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# Experts' Perspectives on Key Ethical Issues Associated With HIV Phylogenetics as Applied in HIV Transmission Dynamics Research

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**Abstract**

The use of phylogenetics in HIV molecular epidemiology has considerably increased our ability to understand the origin, spread, and characteristics of HIV epidemics. Despite its potential to advance knowledge on HIV transmission dynamics, the ethical issues associated with HIV molecular epidemiology have received minimal attention. In-depth interviews were conducted with scientists from diverse backgrounds to explore their perspectives on ethical issues associated with phylogenetic analysis of HIV genetic data as applied to HIV transmission dynamics studies. The Emanuel framework was used as the analytical framework. Favorable risk–benefit ratio and informed consent were the most invoked ethical principles and fair participant selection the least. Fear of loss of privacy and disclosure of HIV transmission were invariably cited as key ethical concerns. As HIV sequence data become increasingly available, comprehensive guidelines should be developed to guide its access, sharing and use, cognizant of the potential harms that may result.

**Keywords**

HIV phylogenetics, molecular epidemiology, data sharing, in-depth interviews, informed consent, people with HIV/AIDS, privacy/confidentiality, qualitative methods, risks, benefits, and burdens of research/beneficence and non-maleficence

## Introduction

Molecular epidemiological techniques have considerably increased the ability of scientists to understand the origin, spread, and characteristics of several infectious diseases, including HIV. One approach used in molecular epidemiology is phylogenetic analysis of HIV genetic sequences. This is a complex scientific process, which involves the inspection of small disparities in viral genes to determine the genetic distance between virus strains.

The technique is increasingly used in HIV epidemiological research and clinical trials to identify sources of the epidemic (Little et al., 2014; Liu, Erion, Novitsky, & De Gruttola, 2015) and epidemic drivers (German, Grabowski, & Beyrer, 2016; Ratmann et al., 2016), as well as to evaluate the impact of prevention interventions (Campbell et al., 2011). More recently, the technique was applied in a large-scale community study, which sought to identify the underlying drivers of HIV-1 transmission at the population level (de Oliveira et al., 2017). A literature review of ethical issues associated with the applications of HIV phylogenetic analysis is presented elsewhere (Mutenherwa, Wassenaar, & de Oliveira, 2018).

HIV phylogenetics research (HPR) is a relatively new but rapidly growing field. Despite the growing interest and increased use of phylogenetic analysis in HIV research, relatively limited conceptual and empirical work has been conducted to explore the ethical issues associated with this work. It could be argued that the ethical issues associated with HPR are not dissimilar to those raised in human genomic studies, an area that has been extensively researched (de Vries et al., 2011; de Vries, Slabbert, & Pepper, 2012; Munung et al., 2016). However, HIV phylogenetics may present distinctive ethical challenges as outlined below.

First, HIV phylogenetics deals with the genetics of a transmissible pathogen and its interaction with its human host. The blood samples for such research could originally have been obtained for other purposes, for example, drug

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resistance testing. This raises questions about participants' understanding of the distinction between clinical care and research, as well as issues around voluntariness of participation in research (Appelbaum, Lidz, & Klitzman, 2009a; Chokshi et al., 2007; Mamotte & Wassenaar, 2015). Second, the pathogen is associated with a highly stigmatized condition and transmission of the virus is criminalized under certain circumstances in numerous countries (UNAIDS, 2013). Third, HIV genetic data are host-specific. Each sequence is, therefore, distinct for each HIV-infected person (Little et al., 2014; Mehta, Vinterbo, & Little, 2014). Fourth, it is widely acknowledged that phylogenetic analysis cannot, by itself, provide definitive proof of the route, direction, and timing of HIV transmission between two people, as there are many reasons why two individuals might share the same virus. For example, there could be missing people in the transmission chain, for example, individuals who were not sampled (Abecasis et al., 2011; Scaduto et al., 2010). Finally, for meaningful conclusions about disease epidemiology to be drawn at the population level, phylogenetic analysis relies heavily on linking clinical, sociodemographic, and behavioral data of HIV-positive individuals to their respective HIV genetic sequences. All of these concerns need to be addressed in the context of HIV phylogenetics.

The aim of the study was therefore to explore the views of experts on key ethical issues associated with HIV phylogenetics as applied to HIV transmission dynamics research. Such an analysis, in turn, could inform current ethics guidelines for researchers and ethics review systems.

## Method

The study is part of a larger project which seeks to improve existing policies and guidelines with a view to maximizing the utility of HPR while ensuring that appropriate safeguards are in place to protect the rights and safety of human participants.

The larger project is divided into three sequential work packages. The first work package was a desk review of related literature, conducted to develop a conceptual framework for the project. This was followed by an empirical investigation of the views of experts in phylogenetics, bioethics, and virology on perceived key ethical issues associated with HIV phylogenetics to supplement the literature review. The last work package will comprise interviews and focus group discussions with key informants in a community exposed to HPR. This article reports on the second work package.

### *Sampling*

This was an exploratory study, which required rich data from experts in the fields of bioethics, epidemiology, virology, and public health. Twenty-nine experts were purposively selected based on their publication history in peer-reviewed journals using the following keywords: HIV phylogenetics, molecular epidemiology, and ethical issues. They were invited to participate in the study via email. Of the 29 experts, 15 confirmed their availability for the interview, while 10 did not respond after three follow-up emails. The remaining four responded to the email but indicated that they were not well placed to give an interview on the topic, so they were excluded. Of the 15 who responded positively to the invitation, one could not be interviewed due to connectivity challenges. Attempts to reschedule the interview were unsuccessful.

We could not establish the reasons for the nonresponse as the available means of communication with the nonresponders was via email, to which there was no reply. It is possible that the email addresses that we used were obsolete. Participant recruitment was stopped after reaching saturation, when additional interviews were no longer yielding new insights on the research topic.

Interviewees were from eight countries in three continents: Africa, Europe, and North America. In some cases, the identified experts referred the researcher to other prospective interviewees whom they thought were better qualified to give an interview on the topic. Four leads were suggested. However, the four were already among the invited participants. The final sample comprised 14 interviewees.

### *Procedure and Data Collection*

Email addresses of experts were obtained from their published scientific articles. Invitations were sent between September and October 2016, accompanied by an information sheet and consent script. If they agreed to participate, appointments were set up and the consent script was reread just before the interview to obtain verbal consent.

Interviews were conducted between November and December 2016. Data collection was predominantly done via Skype calls ($n = 13$) due to the geographical distribution of interviewees, which made face-to-face interviews logistically impossible and costly. Only one interview was conducted face-to-face. Some Skype calls were video-recorded, while some were not, due to bandwidth challenges. In both face-to-face and Skype interviews, prior verbal consent was also obtained from each respondent to digitally record the interview. The Skype interviews were recorded using Skype Recorder, a commercial computer software that records and stores video and audio Skype calls. The face-to-face interview was recorded on tape.

