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Ethical Issues in HIV Phylogenetics and Molecular Epidemiology

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Abstract

Purpose of review: HIV phylogenetic and molecular epidemiology (ME) analyses are increasingly being performed with a goal of improving HIV prevention efforts. However, ethical, legal and social issues are associated with these analyses, and should be considered when performed.

Recent findings: Several working groups have recently outlined the major issues surrounding the use of ME for HIV prevention. First, the benefits of HIV ME remain unclear, and further work is needed to quantitatively demonstrate the benefits that can be expected. Second, privacy loss is an important risk, with implications of disclosure varying by the regional legal and social climate. Inferential privacy risks will increase with technological improvements in sequencing and analysis. Third, data sharing, which enhances the utility of the data, may also increase the risk of inferential privacy loss. Mitigation strategies are available to address each of these issues.

Summary: HIV ME for research and public health pose significant ethical issues that continue to evolve with improving technology, increased sampling, and a changing legal and social climate. Guidance surrounding these issues needs to be developed for researchers and public health officials in an iterative and region specific manner that accounts for the potential benefits and risks of this technology.

Keywords

HIV; phylogenetics; molecular epidemiology; privacy; disclosure

I. Introduction

The rapid and continuous evolution of HIV provides an evolutionary signal that can be exploited to infer links between persons infected with genetically similar viruses. Molecular

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epidemiology (ME) is the analysis of HIV sequence data (phylogenetics) integrated with sociodemographic, behavioral, and geographic information to help understand the epidemiology of a disease. In the past, phylogenetic analyses of HIV sequences have been used to provide clues on the historical origins of HIV, and describe historical and current epidemics. These data, when generated and analyzed in real-time, can be used to improve the understanding of HIV transmission dynamics within a population, information that is critical to developing and implementing effective public health interventions. A number of ethical, legal and social issues (ELSI) are associated with the use of HIV sequence data and phylogenetic analysis for research and public health. Several groups of experts and stakeholders have met to discuss the ELSI issues related to molecular epidemiology (ME) informed approaches to HIV prevention. These meetings include one led by Project Inform and the Third Coast Center for AIDS Research (CFAR) in Chicago in May 2017(1) and focusing on the use of ME in public health, and a second organized by the Ethics Working Group of PANGEA HIV (Phylogenetics And Networks for Generalized Networks in Africa(2)) also in May 2017 in London, and focusing on ME issues in Africa(3). More recently, Dr. Liza Dawson at the NIH (National Institutes of Health) held a workshop in April 2018 to address the ethical issues in NIH-funded ME research, and spin-off discussions continue. This paper will summarize the key points from the work produced from these meetings and other related work, as well as highlight future directions.

II. Molecular Epidemiology Provides Insight into HIV Transmission Dynamics

HIV sequence data that is required for phylogenetic analyses and molecular epidemiology are widely available from the drug resistance tests routinely performed during clinical care to guide selection of antiretroviral therapy (ART). These sequences (typically a consensus sequence obtained from the *pol* gene of the circulating HIV) can be used to infer a phylogeny or a transmission network using models of viral evolution and similarity between sequences to guide these inferences. These approaches have had great success in describing viral transmission dynamics of regional and national epidemics (e.g., Switzerland(4), The Netherlands(5, 6), United Kingdom(7–9), Canada (British Columbia)(10), and the United States [U.S.](11, 12)). HIV molecular epidemiology has also been used to describe emerging epidemics(13, 14), cross-national transmission(15–17), drug-resistance dynamics(10, 18–22), and to predict risk factors associated with transmission(6, 9, 23–25). They have even been used to predict cluster growth dynamics(10, 26) (i.e. which clusters of linked infections are likely to grow faster), including recent work by our group.

III. Ethical Challenges in HIV Phylogenetics

The main ethical challenge that arises from the study of HIV phylogenetics is to balance the urgent need to better understand HIV transmission characteristics with the risk of harms arising from an unintended breach of personal privacy associated with use of these same data. Due to the social stigma that surrounds HIV and the criminalization of HIV transmission in some jurisdictions, the potential harms of disclosure of results could be personally harmful to persons involved in this research. However, the challenge of balancing

advances in HIV knowledge and individual privacy demands is shaped by the context in which HIV ME is used. Here we describe the fundamental technical issues before discussing how we should consider them in the context of HIV phylogenetic analyses.

The characteristics of HIV that allow phylogenetic analyses to provide clues about transmission dynamics also pose potential risk. Given the relatively rapid mutation rate of the virus (i.e. 10^{-5} mutations/per site each generation), each infected individual ends up with a unique viral population. ME using phylogenetic or genetic network analyses uses the similarity of these viral sequences to identify putative transmissions between individuals linked by genetically similar sequences(27, 28). Current methods relying on sequence data alone cannot exclude possible intermediate individuals (i.e., unsampled persons) between two linked individuals along a transmission chain, a common source of infection, nor the directionality of any transmission event based on sequence data alone. However, additional epidemiologic data, such as a history of sexual contact between a genetically linked pair, may increase the probability of a direct transmission. Phylogenetic analyses are also fundamentally relational, and so identifying characteristics of person A included in an analysis might provide information on person B who was phylogenetically related(3). These inferences could be a demographic characteristic such as gender (i.e. person B was part of a cluster of infected males), or the analyses might suggest that person B was a potential source of infection. Phylogenetic relationships may also suggest travel or migration, if a person's virus is more closely related to an epidemic from another region.

