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EDITORIAL COMMENTARY

Phylogenetic Cluster Analysis: Persons With Undiagnosed Infection Drive Human Immunodeficiency Virus Transmission in a Population With High Levels of Virologic Suppression

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(See the Major Article by Bachmann et al on pages 2175-83.)

As the fourth pillar of the Ending the HIV Epidemic campaign, molecular cluster detection and response remains a tool with great potential that has yet to prove its worth. The human immunodeficiency virus (HIV) sequence data used in molecular cluster analyses can provide an intricate picture of how HIV has spread across communities and regions, and the ever-improving tools for sequence analysis allow a more nuanced understanding of transmission history. However, methods by which these data are translated to reports of information that will inform how specific HIV prevention interventions should be deployed, and among which populations, remain limited.

In this issue of *Clinical Infectious Diseases*, Bachmann and colleagues [1] leverage a decade of longitudinal data from the Swiss HIV Cohort Study (SHCS) to study the drivers of HIV transmission among men who have sex with

men (MSM) in Switzerland. Identifying the key drivers of HIV transmission is the first step toward developing prevention interventions tailored to specific populations. This study cohort had several key strengths that separate this work from much of the other published work in the field. The SHCS was established in 1988, with the foresight of Swiss researchers, and is estimated to include 75% of persons living with HIV in Switzerland. The depth and duration (10 years) of sampling in this study reaches the appropriate threshold, suggested by Novitsky et al [2] in a modeling analysis of HIV type 1 (HIV-1) subtype C env sequences from Botswana, for valid molecular epidemiologic analyses. Very few epidemics in the world have this level of data available for analysis, allowing an exceptionally detailed characterization of transmission dynamics associated with the Swiss epidemic. The second key strength of the article was the ability to identify recent infection in a substantial proportion of the study population (Figure 2 [1]). HIV recency was inferred using a midpoint between negative and positive tests, within the past year when available. Among persons for whom prior testing data was not available, the authors used low viral diversity (<0.5%

of ambiguous nucleotides) within the first year after diagnosis to infer recency. While interval seroconversion represents a robust method for estimating incidence, the use of viral diversity to define incident infection is less straightforward given intraindividual variation in viral evolution rates, particularly when using HIV-1 pol sequences [3].

Identifying the major drivers of incident infection in a population can be helpful to prioritize prevention intervention responses. Here, the authors examined infectivity (ie, viremia) and behavioral risk as possible drivers of cluster growth, defined as the number of new infections within each cluster, compared to the previous year, among clusters of at least 50% Swiss MSM. Both infectivity and behavioral risk were assessed as a score for each MSM transmission cluster each year. The infectivity score, essentially a measure of the cluster viral load, was strongly associated with new linked incident infections in 8 of 10 study years. The authors also reported a decrease in the time between HIV diagnosis and start of ART, from a maximum of 22 weeks to a minimum of 3 weeks, during the course of the study. These results are consistent with mathematical models and clinical trials (ie, U = U), and provide additional

support for the population-level prevention benefits of test and treat [4].

The results of the behavioral risk analysis as a driver of cluster growth were not as straightforward. An equivocal relationship was demonstrated between behavioral risk and linked incident infections over time (only 3 of 10 years showed an association), and overall it appeared that although behavioral risk was increasing over time, linked incident infections were decreasing. However, there are potential issues with the variables used to derive the behavioral risk score that may limit its use as an optimal measure of risk. Hepatitis B virus, hepatitis C virus, and syphilis were used as components of the behavioral risk score, and while all may be sexually transmitted, without special testing to identify incident infection, these infections may not reflect recent risk. We and others have shown that better correlates of recent behavioral risk among MSM include primary and secondary syphilis infection, and rectal gonorrhea [5–7]. Also, while condomless sex acts were used as a predictor of risk, the number of partners was not assessed in the model [8]. Finally, it appeared that those who did not answer the question on sex acts were placed into the high-risk category, a conservative measure but not necessarily accurate. Given these limitations with regard to the risk scoring system, an alternative behavioral risk score that included early syphilis, rectal gonorrhea, condomless sex acts, and number of partners in the last 3 months might provide a more accurate reflection of behavioral risk. It seems possible that a revised behavioral risk analysis might improve the association between behavioral risk and new linked infections in this cohort. Another important limitation of the behavioral risk analysis was the absence of information related to pre-exposure prophylaxis (PrEP) use in the population. While studies have demonstrated conflicting results about the role of PrEP and risk compensation, it would be important to know if the increase in behavioral risk demonstrated in the SHCS, without an associated increase in cluster growth, was associated with an increase in the proportion of people without HIV receiving PrEP.

This study also noted that there was an increasing proportion of clusters with zero infectivity (ie, all cluster members had a viral load < 1000 copies) that acquired incident linked infections. Given the linkage analysis and incidence data provided, there are only 2 explanations for cluster growth among clusters with zero infectivity: intermittent viremia among cluster members, or unobserved cluster members. Intermittent viremia would imply sporadic adherence (timed with laboratory draws) and, although that is possible, it seems more likely that linked infections originated from unobserved undiagnosed infectious people with HIV (PWH). Thus, while we should be heartened that viral suppression and reduction of cluster viral load reduces incident linked infections, these results also tell us that in mature MSM epidemics, such as the Swiss MSM epidemic, we need to work harder to identify undiagnosed individuals and link them to care. While this study focused on linked infections (infections genetically linked to existing clusters), incident diagnoses can be independent or unlinked. The sources for these infections may reach beyond the unsampled sexual networks in Switzerland and may include imported infections from travelers and immigrants. The unsampled PWH and the new imported cases represent the last mile in our quest to achieve population-level viral suppression and eliminate further transmission, though these individuals may also represent the most vulnerable, underserved, and hard-to-reach communities. We need to think creatively about how we can find and link these individuals to care before further transmissions occur.

There were several notable findings in this study that may be applicable to mature MSM networks around the world. First and foremost was the strong relationship between cluster infectivity and future linked incident infections. Viral suppression remains the ultimate goal for both treatment and prevention in PWH. This work extends the findings of Quinn et al [9] (showing that transmission risk is related to viral load) from discordant partners to clusters of genetically linked individuals. Second was the finding of new linked infections among clusters with low infectivity, suggesting undiagnosed infectious individuals in the community. However, transforming molecular epidemiology analyses such as these into impactful public health interventions remains an elusive goal. The authors suggest that "the identified high-risk clusters could be used to target social networks harboring undiagnosed individuals spreading HIV," but the HIV prevention community continues to struggle with how to implement these efforts.

Notes

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