Interviews were directed by an interview guide which had two primary questions (Appendix). Interviewees were initially asked about their knowledge and experience of HIV phylogenetics. The second question focused on what

**Table 1.** Respondent Profiles.

| Respondent number | Main area of expertise | Other skills | Country | Gender |
|---|---|---|---|---|
| 1 | Virology | Clinical and epidemiological virology, HIV phylogenetics | Belgium | Female |
| 2 | Public health | Public health ethics, epidemiology, research ethics | Sweden | Male |
| 3 | Ethics | Genetics, genomics, next-generation sequencing, health research ethics | South Africa | Female |
| 4 | Ethics | Global justice and bioethics, global health and international research ethics | United States | Male |
| 5 | Epidemiology | Infectious disease epidemiology, HIV, molecular epidemiology | Uganda | Female |
| 6 | Ethics | Bioethics, research ethics, HIV prevention, clinical trials | United States | Female |
| 7 | Ethics | Applied ethics | United States | Male |
| 8 | Medical anthropology | Medical anthropology, HIV prevention, research ethics | Malawi | Female |
| 9 | Epidemiology | Molecular epidemiology, genetics, microbiology, infectious diseases epidemiology, research ethics | United States | Male |
| 10 | Virology | Molecular virology, molecular epidemiology, bioinformatics | Uganda | Male |
| 11 | Virology | Evolutionary biology and bioinformatics | United Kingdom | Male |
| 12 | Genetics | Genetics, sequencing, RNA, DNA | United States | Male |
| 13 | Ethics | Research ethics, bioethics, governance | New Zealand | Female |
| 14 | Epidemiology | Infectious diseases, biology and epidemiology of HIV transmission, molecular epidemiology | United States | Female |

they regarded as key ethical issues associated with HIV phylogenetics, with a particular focus on its application in HIV transmission dynamics research. A responsive approach to the interviews was adopted whereby the interviewer asked questions, building on what each respondent said while gently guiding the conversation. This approach was adopted to avoid confining the discussion to any predefined themes and to optimize the diversity of views obtained. The first author (F.M.) conducted all interviews in English. Each interview lasted an average of 45 minutes.

The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa (Ref. BE224/16).

### *Data Analysis*

We applied deductive qualitative analytic methods to code text into preselected themes based on the existing literature, previous research, and specifics of the research question (Gilgun, 2005). All interviews were transcribed verbatim by a social scientist and checked by F.M. for accuracy before being exported into NVivo version 10.2.2 qualitative analytic software. The Emanuel framework (EF); (Emanuel, Wendler, & Grady, 2008) was used as the analytical framework for data analysis as has been used in several other recent studies (Koen, Wassenaar, & Mamotte, 2017; Tsoka-Gwegweni & Wassenaar, 2014). The eight ethical principles of the EF formed the nodes or themes at which the transcripts were coded. The eight principles of the EF are as follows: (a) collaborative partnership, (b) social value, (c) scientific validity, (d) fair participant selection, (e) favorable risk–benefit ratio, (f) independent ethics review, (g) informed consent, and (h) ongoing respect for participants. The use of predetermined categories is common in qualitative data analysis and is accommodated in other relatively novel data analytic approaches, for example, the Framework Method (Gale, Heath, Cameron, Rashid, & Redwood, 2013).

F.M. and an independent social scientist independently coded transcripts at the eight nodes. The two later met to discuss any discrepancies identified during the coding process. About 10 discrepancies were noted during the coding process, and each party was asked to justify their reason for coding the text at a particular node. Most of the discrepancies were around what was coded under the two principles of informed consent and ongoing respect for participants. Any differences were resolved by mutual agreement.

## Findings

The findings presented in this section are based on 14 interviews conducted with experts in phylogenetics, public health, and bioethics. Of the 14 interviewees, five were ethicists, three were epidemiologists, and three were virologists. The remainder were a geneticist (1), a medical anthropologist (1), and a public health practitioner (1). Although the interviewees' areas of expertise were coded under the five broad disciplines, most participants had multidisciplinary skills as shown in Table 1.

## Ethical Principles Spontaneously Invoked by Interviewees

We coded all the ethical issues raised by interviewees into eight themes as defined by the eight ethical principles from

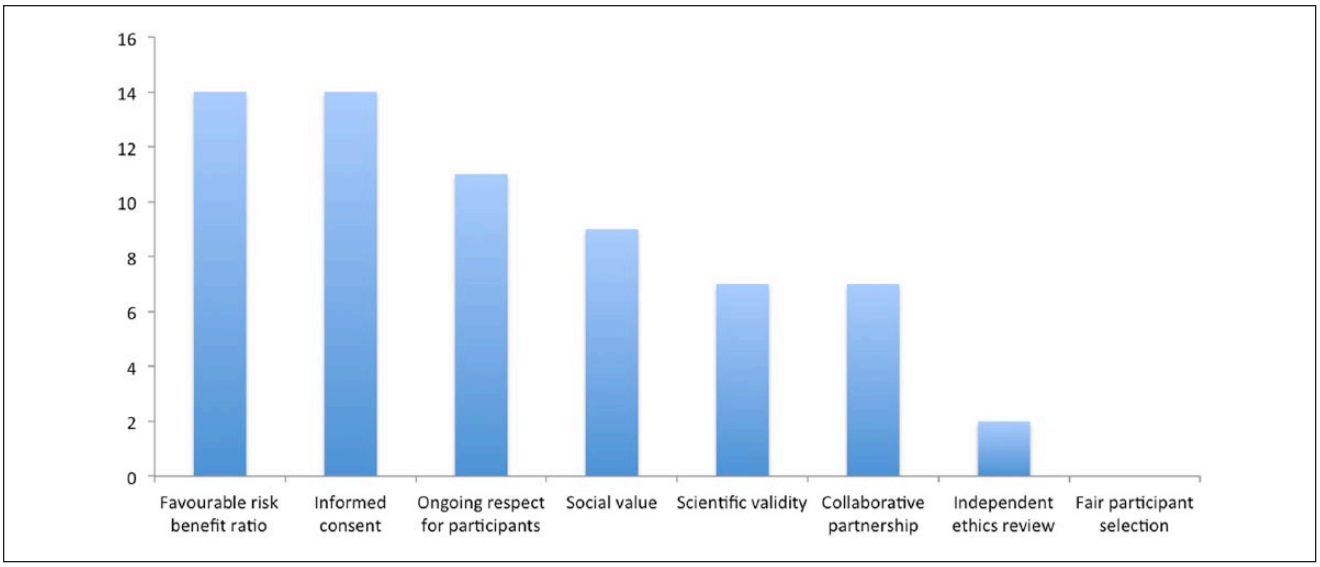


**Figure 1.** Frequency distribution of ethical principles mentioned by interviewees.

the EF, which formed the thematic framework. Figure 1 shows the frequency distribution of the principles in descending order. The graph is merely a visual depiction of the most and least mentioned ethical issues and should not be viewed as a statistical analysis of the interviews.