IV. Risks Associated with HIV Molecular Epidemiology in Research

The ethical issues around the use of HIV ME in research include how best to navigate the landscape of stigma, criminalization, and the risks of privacy loss to individuals and groups given the potential harms posed by this work [72–78]. Re-identification can occur through data breaches, or through inferences made from the relational results of the analysis of de-identified datasets. Data sharing and analyses of combined datasets may compromise data security and increase the potential that identities are inferred. However, limits on data sharing prevent the transparency and dissemination of data and results that are critical to scientific progress and required by journals and funding agencies. Privacy loss can be further compounded by inference of other characteristics of an individual, such as sexuality or location of residence. In extreme cases, inference can lead to putative identification of a source partner in a transmission event.

As viral sequencing and data collection systems become more thorough and efficient, the risks associated with HIV phylogenetics grow. Next-generation sequencing (NGS) is now widely available and rapidly becoming competitive economically with standard Sanger sequencing. With sequencing of a greater proportion of circulating variants (i.e. depth) and sequencing of the entire viral genome (WGS), NGS can provide a more comprehensive picture of circulating virus. The sequence data generated by NGS can be used to infer transmission links and the directionality of transmission events with increasing certainty(29). The addition of metadata (e.g. geography, recency of infection, HLA profiles) can enhance the accuracy of these inferences even further. Improvements in the efficiency and cost of sequencing also allow larger numbers of samples to be sequenced. This will lead

to a greater depth of sample in many epidemics, further enhancing the accuracy of phylogenetic inferences.

The importance of these risks is intertwined with their legal and social implications. Phylogenetic inferences about sociodemographic characteristics or linked infections with directionality could lead to re-identification of the individuals whose data is included in the analyses. The effects of such disclosures becomes magnified by local societal norms, legal code, and the stigma perceived by the infected individuals. The legal impact also remains significant, as 33 U.S. states currently have HIV specific laws criminalizing HIV transmission and non-disclosure of HIV status(30, 31), and in 2016, 61 countries around the world have adopted laws that criminalize HIV transmission(32). Privacy loss and source identification can also lead to the exacerbation of social harms from individual and group level stigma. The impact of re-identification in a socially conservative and anti-gay region such as Chechnya could be significantly worse than in a liberal and open city such as Amsterdam in the Netherlands. Thus, it is important to realize that the ethical issues surrounding HIV and phylogenetics must be interpreted in the local context.

V. Mitigating Risks in HIV Phylogenetic Research

Prior to pursuing HIV ME work, and once it has been determined that the scientific benefits of a study are work the risk of harm to subjects, researchers need to make sure that participants in studies involving HIV phylogenetics are aware of the risks. Obtaining informed consent is no small feat, when many professionals working in HIV care and prevention are not even able to comprehend the risks associated with HIV phylogenetics(33). Further work is needed to improve the informed consent process to explain the risks associated with future planned (and possibly unplanned) ME studies.

Sharing of data and results is a cornerstone of the scientific process and it facilitates progress. Current Health Insurance Portability and Accountability Act (HIPPA) guidelines require the use of data use agreements when sharing limited data sets (i.e. datasets that include limited identifying information). These agreements may restrict users from combining data sets for analysis. However, many funding agencies (e.g. NIH) and journals still require that datasets need to be available for sharing to the scientific community. Restricting access to trusted individuals and groups can be difficult under these circumstances, and the NIH is actively working on guidelines related to these issues. Proposed solutions include the use of “black box” servers, which could store and analyze data but would not allow access to the actual data(34, 35). With such a solution, investigators could query one or more datasets stored on the server and receive the results of the query but not the actual data. The outputs could be designed to further limit the risk of privacy loss.

Presentation of results through publication is standard in scientific research. However, presentation of these data can have unintended consequences including the re-identification of individuals through inferences made from the presented results. This could be true even when the research was performed using de-identified datasets, as the relational results might provide clues to the identity of individuals. Furthermore, analysis of a more geographically focused or concentrated sample will also have a greater risk of privacy loss. Approaches to

mitigating these risks include data smoothing, where a reduction in granularity or the addition of “noise” limits the detailed inferences that can be made from the data. However, the application of too much smoothing may lead to a significant reduction in the utility of the results. Approaches to “tune” the degree of smoothing to minimize risk and maximize utility (e.g. differential privacy(36–39)) are needed.

VI. Risks Associated with HIV Phylogenetics in Public Health

The goals of public health departments are to protect and promote the health of their constituency. However, the goal of protecting and promoting the health of a society may not always be congruent with the concerns of individuals. Numerous examples of these situations exist including the quarantining of individuals with infectious forms of tuberculosis, and partner notification of individuals diagnosed with sexually transmitted infections. In these situations, an individual’s privacy is considered subordinate to the risk of transmission to others. Partner notification is commonly performed with HIV diagnoses, but the privacy related risks may be greater than with other infections given social stigma and the current legal climate in many states and nations.

