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Enhanced use of phylogenetic data to inform public health approaches to HIV among MSM

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Enhanced use of phylogenetic data to inform public health approaches to HIV among men who have sex with men

Abstract

The multi-dimensional nature and continued evolution of HIV epidemics among men who have sex with men (MSM) requires innovative intervention approaches. Strategies are needed that recognize the individual, social, and structural factors driving HIV transmission; that can pinpoint networks with heightened transmission risk; and that can help target intervention in real-time. HIV phylogenetics is a rapidly evolving field with strong promise for informing innovative responses to the HIV epidemic among MSM. Currently, HIV phylogenetic insights are providing new understandings of characteristics of HIV epidemics involving MSM, social networks influencing transmission, characteristics of HIV transmission clusters involving MSM, targets for antiretroviral and other prevention strategies, and dynamics of emergent epidemics. Maximizing the potential of HIV phylogenetics for HIV responses among MSM will require attention to key methodological challenges and ethical considerations, as well as resolving key implementation and scientific questions. Enhanced and integrated use of HIV surveillance, socio-behavioral, and phylogenetic data resources are becoming increasingly critical for informing public health approaches to HIV among MSM.

Keywords

HIV/AIDS; MSM; Phylogenetic; Molecular surveillance

Introduction

Despite impressive advances in HIV prevention options, including oral pre-exposure prophylaxis, early initiation of anti-retroviral therapy as secondary prevention, and socio-behavioral interventions, incident HIV infections remain high among men who have sex with men (MSM) in low, medium, and high resource countries (1). High incidence HIV epidemics among MSM are ongoing in the U.S., with marked severity among young and racial and ethnic minority MSM, and in countries as diverse as France, the UK, Thailand, China, Kenya, and Russia (2). Data from HIV bio-behavioral surveillance surveys and prospective studies that have measured incident infections among MSM confirm that these

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HIV epidemics cannot be understood at the individual level alone—even when personal risk is modest, lifetime acquisition probabilities can reach over 50% among men in high transmission settings (3). This has prompted a more nuanced view of HIV spread among MSM and the extent to which network and structural level factors, such as social mixing and access to HIV services, play critical roles in HIV transmission dynamics. Insights from viral phylogenetics have supported these views by shedding light on critical transmission processes and network structures underlying MSM epidemics (4-7) especially when triangulated with classical risk factor assessments and interview data.

The multi-dimensional nature and continued evolution of MSM HIV epidemics requires innovative intervention approaches. In particular, strategies that recognize the individual, social, and structural factors driving HIV transmission; that can pinpoint networks with heightened transmission risk; and that can help target intervention in real-time are needed. Here, we argue that viral phylogenetics can help advance these goals and could become an invaluable tool in the public health response to HIV among MSM that adds value to ongoing HIV surveillance and other public health data sources. We also highlight promising HIV phylogenetic applications for the MSM HIV epidemic and important methodological questions for the field.

Integrating HIV phylogenetics to understand characteristics of HIV epidemics involving MSM

Identifying characteristics of those at highest risk for HIV incidence and ongoing transmission can help inform the design and implementation of targeted interventions and more effective population-level strategies for curtailing the spread of HIV among MSM. Increasingly, HIV phylogenetics is being used to understand community, regional, and country-level transmission patterns and pinpoint strategies for intervention (8). Because of frequent viral mutation as HIV is transmitted within a community network, each virus acquires a distinctive and evolving genetic sequence that can be analyzed to identify potential epidemiological links between individuals carrying genetically similar virus (9). Importantly, transmission can only be indirectly inferred from phylogenetic links because of the possibility of intermediary persons in a transmission chain. Yet, when combined with rich socio-behavioral and contextual information, HIV phylogenetic analysis can help to reveal social patterns among those with similar sequences (known as clusters) and identify characteristics of rapid transmission networks.