*Informed consent* and *favorable risk–benefit ratio* were the most frequently mentioned principles, with each mentioned by all interviewees ($n = 14$). These were followed by *ongoing respect for participants* ($n = 11$) and *social value* ($n = 9$). Seven interviewees each mentioned *scientific validity* and *collaborative partnership*, while two interviewees mentioned *independent ethics review*. None of the interviewees mentioned *fair participant selection* as an important ethical consideration for HPR.

## *Ethical Issues Raised Under Each of the Eight Principles/Themes*

In this section, we describe the ethical issues that were raised under each of the eight principles mentioned in Figure 1, in descending order.

*Favorable risk–benefit ratio.* Interviewees argued that HPR should be preceded by a careful evaluation of anticipated benefits in comparison with potential risks to different stakeholders. Such stakeholders could include research participants and society at large. Interviewees noted that the information generated by HPR was likely to have different meanings and impact for different stakeholders involved. They felt that assessments of favorable risk–benefit ratios should take into consideration the vested interest of each group of stakeholders.

There was consensus among interviewees that HIV phylogenetics had great potential to impact positively on the human population. The benefits were, however, perceived to come at a cost. For example, it was noted that analysis of the HIV genome could be used to profile high HIV transmitters, allowing for the development of targeted prevention interventions. Although such interventions were perceived to reduce HIV transmission rates and incidence, interviewees were concerned that even without revealing individually identifiable data, results from phylogenetic research could potentially harm individuals as well as identifiable subgroups through stigma and criminalization. Specific population subgroups highlighted included men who have sex with other men (MSM), intravenous drug users, those involved in transactional sex, and minority ethnic groups. The following illustrates these viewpoints:

> So the other thing is that phylogenetics is something that can be used to understand transmission patterns and to identify groups of people that may serve as sources of infection. This could be people grouped in their places or geographic areas or they could be a subgroup of individuals in a particular occupation . . . and we come up and say X% of people are responsible for X% of transmissions. What does that do to those groups? Does that stigmatize them, does that denigrate them and how can we as public health people identify transmission patterns and ongoing sources of infection without compromising the human rights of other individuals. (Epidemiologist, Respondent No. 5)

Our interviewees were concerned that the application of HIV phylogenetics for social network analysis could lead to serious marital disharmony. A typical example cited was the application of HIV phylogenetic analysis in HIV prevention studies involving discordant couples. Typically, these studies are conducted to identify the most effective intervention

to reduce transmission to the HIV-negative partner. In the event that the negative partner gets infected during the study, the virus is sequenced to identify the source of the virus. Participants were concerned that although the two might have enrolled in the study as a couple, it was possible that the source of the virus could be an extramarital or external sexual contact outside the partnership. This leaves the researcher with an ethical dilemma in that they have acquired sensitive information about people's private lives in the absence of clear guidelines and rules about what to do with that information.

Furthermore, considering that the research typically focused on an already stigmatized condition, some interviewees were concerned that, if not properly managed, study results might further aggravate the existing stigma. More worrying was the combined use of phylogenetic analysis of HIV genetic sequences with geo-mapping techniques, which could lead to precise identification of subpopulations. Potentially serious negative legal consequences were also envisaged in jurisdictions that criminalize HIV nondisclosure, exposure, and transmission. Interviewees argued that researchers might be compelled to release incriminating information from their database. All the risks highlighted were perceived as potential barriers to participation of individuals in beneficial health programs, including HIV testing and care. Striking a balance between benefits and risks was viewed as an onerous task, which required broad consultations and community-specific assessments.

Interviewees expressed divergent views regarding the magnitude and probability of risk to privacy for participants in HPR. Some argued that the risk of privacy violations was very low and not worthy of consideration, while others thought this was the most crucial ethical issue. Such diverging views reflect the different disciplinary backgrounds of our interviewees and knowledge levels on HIV molecular epidemiology. Interviewees who were well versed with the scientific aspects of HIV molecular epidemiology were less likely to perceive HPR as a major threat to privacy and vice versa. One respondent, with a background in science and research ethics asserted that concerns about privacy violations were not only exaggerated but also "unreasonable" and not supported by scientific evidence. In her view " . . . it's much more safe to be in a research study than to at least open a bank account" (Ethicist, Respondent No. 6). These views were supported by another respondent, who argued that those who perceive phylogenetics research as risky may not have a clear understanding of what that risk entails. In his view, privacy risks associated with HPR were perceived rather than real:

> . . . it's a risk of perceptions instead of a risk of reality. The perception is that this information can directly implicate somebody in having infected someone else but the reality is that it's not true. But people's perceptions can be seen as more important than realities. (Ethicist, Respondent No. 7)

Some interviewees viewed the monitoring of HIV phylogenetic clusters and hotspots for HIV prevention as generating unique ethical concerns. For example, the tension between individual rights and public health obligations was viewed as a key ethical consideration. On one hand, they noted a public health obligation to protect the community from further HIV exposure by identifying high transmitters, while on the other there was a competing obligation to protect the privacy of individual members of that community. Some interviewees noted that it would be difficult to simultaneously pursue the public health and scientific goals of identifying HIV transmission patterns and sources of infection without compromising human rights. Although some interviewees acknowledged the limits of contemporary phylogenetic techniques to precisely identify HIV transmitters at the individual level, there were concerns that this might change in the future as molecular epidemiology techniques improved:

> Their usual goal is to protect public health. So what would it mean? At some point we knock on someone's door and say, "from the data we have it looks like you are infecting a lot of people and we need you to stop doing that." This then becomes an issue in the public health setting and it seems you cannot do that in a research study if people can now perceive you can knock at individual doors and say you have a problem here, then people might be very reluctant to participate in further research studies and might be very reluctant to provide information to public health professionals because of the fear that they could be singled out. (Ethicist, Respondent No. 7)

Other interviewees, however, highlighted the importance of delineating research from public health practice when using HIV genetic sequences. They noted that researchers have no right or obligation to determine who the person in the epicenter of an epidemic was. One respondent summarized this as follows:

> It's not part of our study. We are observers of HIV transmission and dynamics and we characterize and try to learn from the data about how to interrupt transmission and do something that will impact the epidemic in our community . . . we will never identify an individual and target that individual in a way that might identify the position in the network. (Epidemiologist, Respondent No. 14)

*Informed consent.* The issues raised about informed consent revolved around two of the four elements of consent: disclosure and understanding (Beauchamp & Childress, 2009).