ELSI issues surrounding HIV ME are further compounded when HIV phylogenetics is applied to public health. While all of the issues associated with HIV ME research remain, additional issues arise. The ultimate goals of ME analyses in public health are also to identify persons or groups at risk for transmitting or acquiring HIV. Therefore, the results of an analysis may lead to an intervention directed to these individuals or groups by public health workers. In this situation, the risk of privacy loss comes not only from the data, but also from the actions of the public health department, and the discreteness by which they are performed. The actions (on the ground and through publications) of a public health department may also further stigmatize groups of infected individuals through the suggestion of increased transmission risk. Intensified stigma could have the real effect of keeping people away from care, as well as increase hostility toward those suspected of high-risk behavior or assumed to be living with HIV. In fact, Schairer et al. found evidence of apprehension about public health departments using HIV ME for prevention among a group of stakeholders in San Diego (Schairer et al., under review).

VII. Mitigating Risks in the use of HIV Phylogenetics in Public Health

The consultation led by Project Inform and the Third Coast CFAR highlighted the similarity of the roll out of HIV ME in public health with Data-to-Care, where surveillance data (e.g. CD4+ T-cell counts, HIV viral load) was used to identify persons unlinked or not engaged in care. With Data-to-Care, community engagement and stakeholder meetings allowed officials to feel confident that the community believed that the benefits of the program would outweigh the risks. Given that public health departments do not require consent to use personal data, stakeholders and experts agree that community education and engagement should take place before and during the use of HIV ME for public health purposes.

Reducing the stigma associated with HIV infection could lead to a reduction in the legal and social risks encountered by PLWH. While the laws and the enforcement of these laws vary

from state to state, and country to country, a number of groups are working to decriminalize HIV transmission (e.g. HIV Justice Network, Center for HIV Law and Policy). Given the rapid improvements in HIV phylogenetic data collection and analyses, some investigators have suggested that it may be prudent to deploy HIV ME in public health only when taking local criminalization laws into context.

VIII. Benefits of HIV Molecular Epidemiology

Determining whether the benefits of molecular epidemiology outweigh the potential for harm also requires a clear understanding of the potential benefits, and the limitations around these analyses. Prior work has demonstrated that HIV ME can be used to delineate factors associated with HIV transmission dynamics(40–42). Others have demonstrated how ME could be used to identify “hotspots” of transmission(43, 44), measure the impact of prevention interventions(45, 46), as well as identify and estimate the size of key populations (e.g., PLWH who are unaware, HIV uninfected and at increased risk of acquiring HIV infection)(47, 48). HIV ME could also be used to identify the PLWH at highest risk of spreading HIV, directing the use of tailored, resource-intensive interventions (e.g., linkage to care, long-acting ART, directly observed therapy, etc.) to these persons. The utility of this last approach has been addressed through simulations which have shown that network targeting of interventions can improve the efficiency and efficacy of these prevention efforts compared to random allocation (24, 49). Empirical data to support these approaches remains limited. A handful of reports have demonstrated how ME analyses led to changes in a public health response(43, 44). However, these have been uncontrolled observations, where the potential benefits have been difficult to quantify. No controlled trials or prospective empirical observations have been performed to corroborate these results and quantitatively measure the benefits of HIV ME.

Future technological developments could enhance the potential benefits of ME on HIV prevention. Improving the depth of sampling (i.e. the proportion of PLWH in a given region that have available sequence and demographic data), and the use of NGS, which will improve the accuracy of inferences, may allow a more nuanced understanding of transmission dynamics. This could allow prevention resources to be focused at an even more granular level, but also increase the inferential privacy risk to persons whose data is being analyzed.

At this stage, there are still many unanswered questions about the potential and real-world expectations around the benefits of HIV ME for prevention. Much work is needed to quantitatively understand how ME can be made useful for HIV prevention so we can truly determine if a risk-benefit equipoise can be reached using this technology.

IX. Conclusion

In summary, the use of HIV phylogenetics and molecular epidemiology for research and public health poses significant ethical issues that will need to be addressed in an iterative manner as these technologies are deployed. Furthermore, the benefits of HIV ME need to be better characterized and quantified to allow researchers, public health officials, ethicists and

the public to determine whether the potential benefits outweigh the risks of using HIV ME for prevention. Ideally this would be accomplished using controlled trials, but even observational data are lacking.

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Key Points

- The benefits of HIV molecular epidemiology remain unclear, and further work is needed to quantitatively demonstrate the benefits that can be expected.
- Privacy loss and disclosures are important risks associated with HIV molecular epidemiologic analyses, and the implications of disclosure vary by the regional legal and social climate.
- Inferential privacy risks will increase with technological improvements in sequencing and analysis.
- Data sharing, which enhances the utility of the data, may also increase the risk of inferential privacy loss.
- Guidance for HIV molecular epidemiology work is needed for researchers and public health officials to ensure best practices when applying these analyses.