



## Commentary

## Deciphering How HIV-1 Intersubtype Recombination Shapes Viral Fitness and Disease Progression



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Extreme genetic variability is the hallmark of HIV-1 infection and it represents a major challenge for antiviral treatment and vaccine development. HIV-1 group M dominates the global pandemic. Nine subtypes, 68 circulating recombinant forms (CRF) and countless unique recombinant forms (URF) were described within this group (Los Alamos HIV database, [www.hiv.lanl.gov](http://www.hiv.lanl.gov)). This genetic diversity not only affects viral epidemiology but it is also linked to the mechanisms used by the virus to escape the patients' natural humoral and cellular immune responses as well as anti-retroviral drug's action, thus precluding viral control. As a result, monitoring the genetic diversity of HIV-1 and understanding its consequences on viral fitness is crucial to control the spread of the epidemic.

Intersubtype genomic recombination is one of the main mechanisms that allow achieving such a high diversity level. Indeed, CRFs account for about 10–20% of all new HIV-1 infections while URFs are responsible for over 30% of infections in regions where two or more subtypes cocirculate, clearly contributing to HIV-1 evolution and adaptation to the human population (Tebit and Arts, 2011). As such, this phenomenon has been addressed by several groups and through different means and many (confronting) hypothesis co-exist today on the “biological advantage” (if any) of CRFs over parental subtypes.

In an effort to understand the increasing prevalence of CRFs in particular regions of the world, many researchers initiated the study of the in vitro activity of isolated proteins (Nef, Vpu, Tat) or genomic regions (LTR) derived from CRFs, in comparison to the activity of the proteins/regions derived from the parental subtypes (Woollard et al., 2014; De Candia et al., 2013; Turk et al., 2006, 2009). Others went one step further and analyzed the ex vivo replicative fitness of CRFs (Rubio et al., 2014; Njai et al., 2006). Many of these reports suggest improved biological capacities of CRFs compared to the parental subtypes. However, the in vitro activity of a protein or even the viral fitness measured ex vivo are not necessarily correlated directly to the replication capacity within a subject, its rate of disease progression or, even less, with the dynamic of the epidemic at the population level. Conversely, other authors postulate a different scenario: preferential spread of less fit viral variants (i.e., less pathogenic) due to increased transmission opportunities favored by longer periods of asymptomatic infection. Only just a few studies dealt with the challenge of providing, altogether, virological, epidemiological

and clinical data to better understand the complexity of this phenomenon and its role in shaping HIV-1 epidemic (Li et al., 2014; Huang et al., 2014).

In this issue of *EBioMedicine*, Kouri and colleagues (Kouri et al., 2015) report results of their study on a Cuban cohort of HIV-1-infected individuals aimed at comparatively analyzing parameters that could determine an increasing trend of HIV-1 infected individuals showing extremely rapid progression rates. The researchers used epidemiological, clinical, virological, and immunological approaches to establish putative correlates of disease progression. Several factors were found to be statistically related to the rapid progressor condition. Among them, it is worth highlighting the finding that all patients infected with CRF19\_cpx belonged to the group of rapid progressors. This CRF is a complex recombinant between subtypes D, A and G, apparently circulating exclusively in Cuba (although of African origin) and that it is now reported in clear association with differential rates of diseases progression. Their findings are very interesting since they represent a progress in depicting genomic recombination as a mechanism to gain fitness. Moreover, the study combines clinical follow-up, virological characterization of CRF19\_cpx and immunological approaches to provide potential explanations to the faster progression.

Reports like the one of Kouri and collaborators certainly contribute to our understanding of the forces that drive HIV diversity. However, there exist a myriad of other factors that may be also acting and that are hard to include in these kinds of studies: founder effects, host restriction factors, transmission efficiency and social/behavioral/cultural/geographical components may be all affecting differential spread of HIV variants. Certainly, it is a field that deserves and guarantees further research aimed not only to comprehend viral diversity and spread but also to assist in monitoring the epidemics, in monitoring and treating the infection in those affected individuals, and in vaccine design and development.

**Disclosure**

We declare that we have no conflict of interests.

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