The majority of interviewees were concerned that due to its complexity, the content, packaging, and delivery of phylogenetics research messages would be problematic. The concerns were compounded by perceptions that researchers might have limited knowledge of what HIV genetic data reveal about individuals or communities. The absence of complete information was therefore viewed as a key barrier to information disclosure and comprehension, which are key components of the consent process:

> But I think the idea of truly getting consent from someone, and the moment they get consent they truly understand the risks . . . I think that's a fallacy. I think what we are doing is to say that we trust the people doing this work to work in the best interest of the population and protect individuals to the extent they can. But there are risks that we do not anticipate and we have to make sure that the people who use the data downstream understand the protection that should be applied to this data. (Geneticist, Respondent No. 12)

Some of our participants acknowledged that it was common practice for researchers conducting phylogenetic studies to use samples collected for other purposes. Typically, these samples are collected to genotype the virus for HIV drug resistance testing and alignment to appropriate therapy. A key ethical question raised was whether research participants were required to provide specific consent or broad consent when they give their sample and whether such consent was deemed adequate for future HPR. Commenting on the consent process for phylogenetic studies, one of the participants had this to say:

> Right now its pretty loose. We are asking people if we can use their samples for future studies . . . like laboratory-based studies and that consent has covered that. Whether or not that's sufficient, I am not sure. But I think generally we have told them you know we are going to be using your samples, we will be doing analysis on the content of these samples and if there is information that is relevant to your individual health we will return that information to you. (Epidemiologist, Respondent No. 5)

Recommendations were made to ensure that the consent process was valid. First, interviewees noted that tests of comprehension should be an integral part of the consent process. Second, they encouraged researchers to invest in proper communication strategies to ensure that prospective participants consented or refused to participate in research based on accurate and appropriately packaged information. Third, it was stated that researchers should avoid technical and methodological elements of HIV phylogenetics, as these added minimal value to the consent process. Finally, interviewees also cautioned that even if the four elements of consent were met, informed consent alone should not be seen as a guarantee of the protection of participants.

*Ongoing respect for participants.* Some interviewees said that a governance framework was needed to guide the conduct of HIV phylogenetic studies. Such a framework would outline policies and practices in relation to data sharing and access, particularly the downstream use of HIV genetic sequences and clarification about who should have access to the data and how they should access it. In addition, interviewees recommended guidance on communication and dissemination of research results. In view of the potential risk of social harm to research participants in phylogenetic research, participants were concerned about the content of results presented at dissemination workshops and in scientific publications. It was noted that even though many generic national and international ethics guidelines were available in the literature, specific HPR ethics guidance was probably needed.

The need for researchers to be cautious and attentive to detail when providing information about HIV transmission network analysis was emphasized in the light of its methodological limitations (see section "Scientific validity"). Some interviewees highlighted that it was not accurate to claim that HIV transmission network analysis identifies who infected whom. Rather, what could be shown from the analysis were clusters of sequences that have some degree of similarity based on genetic distance. They argued that clustering was a statistical construct, which relies on sample as opposed to census data from all HIV-positive individuals. There was, therefore, a probability that some missing individual(s) in the sample might have been responsible for the transmission event. Conclusions about direct HIV transmission were likely to be probabilistic rather than precise.

*Social value.* Most interviewees identified phylogenetic analysis of the HIV genome as a unique and powerful tool that provides detailed information on HIV transmission dynamics. They perceived it as complimenting rather than competing with traditional epidemiology methods. As one respondent noted, " . . . *network analysis is really a way to connect people that is complementary to epidemiologic social network analysis.*" Geneticist, respondent No. 12. One of the unique features identified by interviewees was that once phylogenetic analysis is carried out in combination with clinical and epidemiologic information, it reveals how the virus lineages are connected to different social, behavioral, and demographic subpopulations, thereby enabling the profiling of HIV-1 transmitters. For example,

- Are they MSM, sex workers, or in concurrent polygamous relationships?
- Do they have multiple concurrent sex partners?

- What age groups do they belong to, and
- What are their viral loads?

Participants also noted that epidemiological information, such as sexual behavior, the use of injectable drugs, and sexual orientation, was traditionally obtained through self-report interviews. However, because behavioral sexual information is very sensitive, people are notoriously unreliable at disclosing such details, even in research, due to social desirability effects (Krumpal, 2013). Relative to traditional epidemiological approaches, the use of HIV phylogenetics in combination with clinical, behavioral or other demographic data was viewed as more reliable for aligning HIV transmission events to the correct risk group to guide the design of effective HIV prevention and mitigation strategies.

Another related ethical issue raised by some of our participants concerned health system response to the information generated from HIV phylogenetic research and how that intersects with structural level concerns in public health. How are resources distributed across the population? This is summarized as follows:

> You could have some geographical areas that have high rates of transmission of HIV and then you might wanna target those with intervention programmes . . . but there might be questions raised as to why you are targeting one area and not allowing the same level of services across the region or across the country. There maybe distributive justice questions about how you use these resources and how you do health programming in response to information . . . and again with the idea of targeting certain regions or certain communities with HIV prevention or treatment efforts, this could be a benefit but could also then create some stigma around those communities being seen as being high risk areas . . . (Ethicist, Respondent No. 6)

The above views were expressed in a context where the true drivers of HIV could be structural in nature, for example, women's disempowerment. Despite the benefits, addressing structural issues is not easy and requires huge financial resources, social change, and political will. How policy makers and governments reconcile which groups and geographic areas to target and the structural factors to be addressed was raised as an area of concern. Policy makers could opt for superficial HIV prevention interventions out of political expediency rather than anticipated public health impact.

*Scientific validity.* Interviewees first described how HIV phylogenetics works and the related inferences and conclusions that can be drawn. Technical perspectives came mainly from interviewees with backgrounds in genetics and virology. The majority of interviewees highlighted several methodological limitations affecting the interpretation of HPR results. These were *sampling, direction* of transmission, and whether transmission was *direct* or not. For example, participants noted that when doing phylogenetic analysis, it was not possible to get information from every single HIV-positive person for two main reasons. First, some people who are HIV positive are not aware of their status for a variety of possible reasons. It was not possible, therefore, to get their data and include them in the sample and subsequent analysis. The second point raised was that not everyone who is diagnosed has started treatment. In most countries, HIV sequences are only obtained when a person is initiated on antiretroviral treatment. HIV phylogenetic analysis (whether for public health practice or research) is thus typically based on a fraction of the overall epidemic population, so it is not possible to get a precise picture of who infects whom. There may be individuals associated with transmission that researchers have no information about. As a consequence, transmission chains constructed using phylogenetics give only a partial picture of the individuals involved in the transmission process. These views were captured by one of the interviewees:

> Think of it this way, you have 3 individuals X, Y and Z, they all have very similar viruses, right. The question will be; if X is a male, the two are females . . . Y and Z are females. Now if they have similar viruses will you say that X infected Y and Z? How sure are you that there is no person A and B in that network whom you didn't sample who probably infected the three. Probably a very different person infected X, another person differently infected Y and another person infected Z separately. (Virologist, Respondent No. 10)

The main concern regarding the above-mentioned methodological limitations was that perceptions of where transmission patterns are occurring and where interventions should be targeted could be skewed because a significant proportion of those living with HIV might not be included in the analysis. Our interviewees were worried that if researchers do not understand the context in which the data were collected, it would be difficult to interpret the findings correctly. Serious mistakes could potentially be made about the actual meaning of the data, potentially misinforming future decisions about resource allocation for targeted interventions.

