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What proportion of HIV-infected foreign-born individuals in the U.S. have been infected after immigrating to the U.S.?

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To the Editors

The global HIV-1 pandemic does not recognize national borders. The contribution of migrants to the HIV epidemic in Western Europe has long been recognized,¹ and recently, some local health jurisdictions in the U.S. have reported that the proportion of new HIV diagnoses occurring among foreign-born people is increasing over time.^{2,3} Understanding the epidemiology of HIV in this population, including when and where people acquired HIV, is instrumental in developing effective strategies to prevent HIV among international migrants.

Valverde *et al.*⁴ recently reported in this journal (Published Ahead-of-Print, September 2017) that the majority of HIV-infected foreign-born U.S. residents with a genetic link to another infection were linked to a U.S.-born individual. This finding was based on the identification of genetic similarity clusters in a large data set of HIV-1 *pol* sequences from 77,686 individuals in the National HIV Surveillance System (curated by the U.S. Centers for Disease Control and Prevention). From this result Valverde *et al.* concluded that the majority of HIV-infected foreign-born individuals in the putative U.S. transmission network were infected after immigrating to the U.S.

We commend the authors for addressing this important issue with molecular epidemiological methods, which can be informative for this type of public health question. However, we believe the main conclusion may not be fully supported by the data.

In their study, Valverde *et al.* first identified putative transmission linkages as any two or more sequences that were closer than a 1.5% Tamura-Nei⁵ distance threshold (0.015 substitutions/site; implemented via HIV-TRACE⁶). Next they performed a series of

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descriptive and statistical analyses to assess associations between epidemiological characteristics (including region of birth) and linkage status. Of the 77,686 individuals in the data set, 12,064 were foreign-born individuals (16%) — thus 84% were U.S.-born. 28% of the foreign-born individuals were genetically linked to at least one other individual in the data set. Of those 28% of foreign-born individuals, 62% were linked to a U.S.-born individual. This last proportion is the source of the main conclusion: that the majority of HIV-infected foreign-born individuals *in the transmission network revealed by linkage analysis* were infected after immigrating to the U.S.

We see two main problems with the analyses.

First, the analysis does not establish an expected proportion of (linked) foreign-born individuals that link to a U.S.-born individual; *i.e.*, while it is technically true that the majority (62%) of linked foreign-born individuals have a link to a U.S.-born individual, it is unclear whether this is more or less than expected by chance alone. A null expectation might be established as follows: in a randomly mixing population we can expect that any single individual in the current data set, if linked, would link at 84% probability to a U.S.-born individual and at 16% probability to a foreign-born individual, based on the respective frequencies in the database. (For simplicity we ignore potential assortative mixing.) The observed rate of linkage between foreign-born and U.S.-born individuals is 62%. Thus, the proportion of foreign-born individuals linked to U.S.-born individuals was actually *smaller* than expected by chance; this would reverse the authors' conclusion. What might be anticipated is an exploration of why linked HIV-infected foreign-born individuals are not linked *more often* to U.S.-born individuals.

Second, the analysis does not consider the possible direction of transmission in each putative transmission pair. If we assume that 50% of the genetic linkages between a foreign-born and a U.S.-born individual represent a series of one or more transmissions that originate from the U.S. born individual, then 31% ($62\% \times 0.5$) of linked foreign-born individuals are potentially infection sources rather than recipients. Absent epidemiological evidence that may alter this directionality assumption (*i.e.*, that would point to either foreign-born or U.S.-born individuals as more likely to be the source in an HIV transmission pair), one might conclude that a *minority* of HIV-infected foreign-born individuals in the U.S. were infected after immigrating.

We concede that we arrive at this alternate conclusion via simplifying assumptions about mixing patterns and transmission dynamics, and without incorporating recent advances in phylodynamics,⁷ phylogeography,⁸ or source attribution⁹. Yet the discrepancy between our and Valverde *et al.*'s estimates highlights the importance of establishing null expectations when inferring epidemiological parameters from genetic similarity data. Finally, we would like to highlight the 72% of HIV-infected foreign-born individuals diagnosed and sampled in the U.S. who were not linked to any other individual in the data set. A heuristic assumption might be that the sources of these individuals' infections are foreign-born individuals currently living outside of the U.S., and therefore not sampled nor included in the data set. This suggests that the vast majority of HIV-infected foreign-born individuals in the U.S.

were not infected in the U.S. In the context of Valverde et al.'s conclusion, this is a critical point that should not be overlooked.

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