Published in final edited form as:

AIDS. 2013 January 2; 27(1): 135–137. doi:10.1097/QAD.0b013e32835a11a4.

Changing HIV epidemics: what HIV-2 can teach us about ending HIV-1

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Keywords

HIV-1; HIV-2; phylodynamics; phylogenetics; population dynamics; transmission

Both HIV-1 and HIV-2 likely entered the human population from their respective primates hosts sometime in the early part of the twentieth century [1–3], however, despite similar modes of transmission, HIV-1 has evolved into a much more successful human pathogen, spreading globally and to date killing more than 30 million individuals and currently infecting an additional approximately 34 million people [4]. In contrast, HIV-2 has had limited global spread and remains mostly confined to West Africa, with an estimated 1–2 million infected [5–7]. The reasons and mechanisms for the disparate epidemiology and virulence of HIV-1 and HIV-2 are yet to be fully elucidated, however, numerous studies over the last three decades have demonstrated that compared with HIV-1, HIV-2 infection is characterized by a much longer asymptomatic stage, lower plasma viral loads, slower decline in CD4 cell count, lower mortality rate due to AIDS, lower rates of mother-to-child transmission, and lower rates of genital shedding and sexual transmission [8–17].

HIV-2 prevalence in West Africa appeared to peak in the 1970–1980s, with its epicenter in and around Guinea-Bissau [5,18–21]. For example, in a community-based prevalence study of HIV infection conducted in 1987, in 100 randomly selected ‘houses’ (1329 individuals), none were HIV-1 seropositive, and 4.7% were seropositive for HIV-2 (including 0.6% in children, 8.9% in those 15 years old or more, and 20% in those 40 years old or more) [18]. The finding of higher HIV-2 prevalence in the older age distribution in multiple studies from the 1980s suggests that events prior to the recognition of AIDS in 1981 likely caused its rapid spread, and that these factors have since declined. How HIV-2, seemingly poorly adapted to human-to-human transmission, ever got to such high prevalence rates in parts of West Africa has been a matter of some debate and speculation. The multiple wars of independence, human displacement and migration into cities, increase of commercial sex work and unsterile traditional practices and parenteral injections from early medical treatment and vaccination campaigns have been suggested as potential causes [21–24]. What is clear, however, is over the last two decades, HIV-2 prevalence and incidence are slowly waning in West Africa, the reason for that are also not entirely clear [25–32].

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Conflicts of interest There are no conflicts of interest to declare.

The current study by de Silva *et al.* [33] in this issue of the journal provides new insight into this issue by comparing the population dynamics of HIV-2 and HIV-1 and by characterizing ongoing HIV-2 transmission in rural Guinea-Bissau. The authors are in a unique position to perform such a study using the well characterized 'Caio Cohort', a village-based community cohort in rural Guinea-Bissau that has been studied for approximately two decades. The authors use well validated phylogenetic and phylodynamic analyses, using Bayesian methods on both HIV-2 gag and env, as well as HIV-1 env sequences, from 103 HIV-2-infected and 56 HIV-1-infected patients. Bayesian skyline plots showed remarkably similar trajectories for HIV-2 and then HIV-1 (although offset by approximately 20 years), following initial introduction with an initial lag phase, a rapid rise and then plateau phase for the effective population sizes (N_e) of both viruses. One potential explanation the authors provide for this pattern is competitive exclusion of HIV-2 by HIV-1, as it was subsequently introduced into the community. Previous modeling work has suggested that approximately 30% of HIV-2 decline could be explained by competitive exclusion, with approximately 70% attributed to sociobehavioral changes [34]. Data in changes in prevalence and incidence of HIV-2/HIV-1 dual infections during this transition period in might provide additional data for this hypothesis. Seroincident infections, compared with seroprevalent (pre-1989) were found more often in HIV-2 transmission clusters, with approximately 50% of all individuals contributing to ongoing transmission. This finding is not too surprising, given the rural community-based nature of the cohort with limited in and out migration. However, given the long time period between serosurveys in the cohort, 'seroincident' effects should be viewed with some caution. The finding that antiretroviral-naïve HIV-2 phylogenetically linked sexual partners often had discordant viral loads (undetectable versus detectable) is a novel finding and may indicate that host factors predominately dictate viral load and the subsequent risk of disease progression in HIV-2 infection.

There has been recent excitement about possibility of ending the HIV-1 pandemic in the coming decades with current and forthcoming treatment and prevention strategies [35–37]. Recently, Bruhn and Gilbert [38] suggested that a more thorough understanding of the dynamics of the HIV-2 epidemic, its apparent slow rise in the first half of the twentieth century, exponential spread in parts of West Africa, plateau phase of relatively high prevalence in endemic areas, and slowly waning incidence and prevalence over the last two decades can serve as harbinger of what we might hope to expect with the HIV-1 pandemic if appropriate interventions and efforts are successful. Appropriate analysis and modeling of the factors contributing to the waning HIV-2 epidemic may provide crucial insight as how to target these same factors for HIV-1. Similarly, treatment as prevention strategies for HIV-1, that are premised on lowering 'community viral load' and thereby decreasing HIV-1 transmission [39,40], might be informed by further examination and modeling of how the naturally low and often undetectable viral loads, without antiretroviral therapy, in HIV-2 infection have contributed to the waning HIV-2 epidemic. The HIV-2 epidemic may provide a unique opportunity to teach us much about how to end the HIV-1 pandemic, but only if we have the intelligence and foresight to learn from it.

Acknowledgments

I would like to thank Papa Salif Sow and Robert A. Smith for helpful discussions.

Funding: No specific funding for this editorial.

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