Some interviewees encouraged researchers and others working with this technique to be cautious about the conclusions that can be drawn from HIV phylogenetic analysis. Scientists were advised against drawing conclusions about directness of transmission and its direction because many other people are absent from the transmission chain. However, despite these methodological limitations, there was consensus among interviewees that missing people in a

transmission chain have no effect on the validity of the results when applied at population level.

*Collaborative partnership.* A strong community engagement (UNAIDS-AVAC, 2011) component was viewed by most interviewees as an integral component of phylogenetic studies. Community engagement was viewed as a way of protecting communities from exploitation by facilitating the establishment of community-driven research priorities. Considering the difficulties that could be encountered in generating appropriate research messages, interviewees highlighted the important role community members could play in the design of context-specific phylogenetic messages. These messages could eventually be used during the consent process.

Ownership of phylogenetic research and collaboration between researchers from Africa and high-income countries (HICs) was raised as an important ethical consideration. Some interviewees were concerned that African researchers were not meaningfully engaged in the scientific research process in health research in general and phylogenetic research in particular. Several opportunistic reasons were cited why researchers from Western countries want to conduct research in Africa yet may not have "real commitment to either the patients or the communities" or to the disease burdens. For equitable and mutually beneficial collaborative research partnerships to be realized, local researchers were encouraged to take leading and active roles throughout the research process. Interviewees argued that local researchers were more likely to understand their health care and research systems and study results were more likely to be easily translated into policy.

*Independent ethics review.* Only two interviewees commented on independent ethics review. One of the key ethical issues raised was that HPR was a relatively new but advancing discipline, which may present new ethical challenges. There was a perceived concern that research ethics committees/institutional review boards (RECs/IRBs) may not be abreast of advances in molecular epidemiology and hence may be inadequately prepared to review and oversee these studies. Interviewees expressed concern that if RECs were inadequately trained, there was a risk that they may block or delay groundbreaking phylogenetic studies. A key question that was raised was how RECs could be supported to ensure that they were informed about advances in HPR. It was suggested that researchers and members of RECs with an interest in HPR should consider forming and joining platforms where they could discuss topical ethical issues and so remain abreast of advances in the field. Such platforms also help bring together expert knowledge to disseminate key ethical messages about HIV phylogenetics. Similar platforms were created a decade ago in anticipation of HIV vaccine trials (Kaleebu et al., 2008).

In summary, the most frequently cited ethical issues associated with HPR were classified under the ethical principle of favorable risk–benefit ratio and informed consent. These were followed by ongoing respect for participants, social value, scientific validity, collaborative partnership, and independent ethics review, in that order. Fair participant selection was not mentioned by any respondent.

## Discussion

HIV phylogenetic analysis of genome sequences is a rapidly evolving field, which can positively impact transmission dynamics. The ethical issues associated with HIV molecular epidemiology have received minimal attention to date (Mutenherwa et al., 2018). Participants gave spontaneous responses to a single question that asked them to identify key ethical issues associated with HPR. This method allowed us to identify respondent-defined priorities rather than invoking interviewer-defined responses. The approach has been applied in other studies investigating stakeholders' perspectives on ethical issues in vaccine trials (Essack et al., 2010).

The ethical issues raised by interviewees were largely accommodated by the EF and mirrored many of the issues raised earlier in relation to human genomic studies (Munung et al., 2016). However, the study also raises some novel and distinct ethical challenges—for example, the potential risk of HPR to point out individuals or subgroups associated with high transmission and the difficulties of balancing public health benefits against individual privacy.

The discussion is organised around the majour themes from the Emanuel Framework and addressed in order of frequency of being mentioned by the respondents.

*Favourable risk benefit ratio.* Ethical research should typically offer participants a favorable net risk–benefit ratio (Emanuel et al., 2008). Although interviewees in our study could not state categorically whether phylogenetic studies offer a favorable risk–benefit ratio, they viewed privacy violations and threats to confidentiality as the two major risks associated with use of HIV sequence data. Privacy has been cited in the literature as a major source of public concern, particularly for human genomic research (Majumder, Cook-Deegan, & McGuire, 2016). Traditionally, threats to privacy were addressed through data deidentification. However, emerging literature has challenged this paradigm following demonstrations that reidentification of participants was possible from anonymous human genetic data (Gymrek, McGuire, Golan, Halperin, & Erlich, 2013). Similar privacy concerns have recently been raised with HIV genetic data (Mehta et al., 2014; Schairer et al., 2017). Fears of privacy violations are compounded by the absence of a clear definition of what constitutes a true benefit or actual risk to personal privacy for phylogenetic studies; hence,

risk–benefit assessments for such studies are problematic (Mehta et al., 2014).

It is widely acknowledged that when assessing risk, it is critical to consider the probability of the harm occurring, as well as its severity (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1979). Although our interviewees were quick to highlight the risks and the benefits separately, it was not easy to say whether HIV phylogenetics offers a favorable risk–benefit ratio. Such assessments are not obvious due to the absence of appropriate matrices for evaluating risk in genomic studies in general and in phylogenetic studies in particular (Mehta et al., 2014). Even more challenging is the application of risk rating using concepts like "minimal risk". The minimal risk standard is defined by "comparing the probability and magnitude of anticipated harms with the probability and magnitude of harms ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (Council for International Organizations of Medical Sciences, 2016). The standard definition of minimal risk, therefore, depends on individual circumstances and context—for example, whose everyday life, where?

Interviewees also highlighted distinctive ethical issues associated with the growing use of HIV genetic sequences in public health, particularly HIV surveillance. Concerns have also been raised in the literature that potential misuse of HIV sequence data in public health could lead to serious legal and social harm, such as criminal prosecution, HIV-related stigma, and discrimination (Brooks & Sandstrom, 2013; Gilbert, Swenson, Unger, Scheim, & Grace, 2016). These concerns have led to recent calls for robust and inclusive ethics review systems for monitoring HIV phylogenetic clusters (German et al., 2016; Gilbert et al., 2016) for HIV prevention. While new guidelines have been published for public health surveillance (World Health Organization [WHO], 2017), these do not address the distinctive ethical issues associated with the use of HIV genetic data.

