Cartwright notes “anecdotal reports of HIV-1 viral-load testing failures attributable to genetic variability continue to appear in the literature, and ongoing surveillance either by manufacturers or, preferably, by independent groups, to assure the reliability of all FDA-approved viral-load assays on emerging viral variants seem thoroughly warranted.”

A number of studies have been published recently that evaluate the performance of viral-load assays with these diverse subtypes. A recent study published in the Journal of Acquired Immunodeficiency Syndrome compared the performance of the new real-time PCR assays on their ability to quantify these variant subtypes. Only one assay quantified group O, and a number of the specimens were underquantitated by another assay, leading the authors to conclude that limitations of viral-load assays need to be considered during treatment monitoring and resistance studies.

Successful monitoring of patients on HIV-1 drug-therapy mandates use of viral-load assays to effectively identify and quantify all variant HIV-1 subtypes. Yet, current regulatory policy shows a discrepancy in standards for donor screening and patient monitoring for HIV-1. Immunoassays for screening donors must be sensitive and specific for HIV-1 group O, in addition to all the group M subtypes. There is, however, no such requirement for viral-load tests. As a result, as the prevalence of HIV-1 subtypes rises, clinicians could be hindered in their ability to accurately diagnose and treat newly infected patients harboring variant HIV-1 subtypes. Clinicians and laboratorians, therefore, are advised to carefully review and compare the performance of HIV-1 viral-load assays for accurate quantitation of variant subtypes, especially when treating immigrant patients.

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