HIV phylogenetics includes two major categories of genetic analysis (8): 1) molecular epidemiology to assess viral genetic diversity (e.g., subtype distributions), identify phylogenetic clusters, and explore risk factors for viral spread, and 2)viral phylodynamics to assess changes in epidemic dynamics over time and interactions between HIV epidemiologic, immunological, and evolutionary processes (10). The identification of phylogenetic clusters has helped to elucidate social and spatio-temporal dynamics of HIV transmission independent of participant-reported histories (11) and proved useful in causal investigations of structural level changes on HIV epidemic trajectories (12). HIV phylogenetics has also been used to identify sources of HIV outbreaks (13, 14), demonstrate

social mixing within and across communities and risk groups (15-17), identify patterns of viral introduction into communities (18, 19), and refute suspected transmission links (20). Recent phylogenetic analyses focused on HIV epidemics among MSM have provided evidence of assortative sexual mixing by race, ethnicity, and age (21, 22), revealed heterosexual mixing within transmission chains (21), identified transmission links between high risk venues (23), as well highlighted as other key social dimensions that have added to our understanding of how HIV is transmitted within and across communities.

Using HIV phylogenetics to gain insight into social networks influencing transmission

Detailed examination of transmission networks consisting of recently infected HIV positive individuals can be especially informative for intervention targeting (24). HIV travels between pairs of individuals who are positioned within a larger network structure. Even with similar behavioral characteristics, an individual's position within a network can influence the likelihood of HIV exposure (25, 26) within and across geographic regions (25, 27). Higher network connectivity, which is often observed in MSM epidemics, heightens HIV transmission potential, while segmentation impedes it (28).

Despite the importance of sexual networks to HIV epidemic dynamics, many analyses of contact networks are limited to reported and known contacts at the time of HIV diagnosis that may have changed since transmission occurred. Moreover, social networks can be logistically difficult and costly to study using traditional approaches and linkage between HIV-positive individuals cannot be confirmed with self-reported data alone. HIV phylogenetics can corroborate and enhance social network research by adding viral link age information to self-reported contact data (11). For example, a study of HIV-positive MSM in Hong Kong found that social and HIV phylogenetic networks were both largely partitioned into distinct clusters consisting of “sauna-centered” and “internet-centered” groupings (23). Linking molecular to socio-demographic data, they found that the aggregate behaviors, characteristics, and viral strains of the two cluster types differed: the internet clusters were composed of younger, more educated MSM in denser viral networks compared to those in the sauna clusters. Furthermore, they identified a small number of individuals with multiple partners that bridged the two clusters. Such findings suggest a need for setting-specific interventions with heightened attention to those who cross social boundaries. Likewise, a study in El Salvador found that respondent driven sampling methods were successful for identifying MSM transmission networks and that MSM who were in phylogenetic clusters were more likely to report larger social networks of MSM compared to those not in clusters (29). This study suggests that social network and phylogenetic strategies can together help to refine intervention targeting and contact with those at increased risk for transmission.

In North Carolina, researchers collected HIV phylogenetic sequences among 30 black MSM who also completed partner notification services and reported a total of 95 sex partners and social contacts (30). Although none of the 30 participants were sex partners, eight belonged to one of four identified phylogenetic clusters. Analysis of the reported sexual networks showed they were largely similar by age, race/ethnicity, and geography. Together, the HIV phylogenetic and sexual network analyses demonstrated high connectivity and homogeneity

within sexual networks among black MSM, suggesting that targeting prevention efforts centrally within sexual networks may be an efficient strategy for decreasing transmission.

Using HIV phylogenetics to characterize HIV transmission clusters

Increasingly, latent class approaches are being used to thematically characterize HIV phylogenetic clusters (31). Rather than examine relationships among variables, these studies examine patterns of variable co-occurrence to identify hidden sub-groups of individuals who have similar characteristics. This typology approach results in a thematic understanding of cluster characteristics (e.g., urban, homeless, white), which can then be monitored over time for changes.

