Hot News

A greater virulent HIV-1 subtype B variant has circulated in The Netherlands since the 1990's

Despite being COVID-19 the global focus of attention nowadays, other pandemics caused by RNA viruses are ongoing. This is the case for AIDS. Roughly, 38 million people are, at present, living with HIV-1 infection worldwide and more than 33 million have died since the beginning of the pandemic 40 years ago (*de Cock K. Emerg Infect Dis 2021; 27: 1553-60*). Furthermore, despite the success of antiretroviral therapy, hospital admissions in HIV individuals still represent a significant health burden in most countries (*Ramos et al. AIDS 2022; 36: 249-56*).

In the absence of antiretroviral therapy, more than 90% of HIV-1 carriers progress to severe immunodeficiency and develop opportunistic infections and/or cancers. However, from the earlier times, a small subset of long-term non-progressors (LTNPs) was identified (*Rodés et al. AIDS 2004; 18: 1109-16*). These individuals constitute a heterogenous group and occasionally depict either host or virus characteristic genetic determinants, including delta-32 deletions in the CCR5 co-receptor (*Eugen-Olsen et al. AIDS 1997; 11: 305-10*) or viral *Nef* gene deletions (*Dyer et al. AIDS 1997; 11: 1565-74*). In other LTNPs, the favorable prognosis seems to be dictated by other factors that in conjunction establishes a unique viral load set point for each infected individual (*Bertels et al. Mol Biol Evol 2018; 35: 27-37*).

To date, the recognition of HIV-1 super-variants, either more transmissible or pathogenic, has been controversial (*Mohri et al. J Acquir Immune Defic Synd 2008; 48:511-21*). In some instances, these variants harbored multi-drug resistance mutations to antiretrovirals and, indeed, this was the mechanism underlying its overall high transmissibility (*Markowitz et al. Lancet 2005; 365: 1031-8*). However, firm evidence for the emergence of HIV-1 variants intrinsically more virulent than others is lacking.

Dutch researchers have recently identified a group of 109 individuals in the Netherlands, Belgium and Switzerland that carried a unique HIV-1 subtype B variant that on average produced 3-fold greater viral load values and CD4 declines twice as fast as the rest of HIV-1 subtype B variants, after adjusting for age and sex (*Wymant et al. Science 2022; 375: 540-5*). Most individuals were white men having sex with men. In the absence of antiretroviral therapy, estimates for AIDS-related complications would have appeared 2-3 years after diagnosis for virulent B (VB) carriers compared to 6-7 years after diagnosis in non-VB individuals. In other words, CD4 declines to <350 cells/mm^3 ('*advanced HIV disease'* according to WHO) would have occurred at 9 months in VB variant carriers compared to 36 months in regular HIV-1 B carriers. Interestingly, the effect of the VB variant on CD4 declines remained after adjusting for the effect of higher viral load.

The new VB variant did not show a unique mutation at one position that could account for its high replication capacity. It depicted many changes across the whole HIV-1 genome. Moreover, only 1 out of 19 strains showed CXCR4 tropism, which has been associated with increased virulence. Finally, the VB variant does not exhibit drug resistance mutations but a M41L change that slightly reduces zidovudine susceptibility. Using phylogenetic studies, the authors concluded that the VB variant arose in Amsterdam in the 1990s from de novo mutation, not recombination, with increased transmissibility. The proportion of VB variant cases among all new HIV-1 subtype B patients increased until a peak in 2008 and subsequently decreased. The explanation for its greater virulence remains uncertain. Thus, although the observation has thankfully not translated in a worsening of the HIV-1 pandemic, the Dutch clinicians should be congratulated for their close look at their patients. In a wider landscape, their insights might enlighten and help to predict the evolution of other human RNA viruses -including SARS-CoV-2- once put under pressure with antivirals and/or vaccines (*Soriano et al. AIDS Rev 2022; 24: 41-9*).

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