An evolving genetic tapestry of HIV-1 recombinants

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HIV-1 strains circulating globally are classified into four groups; within the major group M, strains are classified into nine pure subtypes (A, B, C, D, F, G, H, J, and K), several sub-subtypes (A1, A2, etc), and recombinant forms. The latter are further divided into circulating recombinant forms (CRFs), which have been detected in three or more epidemiologically unrelated individuals, and unique recombinant forms (URFs).[1] Recombination is one of the major mechanisms driving genetic heterogeneity of HIV-1 and can provide a more efficient way of altering the genetic make-up of the virus than mutations inserted during the reverse transcription process.

Unique and mosaic forms of HIV-1 have increasingly been detected, and to date more than a hundred different CRFs have been recorded in the HIV sequence database. Some of these forms are second-generation recombinants, either between CRFs and pure subtypes, such as between CRF01_AE and C (eg, CRF100_01C),[2] or between CRFs (eg, CRF70_0107, identified among men who have sex with men in China).[3] Therefore, the global genetic complexity of circulating viruses has been increasing, with large numbers of first-generation and second-generation recombinants, some of which have been associated with concentrated or generalised epidemics. Molecular surveillance of the HIV clades, including recombinants, can be useful for epidemiological purposes, vaccine development, and the development of diagnostic assays. Specifically, monitoring the global distribution and proportions of CRFs can be important for monitoring the epidemiological trends of novel or existing recombinants in regions with concentrated or generalised epidemics.

In *The Lancet HIV*, Joris Hemelaar and colleagues[2] show the global and regional prevalence of recombinant forms (CRFs and URFs) based on a systematic review of published and unpublished data for the time period 1990–2015. Global estimates of the distribution of recombinants were based on the proportion of recombinants of each region combined with the UNAIDS estimates for the mean number or people living with HIV in each year (appendix). Hemelaar and colleagues show that the proportion of global HIV-1 infections attributable to recombinants in 2010–15 was 22·8% and has increased over the study period.[2] The proportion of infections attributable to CRFs also

For the **HIV sequence database** see http://www.hiv.lanl.gov

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increased over the study period and reached 16·7% in 2010–15. The proportion of URFs was 6·1% in 2010–15.

The most prevalent CRFs were CRF02_AG and CRF01_AE, accounting for 33·9% and 23·0% of the global recombinant infections, respectively, in 2010–15. Both CRFs emerged during the early stage of the HIV-1 epidemic, specifically in the early 1970s in Africa.[5,6] CRF01_AE has been associated with a large epidemic among heterosexual people in Thailand and subsequently migrated to southeast Asia, and more recently to China. In addition, people who inject drugs have also been infected with CRF01_AE in China, which is a hotspot for second-generation recombinants including CRF01_AE. Southeast Asia and east Asia provide sources for viral migration to other regions, including Europe and America.[7] However, CRF02_AG dominates in west Africa, with transmission mostly occurring via heterosexual contact.[6] CRF02_AG is the most prevalent CRF in Europe, associated mostly with migration from areas with generalised epidemics.

Although HIV transmission rates depend on wseveral factors, such as founder effects and social networking, evidence suggests the genetic make-up of viruses is probably not negligible. In principle, recombinants have a selective advantage over their ancestors. For example, CRF19_cpx was proposed to cause rapid progression to AIDS,[8] and the CRF01_AE/B inter-subtype recombinants were reported to replace progenitors in Malaysia.[9] Of note, western and central Europe and north America had the highest number of CRFs across all time periods, even though they do not provide hotspots for the generation of new recombinants. This complexity was probably due to high human mobility to Europe, mostly from sub-Saharan Africa. URFs are found more frequently in geographical areas where co-infection is likely and more than one subtype is circulating (eg, Latin America and east, west, and central Africa).

The overall picture indicates that new recombinants are continuously accumulating and some are associated with large regional epidemics, such as CRF35_AD in the Middle East and north Africa or CRF63_02A1 in eastern Europe and central Asia. URFs are found more frequently in geographical areas where co-infection is likely and more than one subtype is circulating (eg, Latin America and east, west, and central Africa), providing hotspots for new mosaic viruses. Recombinant viruses are thought to have an evolutionary advantage over their ancestors, a hypothesis supported by the increasing number and proportion of CRFs over time. Epidemiological studies, however, cannot provide direct evidence about the potential evolutionary advantage of the recombinant viruses due to confounding by many factors.

The study by Hemelaar and colleagues provides an informative picture about the proportion of HIV-1 infections caused by different recombinant forms. This information is useful for the global molecular surveillance of HIV-1 and the development of an effective vaccine and viral assays. HIV-1 is one of the few viruses spreading through continuous generation of new recombinant forms, and molecular surveillance is necessary to monitor this complexity.

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