For example, a latent class analysis of the Rhode Island HIV epidemic revealed key behavioral features of actively growing phylogenetic clusters. The study included viral sequence data from 75% of all HIV-positive individuals in Rhode Island (32). A total of 114 clusters were identified from 1,166 sequences and approximately half of the clusters were formed by MSM sequences. The clusters were then assessed for socio-demographic mixing, diagnosis time frame, and cluster size. Larger clusters were composed exclusively of MSM, and those MSM in clusters with a high probability of growth were more likely to be younger, present with primary HIV infection, and meet partners at bars/clubs or online. A study of the Swiss HIV epidemic found that latent classes identified based on transmission group (e.g. MSM, IDU)and socio-economic status overlapped with phylogenetic clusters and showed that links between older heterosexual and gay individuals receiving welfare benefits may be an important source of epidemic bridging between heterosexual and MSM networks (31). By combining molecular and behavioral information, both of these studies demonstrate that public health responses may be able to identify and intervene on factors associated with emergent and growing transmission clusters.

Using HIV phylogenetics to target antiretroviral interventions

The development and rollout of antiretroviral therapy (ART) has been critical in reducing HIV-related mortality in HIV-positive persons worldwide (33). The results of the HPTN-052 clinical trial also demonstrated that ART substantially reduces the probability of HIV transmission in heterosexual and same sex couples by lowering the viral load in HIV-positive partners (34): a critical finding that has served as the foundation for treatment as prevention, a strategy whereby HIV-positive persons are provided ART regardless of their CD4 count (35).

While it remains unknown if HIV-positive persons can be identified and linked to ART within the timeframe and at a scale necessary to reduce population-level HIV incidence, HIV phylogenetic research has helped to identify key intervention points along the HIV care continuum, including among those who may not be adequately virally suppressed. Viral phylogenetic studies have proved especially critical in evaluating the early impact of treatment as prevention programs in Europe, which has experienced a recent resurgence of HIV infection among MSM (36, 37). A phylogenetic analysis of the Dutch HIV epidemic using data from the ATHENA observational HIV cohort study evaluated sources of HIV transmission among recently infected MSM (7). The investigators estimated that 71% of all

HIV transmissions among MSM in the Netherlands occurred prior to diagnosis and that just 6% of infections were transmitted by those who have already initiated ART. These results demonstrated that gaps in testing and linkage to care rather than inadequate retention in care among those already on ART were the primary drivers of incident infection. Another phylogenetic study, also using data from the ATHENA-HIV cohort, revealed that more than half of ongoing HIV transmission chains containing MSM originated prior to the availability of ART suggesting widespread gaps in the treatment cascade across a diversity of social networks (38).

HIV phylogenetic studies in Europe and North America have found that early HIV transmission is a critical driver of HIV incidence among MSM and may be one of the key factors undermining the success of treatment as prevention in MSM populations (39). The importance of early HIV infection was first demonstrated by Lewis et al. who identified large phylogenetic clusters of incident HIV infection containing a large proportion of MSM HIV infections in the United Kingdom (5). A similar phylogenetic analysis of the HIV epidemic in Montreal, Canada found that only large phylogenetic clusters with substantial co-clustering of early infections were those most likely to grow following the widespread availability of ART (40). In another study, Volz and colleagues applied phylodynamic methods to HIV sequence data from MSM attending clinics in Detroit, Michigan and quantified the fraction of new HIV cases arising from early HIV infection: the investigators estimated that 44% of all new HIV cases were transmitted within the first year of an index partner's infection (6).

The rapid spread of HIV among MSM underscores the need for prevention interventions that are also targeted to HIV-negative persons. Randomized controlled trials have shown that pre-exposure prophylaxis for HIV prevention (PrEP) is highly efficacious and can be used on an as needed basis (i.e. “on demand” PrEP) among MSM (41, 42). However, the global rollout of PrEP to populations most at risk has been slow and limited to only a few countries in Europe and North America (43). HIV molecular data can help inform modeling of targeting of PrEP and other HIV interventions. For example, Ratmann and colleagues evaluated various combination HIV prevention packages using phylogenetic data, including high frequency HIV testing, TasP, and PrEP, and showed that only those combination HIV prevention packages including PrEP substantially reduced HIV transmission among MSM in Europe (7).

