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# Editorial: Characterization of HIV-1 variants: implications for HIV-1 prevention, treatment and cure

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Editorial on the Research Topic
Characterization of HIV-1 variants: implications for HIV-1 prevention, treatment and cure

HIV-1 group M (HIV-1M) strains are incredibly diverse, both between different HIV-1M subtypes and within a single subtype (1). Even within the course of infection of a single individual, different variants of HIV-1 arise. Studying this variation gives important insights into pathogenesis and transmission, and needs to be taken into account when designing preventative measures, implementing treatment regimens and identifying potential cure strategies. This Research Topic is a collection of four articles that bring attention to how intra- and inter-subtype variation affects pathogenesis, transmission, drug resistance and latency establishment.

HIV-1M subtypes have uneven spread and prevalence (2). Previous work indicates that subtype-specific variation in the fitness of isolates or function of different HIV-1 proteins could influence pathogenesis and spread of these subtypes (3). Sonela et al. investigated whether or not HLA-I and CD4 downregulation functions of the pathogenic accessory HIV-1 Nef protein may be partially responsible for the differences in prevalence of viruses from different subtypes that co-circulate in Cameroon, which is one of the countries where HIV-1 diversity converges to its maximum (4). Although previous reports indicated that these Nef functions may differ between some of the major HIV subtypes (5, 6), Sonela et al. observed no overall significant differences in CD4 and HLA-I down-regulation functions across the HIV-1 subtypes represented in their cohort, suggesting that these Nef activities do not substantively influence the prevalence of different HIV-1 lineages in Cameroon. Consistent with reports of HIV-1 attenuation over time (7), Sonela et al. showed some evidence for a decline in HLA-I downregulation activity from 2000 to 2013, yet CD4 down-regulation activity was well-conserved, highlighting the importance of this Nef function for the virus. Their study provides further insights into mutations specific to the CRF02_AG lineage that may affect these Nef functions, which may have relevance for antivirals targeting the Nef protein.

Zhou et al. zoom in further to consider the phenotypic HIV-1 variants that evolve within an individual host and shed light on the role of these HIV-1 variants in pathogenesis and how they relate to transmission. They provide a helpful review of the history of discovery of the different HIV-1 entry phenotypes (which was an evolving understanding that was corrected over time), with the aim of dispelling any lingering confusion created from having an initially missing phenotypic form. The entry phenotypes are based on evolution of the HIV-1 Env protein. Zhou et al. clarify that the R5 T cell-tropic virus is the "wild-type" form, and the most frequent form identified soon after transmission that may be best suited for the host environment during early infection, and that two other phenotypes may evolve with advancing disease – X4 T cell-tropic virus (which could be selected a result of depletion of CCR5-expressing CD4+ T cells) and R5 macrophage (M)-tropic virus that is adapted to replicate in the central nervous system and is associated with HIV-associated dementia. They identify an important knowledge gap, which is a lack of understanding of how M-tropic variants evolve and whether or not viral proteins other than the HIV-1 Env evolve to accommodate the change in target cell from T cells to macrophages. Interestingly, the propensity of these entry phenotypes to change differs by HIV-1M subtypes. While Zhou et al. mostly focus on the insights derived from understanding the different entry phenotypes, they also review the body of knowledge on phenotypes associated with transmission. They discuss the relevance of HIV-1 variation for prevention strategies that involve infusion of broadly neutralising antibodies and highlight the important finding that HIV-1 diversity influences the amount of antibody that is required to block infection.

Zhou et al. touch on the importance of HIV-1 diversity for drug resistance, but this topic is dealt with in further depth in a review article by Kamori and Barabona, with a specific focus on mutations that confer resistance to dolutegravir (DTG). The review explores the emerging resistance to DTG that has been reported in Africa a few years after its rollout. It points out early indications that the selection of DTG resistance could be more common in African settings compared to the developed world. This is despite the fact that the African studies referenced therein indicated very low to no prevalence of predisposed genetic polymorphisms at DTG resistance-associated sites prior to the DTG rollout. The review discusses the available evidence suggesting that different subtypes have differing susceptibility to development of DTG resistance and that the pattern of DTG-selected mutations may vary considerably between subtypes and subregions within Africa. Studies are therefore needed to understand DTG resistance patterns in African settings to better inform treatment programs in this region. Kamori and Barabona also recommend estimation of viral loads before switching individuals from other treatment regimens to DTG-based regimens, as DTG resistance was associated with unsuppressed viral loads during transition.

Drug resistance and other limitations of antiretroviral treatment have made a case for the development of an HIV-1 cure (8). The main barrier to HIV-1 cure is a stable reservoir of latently infected cells which is present during suppressive therapy (9). Doolabh et al. present an original research report focussing on the establishment of the latency since understanding of the mechanisms of latency are likely needed to inform effective cure strategies. While host mechanisms involved in latency establishment have been well-studied, less is known about viral characteristics that may influence latency. Strategies to reverse latency that are based on known host properties involved in latency have not been that successful (10), and understanding of viral properties involved may offer alternative strategies for addressing the latent reservoir. Doolabh et al. demonstrate that, in addition to previously shown subtype-specific effects of the HIV-1 LTR on propensity for latency (11), intra-subtype variation in the LTR significantly contributes to the potential for latency establishment. Future work will be needed to understand the exact sequence determinants governing these differences in latency potential. Overall, this article together with the other articles presented in this Research Topic highlight the relevance of studying viral variants to inform strategies to prevent, treat or cure HIV-1.

## Author contributions

JM: Writing – original draft, Writing – review & editing. MT: Writing – original draft, Writing – review & editing. TU: Writing – original draft, Writing – review & editing.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Publisher's note

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