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Phylogenetic insights into age-disparate partnerships and HIV

Published Online
November 30, 2016
[http://dx.doi.org/10.1016/S2352-3018\(16\)30184-9](http://dx.doi.org/10.1016/S2352-3018(16)30184-9)
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In *The Lancet HIV*, Tulio de Oliveira and colleagues¹ present phylogenetic evidence supporting the hypothesis that HIV incidence in young women (aged 15–25 years) is driven by age-disparate partnerships (ie, those between individuals with an age difference of >5 years). HIV prevalence is more than 60% higher in women than in men in sub-Saharan Africa, and young African women have the highest HIV incidence of any demographic subgroup.^{2,3} The hypothesis that age-disparate partnerships drive incidence in this group has motivated HIV policy and programmatic responses in sub-Saharan Africa, and might be important to the success of programmes such as the DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe women) partnership.⁴ Although recent reports of prospective data from the Africa Center for Health and Population Studies and the VOICE (MTN-003) trial suggested that incident HIV infection in women was not associated with age-disparate partnerships, difficulties exist with accurately collecting the type of self-reported sexual partnership and HIV exposure data on which these studies were based.^{5,6}

Phylogenetic analyses like that done by de Oliveira and colleagues group people into putative transmission clusters on the basis of similarities in their infecting viruses, and provide a method for assessing the effects of transmission network structure on HIV epidemics independent of self-reported partnerships.^{7,8} The evidence presented by de Oliveira and colleagues shows close genetic linkages between younger women and older men, supporting the existence of short chains of transmission that

quickly seed HIV infections into younger age groups from older ones. However, we feel the authors go beyond what can be inferred from the evidence when they postulate a cycle of HIV transmission on the basis of heterosexual phylogenetic clusters interpreted as capturing direct transmission.

In this study, because of the proportion of individuals in the community sampled (4%, with no reported oversampling of HIV-positive people), we cannot conclude that any two phylogenetically linked individuals represent a direct transmission pair or infer the directionality of transmission, without additional evidence about the potential partnership. Because there are 299 women younger than 25 years with viral sequences, the number of infecting partners we would expect in our sample for this group is 12 (0.04 × 299). de Oliveira and colleagues presume that all (or nearly all) 41 men older than 25 years who are linked to a woman younger than 25 years are infecting partners, but the probability of obtaining 41 infecting partners for 299 women from a 4% random sample is less than one in a billion. Because the sample is structured, the probability of including infecting partners could be somewhat higher, but finding the number the investigators claim would still be extraordinary. Noting that their clustering criteria also link several individuals of the same sex, we think it likely that some intervening partnerships exist in the chains of transmission that link clustered individuals.

Network theory tells us that only a small number of connections between clustered groups are needed to cause so-called small world effects, such that the distance between any two individuals in the population

will be quite small.⁹ Hence, one could hypothesise that men near, but not directly linked to, young women on transmission chains are essentially randomly selected from the population. If de Oliveira and colleagues' hypothesis is correct, we would expect more pairings of women younger than 25 years with men aged 25–40 years than suggested by this at-random hypothesis. In their sample, 73 (15%) of 487 men with viral sequences are younger than 25 years, 329 (68%) are 25–40 years, and 85 (17%) are 41–49 years. However, for women younger than 25 years, 18 (30%) of 60 linked male partners are younger than 25 years, 37 (62%) are 25–40 years, and five (8%) are 41–49 years, skewing substantially younger. Hence, the phylogenetic results from this study might be read to provide evidence against the investigators' hypothesis; however, we believe the sampling fraction to be so low that the phylogenetic analysis can neither prove nor disprove the proposed hypothesis.

Our intention is not to discount this study's important contribution to understanding how quickly chains of HIV transmission are traversing age groups, but rather to highlight the potential for extrapolating too much from viral phylogenies. Recent methodological work emphasises the difficulties in disentangling network structure from the independent effects that epidemic and evolutionary processes also have on phylogenies.¹⁰ Notably, several studies show that phylogenetic approaches for identifying direct transmission pairs and characterising network structure perform poorly at low sampling fractions, and inferring directionality can be difficult even with linked, deeply sequenced samples.^{11–14} Likelihood-based approaches can help to account for sampling and censoring biases, as in a study of HIV transmission in the Netherlands, but are computationally intensive and require a specialised skill set and more data.¹⁵

The hypothesis put forth by de Oliveira and colleagues is reasonable and important; and the proposed cycle by which age-disparate partnerships maintain the African HIV epidemic could inform effective HIV control programmes. However, we believe more evidence is needed to answer the questions of if and how age-disparate partnerships are driving HIV transmission. Studies that use detailed epidemiological data, a greater density of sequence

data, or a combination of the two could resolve the issue. Initiatives such as PANGEA-HIV are generating large numbers of viral sequences from densely sampled subepidemics in South Africa and elsewhere in sub-Saharan Africa.¹⁶ Hopefully, these data combined with epidemiological information and analytic advances will build on the work of de Oliveira and colleagues to further elucidate how HIV transverses age groups in the region.

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We declare no competing interests.

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