Using HIV phylogenetics for epidemic response

Increasingly, stakeholders are exploring ways in which health departments can incorporate HIV phylogenetics into epidemic monitoring, response, and prevention activities. As large databases of HIV sequences become readily available for analysis at local and regional levels (44), phylogenetics offers novel opportunities to effectively respond to emerging epidemics. For example, identification of rapidly growing HIV phylogenetic clusters could be used to initiate strategic contact investigations or target ongoing preventive responses to those in connected social and sexual networks. Because HIV phylogenetics cannot demonstrate direct linkage between individuals in a transmission chain absent additional epidemiological data, traditional tools for elucidating relationships among individuals such

as HIV partner services and qualitative research methods remain critical components in the public health response (20). Nevertheless, phylogenetics can supplement these conventional approaches. Real-time health department monitoring of phylogenetic clusters can prompt targeted client engagement, expedited enrollment into HIV care and supportive services, as well as PrEP prescriptions for HIV-negative contacts of key network members (45, 46). Results from phylogenetic analyses may also trigger recommendations for directed HIV and STI testing or identify critical social or structural facilitators of transmission such as lack of harm reduction services, access to care, homelessness, unemployment, or shared venue affiliations.

In 2008, investigators from CDC used HIV phylogenetics as part of a comprehensive investigation into an HIV outbreak among young black MSM in Jackson, Mississippi (13). Preliminary qualitative research revealed three primary concerns among community members affected by the outbreak: 1) the potential for transmission between MSM and women, 2) differences in between younger and older MSM in the gender of their partners and potential overlap between MSM and heterosexual transmission, and 3) introductions of HIV into the community by individuals who travel to meet partners. Phylogenetic results showed that clusters containing younger MSM were composed of individuals who were demographically similar and not limited to Jackson residents. In contrast, phylogenetic clusters with older black MSM contained more socio-demographic diversity that included heterosexual women. Ultimately, the HIV phylogenetic analysis was able to directly address community questions about transmission patterns in this setting. The results also helped tailor local prevention recommendations to provide age-group specific programming with appropriate geographic reach and prioritize comprehensive interventions for younger MSM.

The recent HIV-outbreak in southeastern Indiana highlights the utility of viral phylogenetics in real-time outbreak investigation and management (14). Rapid analysis of HIV sequences from HIV positive persons living in the state showed a single linked transmission network of drug users with limited evidence of viral spread outside of the predominately affected Scott County, which helped demonstrate the need for a localized response. Molecular data also suggested that the epidemic was spreading rapidly within the community, requiring prompt programmatic action that ultimately included syringe exchange policy changes, expanded treatment access, and attention to HIV, substance use, and other health care resources.

As HIV molecular surveillance improves, it will become more feasible to use phylogenetic data on a real-time basis to monitor changes in the epidemic and evaluate the impact of population-level intervention strategies. However, additional research is needed to determine the most cost effective and timeliest strategies for identifying growing transmission clusters as well as ethically-sound methods for targeting members of these clusters with relevant and culturally-appropriate interventions.

Methodological challenges in phylogenetic studies of MSM

In order to gain insight into HIV transmission networks from viral phylogenies, a representative sample of adequate size of the HIV-positive population is necessary (47). This can be especially challenging in settings with high social stigma against HIV and/or same-

sex sexual behavior, because individuals may be reluctant to disclose MSM status in research or care settings due to fears of discrimination, marginalization, and potential legal prosecution (48). Within jurisdictions, uncollected sequences from those with newly diagnosed HIV limit the generalizability of analyses (49) and ability to effectively monitor the evolution of epidemics. A limited sampling fraction can also affect interpretation of phylogenetic results. For example, examination of HIV transmission patterns across the U.S. identified a large number of links between women (44). With incomplete sampling, these seem to be examples of female-to-female transmission but could also be explained by injection risk behavior or indirect connections through heterosexual partners.

Routine drug resistance testing has proved a critical resource for obtaining large sampling fractions of viral populations among MSM in Europe and North America (e.g., the UK HIV Drug Resistance Database and Stanford University HIV Drug Resistance Database). However, these systems are not a mainstay in most parts of the world, especially in resource-constrained settings such as Sub-Saharan Africa. Moreover, viral sequence data obtained in clinical settings, which include drug resistance surveillance, may not represent a non-random sample of transmission network members. The extent to which biased network sampling affects phylogenetic inferences remains an understudied area. Improvements in molecular surveillance data to include complete sequence reporting within and across HIV surveillance jurisdictions will enhance completeness of databases and confidence in the results of transmission cluster analyses. Improvements in data systems to enhance the validity and reliability of HIV surveillance data (49), including reported transmission category, socio-demographic data, and clinical data procedures, will also be critical for analyzing molecular HIV surveillance data to inform real-time prevention.