*Informed consent.* The dominance of informed consent–related issues was not unexpected in our study. It resonates with observations in the scientific literature, which highlight informed consent as the most invoked ethical issue in research (Essack et al., 2010). Historically, informed consent was mistakenly considered the only determinant of ethical research (D'Agostino, 1995). Interviewees in our study were concerned that due to its complex scientific nature, developing and packaging HPR messages in plain comprehensible language could be a challenge. This finding is consistent with results from a recent study conducted in the United States, which showed common misunderstandings among professionals and lay persons of molecular epidemiology and in particular HIV network analysis (Schairer et al., 2017). Previous studies on human genomics also showed that researchers identified challenges in explaining study goals, methods, and procedures to research participants (Marshall et al., 2014; Traore et al., 2015). Similar concerns have also been raised in clinical trials (Mystakidou, Panagiotou, Katsaragakis, Tsilika, & Parpa, 2009). Tests for comprehension could play a major role in ensuring that participants understand what they are consenting to (Addissie et al., 2016; Lindegger et al., 2006).

*Ongoing respect for participants.* Respect for participants typically incorporates (a) protecting confidentiality of data collected from participants, (b) informing them of their right to withdraw from a study, (c) providing them with new information relevant to the study, and (d) informing them about the research results (Emanuel et al., 2008). The ethical issues raised by interviewees revolved around confidentiality, communication of research results, and provision of accurate information on HIV transmission network analysis. It is widely acknowledged that although researchers have an ethical duty to communicate research results, there is a parallel obligation to minimize any foreseeable harm to research participants and host communities (Weijer & Emanuel, 2000). With phylogenetics research, balancing the two competing obligations can be problematic because HIV genetic data can potentially reveal the person from whom the sample was collected (Little et al., 2014; Mehta et al., 2014). Concerns about breaches of confidentiality are not unique to HIV phylogenetics. They have been reported in human genomic research (Gymrek et al., 2013) and are likely to be more prominent with increasing accessibility of data via the Internet (Gutmann & Wagner, 2013). It is, however, worth noting that, despite the concerns about possible confidentiality breaches, information on the frequency of such cases in research is not available. Could this be a case of smoke without fire?

Although participants mentioned most of the ethical benchmarks under the principle of respect for participants, the right to withdraw from a study—a key element of voluntary participation in research—was overlooked. It is possible that participants downplayed its importance due to limited knowledge about what constitutes a voluntary decision. Considering that most sequence data are generated for routine clinical management, its subsequent use for research and surveillance might have been underestimated. This observation is consistent with the literature regarding consent for samples used for clinical management (German et al., 2016; Hecht, Wolf, & Lo, 2007). In addition, what constitutes voluntary participation in health research and its measurement has also been debated and researched (Appelbaum, Lidz, & Klitzman, 2009b; Mamotte & Wassenaar, 2017).

*Social Value.* The social value of health research is realized from knowledge generated on how to improve health and health care (Emanuel et al., 2008; Wendler & Rid, 2017). Its assessment is guided by four key questions: (a) To whom will the research be valuable? (b) What is the potential value of the research? (c) How can the value be

enhanced and (d) What impact does the study have on existing health infrastructure? (Emanuel et al., 2008). Interviewees highlighted the unique qualities of HIV phylogenetic analysis in providing an accurate determination of the characteristics of individuals and subpopulations associated with continued spread of the virus. The utility of HIV phylogenetics and molecular epidemiology to identify ongoing transmissions (who is transmitting the virus) as opposed to characteristics of HIV-positive individuals (who is currently infected) is increasingly recognized (Dennis et al., 2014; Pasquale et al., 2018). For those responsible for a disproportionately high number of HIV transmissions, it is critical to establish whether the infection was recent, undiagnosed, diagnosed and untreated, or diagnosed and treated (Brenner, Wainberg, & Roger, 2013; Frost & Pillay, 2015). Such detailed information is needed to make inferences about transmission dynamics and to design targeted prevention strategies. Although the social value of molecular epidemiology studies is evident at population level, it might also yield individual benefits, but these have not yet been fully explored.

Despite positive views expressed by interviewees on the social value of HIV phylogenetics, it must be acknowledged that the approach has its limitations. One of the biggest problems with HIV phylogenetics is that it focuses heavily on individual behavioral determinants of risk to HIV infection. However, the association between HIV and structural factors is also quite significant. For example, issues related to access to health care services, stigma, poverty, and domestic violence could determine the success or failure of an HIV intervention. In resource-limited settings, the epidemic might be driven and sustained by HIV-positive patients with high viral loads due to increased virologic failure or a decrease in virologic suppression because of poor access to health care services (Kimmel et al., 2018), particularly access to antiretroviral therapy. People living with HIV may also avoid visiting clinics due to stigma and discrimination based on their HIV status (UNAIDS, 2017). Stigma could result in poor patient management and may impede access to health care services. Similarly, poverty (Mbirimtengerenji, 2007) and domestic violence are also associated with increased HIV transmission as a result of demands and pressure that make it difficult for affected individuals to practice safe sex. While hard science technology is seen as more reliable, objective, and perhaps more valuable than other forms of research, if researchers do not understand the socio-behavioral and even political context of what is happening with people living with HIV, it would be difficult to obtain practically useful information from this technology.

*Scientific validity.* Like any other scientific method, the application of phylogenetics for HIV molecular epidemiology has limitations. Broadly, these could be classified under measurement and sampling biases (Grabowski & Redd, 2014; Hassan, Pybus, Sanders, Albert, & Esbjornsson, 2017), characteristic features of most traditional epidemiology designs. Specific threats to valid inferences include selection bias and uncontrolled confounding (Comas, Homolka, Niemann, & Gagneux, 2009; Pocock et al., 2004), which may be worsened by poor reporting (Field et al., 2014).