Elucidating network structure from viral sequence data is also another major challenge in HIV phylogenetic studies (50, 51), since phylogenetic networks are almost always partially sampled transmission chains and because connections between viruses in a phylogenetic tree are not only a consequence of the underlying network structure but also of evolutionary and epidemic processes. Simulation of viral evolution on contact networks has demonstrated that common phylogenetic methods for assessing network structure (e.g., tree balance statistics) perform poorly under certain conditions, such as when networks are dynamic and the sampling fraction of the network is low (<20%) (52, 53). Broadly, these studies highlight the need for detailed knowledge of the sampling methods that were used to generate the HIV sequence data, the size of the target population under study, and the epidemic dynamics in the target population.

Ethical and human rights considerations

Phylogenetic tools have the potential for markedly increased granularity in our understanding of MSM transmission dynamics, but also raise a number of ethical and human rights questions. Ideally, insights from phylogenetic advances will be used to improve HIV prevention and treatment programs for these men without increasing the risk of social harms. But caution may be warranted in some settings, where gay, bisexual, gender variant and other MSM may be subject to forced testing, criminal sanction, and other abuses as a consequence of persecution based on sexual orientation and gender identity (54).

Researchers will need to proceed with caution, and work in close collaboration with LGBT community members and leaders, and with others focused on human rights, in contexts where same sex behavior among consenting adults remains a crime. This is also a potential concern in other settings, including many U.S. States, where criminalization of HIV transmission, or even of exposure, is increasingly common at the State level. As an example, an African American college athlete is currently serving a 31 year prison sentence in Missouri for failure to disclose his HIV infection to a sex partner (55). Currently, HIV phylogenetic data is in fact better at demonstrating when there is no link than it is at confirming direct transmission (56). Yet members of sexual and gender minorities are concerned, and have reason to be concerned, about new surveillance tools leading to legal and human rights threats in such contexts.

Using HIV phylogenetic data to inform the response to HIV currently relies heavily on sequence data collected as part of routine clinical care, often without explicit consent for surveillance and public health follow-up. Thus, inadequate attention to community concerns about these data risks exacerbating existing challenges to HIV treatment for MSM and damaging public trust. As with other components of HIV surveillance (58), it will be important to talk with community members about the use and meaning of these data and especially to address concerns about privacy, confidentiality, and potential stigma related to status or transmission cluster characteristics. As real-time and other intervention strategies that build on HIV phylogenetic information continue to emerge, it will also be critical to address questions of efficacy for cluster growth interventions to ensure that the benefits outweigh potential risks. Implementation science research may also inform best practices for discussing the meaning and limitations of sequence data and cluster membership with community members and help to identify acceptable and evidence-based approaches that impose the least risk to persons within specific contexts (57, 58). These might involve partnerships with providers for non-intrusive patient follow-up related to clusters, more detailed consent procedures for future follow-up related to HIV test results or partner services referrals, and specific guidelines and education to mitigate criminalization risks.

One critical step will be to ensure that HIV phylogenetic information, including links with personal information and potentially identifying cluster details, is protected under the same strict security and confidentiality protections applied to other HIV surveillance information (58). For example, anonymized sequence data systems may be structured to report only cluster level characteristics at specific size thresholds or recognize only that a new infection is connected to an existing or growing cluster of infections. These approaches provide additional background for public health response but strongly limit confidentiality risks. As advances in molecular techniques improve the ability of HIV phylogenetic data to pinpoint timing and direction of infection, these cautions will be even more important to protect against risks of harm. Researchers and practitioners must prioritize attention to ethical and human rights considerations of these evolving new tools and do due diligence to assess the potential misuse of their findings where rights may be threatened.

A view to 2020: Key questions for research and program implementation

We currently lack sufficient understanding of how the social organization and structure of MSM communities, and their engagement with physical and virtual meeting spaces, may influence the mechanisms of HIV transmission (59-61), and thus how interventions might fill important gaps. With new insights about community-level transmission dynamics from HIV phylogenetic analyses, we can envision a future in which we are able to pinpoint what community networks, organizations, and settings should be targeted to interrupt transmission chains through treatment as prevention, pre-exposure prophylaxis (PrEP), and other social and structural interventions, and which should be bolstered to change social norms and enhance supportive resources for HIV care and prevention.

In the U.S., CDC's molecular HIV surveillance project is now informing large-scale patterns of population mixing from HIV transmission clusters identified across the country (44). Results to date show notable assortative mixing within social and sexual networks of communities at increased risk for HIV transmission, which are particularly homophilous among African-Americans and more heterogeneous among other race/ethnicities. Transmission patterns observed across risk groups further suggest that addressing the HIV epidemic among MSM will also reduce HIV acquisition among other populations (44). Homophily by age group and race/ethnicity is emerging as a clear hallmark of transmission among young MSM (4), which continues to strongly support the role of social networks as a driver of MSM transmission (62, 63).

Social science theoretical lenses offer great potential to enhance understanding of phylogenetic results and their implications for intervention. Theories and metrics commonly used to guide social network analysis, including diffusion of innovations and measures of cluster structure and composition, may be particularly valuable as the field evolves. We are also currently missing the perspectives, needs, and preferences of MSM and other communities at high risk for HIV transmission regarding the use of HIV phylogenetic information for prevention planning. Their insights on the meaning and implications of HIV phylogenetic analyses will no doubt provide deeper understanding and help to prioritize protection of human rights and stigma minimization (31).

Effectively harnessing the potential synergy of molecular HIV surveillance, contact tracing, and other enhanced data strategies will require greater understanding of how best to efficiently track the evolution and characteristics of large and growing clusters and fit public health initiatives accordingly. Current methods to identify individuals at high risk of HIV acquisition are challenging, especially when the duration of infection is unknown and there are higher numbers of sex or injection partners. Although HIV sequence data can help to characterize aspects of social networks or partner meeting places most likely to foster onward transmission and implement combination preventive strategies accordingly, real-time response is limited without timely availability and analysis of HIV sequences. Innovative programs in British Columbia, Canada (64, 65) and New York City (66) suggest that real time sequencing is feasible using new analytic approaches and routine HIV resistance genotype surveillance. They further show that phylogenetically identified links can usefully supplement contact tracing activities to identify and monitor emergent and growing clusters

of new infections. Additionally, New York City has shown that HIV phylogenetic data could help identify previously unknown segments of transmission networks, overcoming the perpetual challenge of unnamed partners.

Ongoing data system enhancements will complement development of the most informative integrated socio-behavioral and phylogenetic analyses, which may then be automated for interpretation and application in data to care initiatives in a timely manner. Implementation research and cost-effectiveness studies will be needed to evaluate these strategies and develop best practices. For example, is it necessary to investigate all emergent clusters? Only those of a certain size, certain rate of change, certain geographic or social spread, demographic diversity? It will be important to balance the population level promise of HIV phylogenetic insights with the operational capacity within public health practice settings to avoid unnecessary operational burdens.

Conclusion

Using HIV phylogenetic approaches to identify and intervene within social networks at high risk for transmission is a rapidly evolving field with strong promise for informing innovative responses to the HIV epidemic among MSM. Currently, HIV phylogenetic insights are providing new understandings of characteristics of HIV epidemics involving MSM, social networks influencing transmission, characteristics of HIV transmission clusters involving MSM, targets for antiretroviral and other prevention strategies, and dynamics of emergent epidemics. Maximizing the potential of HIV phylogenetics for HIV responses among MSM will require attention to key methodological challenges and ethical considerations, as well as resolving key implementation and scientific questions. As we look to 2020, we anticipate that enhanced and integrated use of HIV surveillance; socio-behavioral; and phylogenetic data resources will help to facilitate the strongest possible response to end the spread of HIV among MSM.

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