Interviewees expressed concern about the validity of inferences and conclusions that could be made from phylogenetic analysis of HIV sequence data. These misgivings reflect existing controversies around the application of HIV phylogenetics in both HIV forensics and in molecular epidemiology (Little et al., 2014). A commonly acknowledged drawback in the literature is that HIV phylogenetics alone cannot provide definitive proof of the route, direction, and timing of HIV transmission between two people (Abecasis et al., 2011; Pillay, Rambaut, Geretti, & Brown, 2007), hence the need to treat inferences about direct transmission with great caution. Similar concerns could be raised in molecular epidemiology, but current considerations in this field have focused more on the definition of standard cutoffs for the identification of an HIV transmission cluster (Frost & Pillay, 2015; Hassan et al., 2017), which are not clearly defined. The lack of a standard definition and variability in cluster meanings in the literature could potentially lead to biased results as researchers may pick convenient cutoff points to validate their results (Fanelli, Costas, & Ioannidis, 2017). Scientific misconduct is not unique to molecular epidemiology, but the increasing pressure to publish (Fanelli, 2010; Sarewitz, 2016), prevalence of questionable research practices (Fanelli, 2009; Fang, Steen, & Casadevall, 2012), and increasing irreproducible findings (De Los Angeles et al., 2015; Mullane & Williams, 2017) might warrant the development of elaborate and standard guidance on cutoff points for cluster definitions. In the context of HIV surveillance using genetic sequences, once clusters are identified, they are prioritized for investigation and potential intervention (Centers for Disease Control and Prevention, 2017). From an ethical point of view, a poorly defined cluster might result in flawed priority setting, misallocation of resources, and ultimately inappropriate prevention and/or intervention strategies, which may violate the principles of distributive justice (Drake et al., 2017).

*Collaborative partnerships.* The requirement for collaborative partnerships and community involvement has become an integral component of many complex research projects. It is widely promoted in biomedical research for both its intrinsic and instrumental value (Molyneux & Bull, 2013). Although the broad goals of collaborative partnership are widely acknowledged and specific guidance is available (Council for International Organizations of Medical Sciences, 2016), its key elements and indicators of success are

subject to ongoing scholarly debate (MacQueen, Bhan, Frohlich, Holzer, & Sugarman, 2015; Molyneux & Bull, 2013). Key areas of contestation were the definition of community and which one to work with, who qualifies as an appropriate representative and by whose definition as well as what activities or interventions constitute engagement. Interviewees in our study highlighted the marginalization of local researchers in collaborative partnerships with researchers from HICs. These concerns are consistent with the literature, which highlights that local researchers are not seriously considered as intellectual contributors (Chersich et al., 2016; UNAIDS, 2011) despite their extensive scientific and intellectual contributions. This inequity is also reflected in author lists in major scientific journals, which are dominated by researchers from HICs (Aluede, Phillips, Bleyer, Jergesen, & Coughlin, 2012; Patel & Kim, 2007), even when the research was conducted in low-income and middle-income countries (LMICs).

While there is little empirical evidence on the causes, sidelining of local researchers could be attributed to limited financial contribution by African governments to research and innovation programs (Anya, 2004; CAAST-Net Plus, 2016). For fair collaborations to be realized, it is critical that the statements of intent made by African governments to support research be backed by co-investment. The absence of such commitments could perpetuate the sidelining of local researchers, leading to lack of interest and involvement of local researchers, which could eventually evolve into lack of trust in future collaborative studies (CAAST-Net Plus, 2016). Fair research contracting is thus also required to address concerns of uneven sponsor and host country power dynamics with a view to optimizing global research partnerships (Council on Health Research for Development [COHRED], 2017). COHRED has already started similar programs through the Research Fairness Initiative (RFI). In addition, *fair research contracting* could also be considered as an extra benchmark under the principle of collaborative partnerships.

*Independent ethics review.* Considering that the field of HIV phylogenetics is relatively new and evolving rapidly, our interviewees were concerned about the limited capacity of all RECs to address ethical issues associated with HPR in research settings. The capacity of RECs to review scientific studies has rarely been called into question compared with other disciplines, for example, the social sciences (Mutenherwa & Wassenaar, 2014). Part of the explanation could be the presence of adequate expertise (Kass et al., 2007; Nyika et al., 2009). However, although natural scientists and clinicians dominate most RECs, focused training might still be required to address emerging ethical issues associated with the combined use of HIV phylogenetics and molecular epidemiology techniques. Continuous training of REC members has frequently been cited as a need by most RECs (Abbott & Grady, 2011; Mokgatla, Wassenaar, & Kasule, 2017) to ensure optimal review and oversight of studies in line with international standards (WHO, 2011). Focused training could improve thorough and appropriate review of phylogenetic studies. Similar preparatory work was done previously to ensure that RECs in Africa were equipped with requisite skills and resources to handle HIV vaccine trials in Africa (Andanda et al., 2011; Kaleebu et al., 2008; Milford, Wassenaar, & Slack, 2006). Ethics reviews of health research protocols by independent properly constituted and competent RECs is one of the cornerstones of human research protection. A dispassionate view of the protocol will not only offer protection to research participants against diverse and often conflicting interests of researchers but also ensure public accountability (Emanuel et al., 2008).

*Fair participant selection.* An area of concern in most health research is how research participants and communities are selected for research participation. From the literature, it appears a tension exists between the need to enroll participants, protecting vulnerable populations and willingness to participate in research (Chen, 2016; Niemansburg, Habets, Dhert, van Delden, & Bredenoord, 2015). Concerns about the fair selection of research participants are not new, particularly among historically disadvantaged social groups. This may be a result of transgressions of past research (Gamble, 1997; Washington, 2008), such as the infamous Tuskegee Syphilis study. Fears that health research might perpetuate existing social injustices have also received extensive coverage in the literature (Barsdorf & Wassenaar, 2005; Shavers, Lynch, & Burmeister, 2002). However, despite the centrality of *fair participant selection* in health research in general, none of the participants in our study mentioned this principle as an area of ethical concern. Participants could have flagged the discord between the high volumes of HIV genetic sequences generated from HICs (Frost & Pillay, 2015) against the disease burden. Africa bears the greatest HIV burden, with 70% of all new HIV infections occurring on the continent, while sub-Saharan Africa bears the highest HIV transmission rates. Justice calls for novel molecular epidemiology approaches to be directed towards populations with the greatest need so that results from molecular epidemiology are used to guide policy and to inform public health practice to mitigate the devastating effects of the HIV epidemic. While such outcomes cannot be guaranteed, they should be included in ethical deliberations and analyses, together with the possibility that positive outcomes could be offset by stigma and social harm to specific population subgroups.

## Limitations

Most of the ethical issues raised by interviewees could easily be categorized under the eight ethical principles outlined in

the EF. However, because preconceived categories were used, there were instances where an ethical issue could potentially be classified under two or more ethical principles. For example, it was difficult to clearly delineate issues that could be classified under *ongoing respect for participants, informed consent*, and *collaborative partnership* as the three principles are interrelated (Molyneux & Bull, 2013). It may sound paradoxical to respect a participant without paying due attention to their privacy or safeguarding confidentiality of their data. In the same vein, it could be disrespectful to conduct a study without asking for consent, which is a principle on its own.

Furthermore, certain themes could not be captured neatly under the eight principles of the EF. A case in point is the scientific challenges of phylogenetics and the difficulty of accurately representing this methodology to key stakeholders, including community members, health care workers, policy makers, public health experts, and the general public. Although this is a significant qualitative finding, we think that it does not fit neatly into any of the eight principles under the framework.

Interviewees probably represented different levels and types of expertise. Some were very strong in bioethics with limited knowledge on the practical applications of HIV phylogenetics, while some had a strong background in HIV phylogenetics but limited training in bioethics. The interviewer had to explain HIV phylogenetics to those interviewees who had limited exposure to HIV phylogenetics in a way that made them understand and anticipate relevant and critical ethical issues associated with it. Their responses therefore depended on the knowledge imparted to them by the researcher, which could potentially bias their responses.

## Conclusion

The purpose of this qualitative study was to explore the perceptions of experts on key ethical issues associated with HPR—in particular, HIV network analysis. Limited empirical work has been conducted to explore these issues. We used the EF as our analytical framework. Our study suggests that HPR is perceived as having the potential to contribute positively to HIV research. A central ethical issue that emerged was the difficulty in balancing the risks and benefits of HPR across the broad spectrum of potential beneficiaries. Participants also recognized the scientific challenges of the technique and challenges that could arise in efforts to present accurate information about the technique to the different stakeholders—community members, policy makers, and specific population subgroups. Strong views were also expressed about power imbalances between researchers in HICs and LMICs with regard to benefit sharing. Although most of the issues could be accommodated in the EF, some viewpoints and themes could not fit neatly into any one of the eight principles. As HIV genetic sequences become increasingly available, key stakeholders in HPR should consider the following recommendations to address the ethical concerns raised.

### Educational Implications

Participants in the study expressed concerns and reservations about the use of HIV phylogenetics in molecular epidemiology. A common misgiving was its potential for privacy violations and unintended HIV disclosure for individual sample donors. Some of the reservations can be attributed to limited understanding of HPR, which may lead to unfounded concerns about what phylogenetic analysis of HIV sequences can reveal about individuals or communities. We advocate for the design and delivery of tailor-made courses on HPR for both investigators and REC members. These could be incorporated into already existing research ethics programs such as the South African Research Ethics Training Initiative (SARETI) (SARETI, 2017) and offered on a modular basis. The modules could incorporate basic scientific aspects as well as key ethical issues associated with HIV phylogenetic studies, including practical sessions on risk–benefit assessments. A dedicated online module based on our data could be drafted and added to the TRREE[1] online platform.

### Best Practices

As HIV sequence data become widely accessible, it is imperative to establish an ethics and governance framework for best practices in HPR. The description of the study population during results dissemination and in publications should take into account the risk of community identification, prejudice, stigmatization, marginalization, persecution, or prosecution of subpopulations. Strong collaborative partnerships involving key stakeholders should be considered an integral component of HPR. Apart from identifying potential risks and benefits, such partnerships will enhance the appropriate interpretation and translation of research results into health policy and clinical practice.

Researchers and research institutes are encouraged to adopt and implement reporting mechanisms developed by the RFI (COHRED, 2017). These are designed primarily to optimize global research partnerships. Through the RFI report, stakeholders are expected to explain the foundations upon which their partnerships are based as an internal control mechanism against inequity and unfair practices in research partnerships.

### Research Agenda

Our findings may have useful implications for further research. Future studies on perceptions of stakeholders on HPR should provide participants with standardized factual information

about the technique at the beginning of the study to standardize the background information, considering that respondents and interviewees will have different background knowledge levels of HPR. In addition, data from the study could be reanalyzed using a grounded theory approach to ensure that viewpoints are not glossed over or ignored due to preconceived ideas. The EF principles could subsequently be compared with the emerging themes from the inductive analysis to assess their relevance to addressing ethical issues in HPR or other research techniques. Future exploratory studies could benefit from this approach using inductive qualitative data analysis to supplement the deductive analysis reported in this article.

As the field of molecular epidemiology advances and becomes more sophisticated, the social, ethical, and public health aspects of the techniques may not keep up with such technological advancements; hence, further research and deliberation will be warranted. Experts in social and behavioral research could play a pivotal role in exploring conceptual and normative aspects of HPR backed by empirical studies. In the case of HIV prevention studies involving discordant couples, for example, it would be essential to assess the sense of responsibility that people may develop when they learn about how they became infected with HIV using evidence from phylogenetic studies. Could such knowledge help them to cope constructively with their condition or not? Questions also need to be asked about the best and most responsible way to manage the sensitive social data that researchers collect from research participants. Furthermore, a broad social and policy analysis could help inform an appropriate response to situations where patterns of transmission are identified among people with behaviors considered risky, stigmatized, or even criminalized in some settings, for example, MSM, people who inject drugs, or commercial sex workers. Will results from phylogenetic studies help protect these groups, advance their health needs, and advance public health or will the information be used to aggravate existing stigma, marginalization, or punishment of subpopulations? Addressing these questions could considerably demystify the ethical concerns raised about the conduct of HPR, with a view to enhancing its social value.

Establishing appropriate models of consent for participation in HIV phylogenetic studies should be prioritized. Future research could focus on the following research questions: (a) How is HIV phylogenetics described in consent documents? (b) What do participants understand from the material presented? and (c) How would such consent affect future international collaborative research and data sharing? Similar efforts to introduce effective and ethical conduct of HIV vaccine trials in Africa (Kaleebu et al., 2008) were effective. Something similar could be done for HPR.

Studies exploring the nature of existing collaborative partnerships between researchers from LMICs and HICs would also help determine the extent of the inequities in international collaborative research involving HIV genetic sequences. The study could explore team composition and the distribution of roles among research team members, including contribution to intellectual property. This could focus both on planned and completed studies. A key question could be to establish whether current guidance and practice are adequately protecting the interests and welfare of host communities and local researchers.

## Appendix

### *Interview Guide for Experts*

*Respondents: Experts in phylogenetics, genetics, virology, and bioethics*

1. Could you tell me tell me what you know about phylogenetics and your experiences in this area?
   - Application of phylogenetic analysis results
   - Knowledge of studies or cases that involve use of phylogenetic evidence and respondent's involvement
2. What are your perceptions on the use of phylogenetic analysis results as evidence to prove HIV transmission?
   - Implications of characterizing individuals and subpopulations considered as responsible for transmission
   - Vulnerable populations
   - Notion of responsibility—how is it understood and negotiated between researchers, research participants, families, and the community at large?
3. What do you think might be the potential ethical challenges arising out of the use of this technique?
   - Public health benefits versus risks of harm
   - Balance between the benefits and risks
   - Acceptability and appropriateness of benefits and risks
   - Researchers' possible duty to report some findings versus confidentiality
4. What do local regional and international regulations and guidelines say about the use of this evidence?
   - Legal cases, research?
5. Is there anything else that you want to tell me about linking HIV genetic data to HIV transmission?

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## Note

1. https://elearning.trree.org/

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