HIV ONLINE LEARNING AUSTRALIA

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MOLECULAR EPIDEMIOLOGY AND PHYLOGENETICS – WHAT IS IT REALLY?

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HEALTH EQUITY MATTERS
HIV. LGBTIQA+. COMMUNITIES.

napwha national association of people with HIV australia

Hola

BACKGROUND

Molecular epidemiology is a field of study that uses genetic data to better understand the patterns of disease transmission. By looking at the genetic variations of a virus or bacteria, researchers can track how pathogens spread and evolve over time. This information can be used to develop more effective strategies for preventing and controlling disease outbreaks.

Molecular epidemiology has been instrumental in our understanding of HIV transmission patterns. Studies using genetic sequences of different HIV strains have recreated the movement of HIV from its origin in Africa to North America and beyond. Other studies have used molecular epidemiology to better assist high-risk populations and find gaps in the public health response, allowing for more targeted prevention and early treatment efforts. Molecular epidemiology has been a powerful tool in the fight against HIV/AIDS, such that it has been implemented as a public health pillar in the United States and Canada, and it has become a priority factor to explore for a public health response as noted in in the latest New South Wales HIV Strategy,[1] and the Health Equity Matters (formerly AFAO) Agenda 2025 technical paper.[2]

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ABOUT THE AUTHORS

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Francesca is a trained virologist and expert in molecular biology with major research interests in evolutionary biology, disease emergence and genomics. Her work includes determining the evolutionary dynamics of different viral pathogens and revealing the association between aspects of viral phenotype and viral emergence. Her current work focuses on the evolutionary history of HIV-1 in Australia and what factors most characterise the transmission dynamics within specific geographic areas and individual risk populations. Francesca's research vision is to expand her research area into applied translational science and develop methods for tracking outbreaks in real-time and how to translate these findings to adaptable and effective public health interventions.

Dr Alison Castley,[2,4]

Dr Alison Castley (PhD) is a senior medical scientist associated with the Immunology Department at Fiona Stanley Hospital, and previously with Royal Perth Hospital. Alison has been working in the field of viral Immunology for more than 20 years, primarily focusing on the HIV service provided by the institute. Her work through this time, including her PhD focus on "Filling the gaps in HIV surveillance in Western Australia" and translating concepts into laboratory, clinical practices and MCDC engagement. This work delves into exploring HIV diversity, drug resistant mutations and HIV mobility, in real time, in Western Australia and has also implemented HIV-1 next generation sequencing techniques. Alison is a member of the H2Seq, a national collaboration aiming to improve near real time surveillance of HIV/HCV in Australia, and she is also a member of Immunodeficient Foundation (IF) in Western Australia.

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Dr Karen Hawke is a senior research fellow at the South Australian Health and Medical Research Institute in Adelaide, working in the fields of infectious disease research and Aboriginal Health research for over 10 years. She is a founding member of the Aboriginal Communities and Families Health Research Alliance (ACRA) which formed in 2015; bringing together researchers, Aboriginal community members, policymakers, and service providers to facilitate community-driven, culturally respectful research to benefit Aboriginal families and communities in South Australia. Karen is also part of H2Seq, a national research collaboration aimed at improving near-real time surveillance of HIV/HCV in Australia. She is currently co-chair of the data analysis and management stream. Karen's experience includes ethical considerations of using HIV genomic data in public health, particularly for Indigenous populations.

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HIV IN AUSTRALIA – CURRENT SUCCESSES AND BARRIERS

More than 35,000 people have been diagnosed with HIV in Australia since 1982, with a further 12% possibly living with HIV and undiagnosed.[3] As of 2021, approximately 29,460 people were living with HIV in Australia; 92% of those people were receiving treatment and 98% of those on treatment had an undetectable viral load, making Australia very close to reaching the UNAIDS target of 95/95/95. Australia has experienced a significant decline in new infections in the past five years, mainly thanks to increased uptake of PrEP (Pre-Exposure Prophylaxis) and sustained community-led responses such as increased testing and early treatment initiation. Despite these encouraging figures, almost half (44%) of people diagnosed with HIV in 2020 were late diagnoses (>4 years post infection). For the individual, this is a missed opportunity to initiate treatment early for better health outcomes, and from a public health perspective, it's a long period of time someone is unaware of their HIV status, increasing the risk of further HIV diagnoses.

In Australia, there have been reductions in the prevalence of new HIV diagnoses amongst men who have sex with other men (MSM), but not among heterosexual men and women, including those from migrant and Aboriginal and/or Torres Strait Islander populations. Though the number of Indigenous Australians living with HIV remains relatively small, an increased vulnerability to HIV is a barrier to health care access, testing, treatment and contact tracing for those diagnosed with HIV.[6] This is reflected in the proportion of late stage infections at diagnosis which is significantly higher for Indigenous people compared with the national average (30% vs 22%, 2010-2014).[4] Thus, to achieve the 95/95/95 target, we need to intensify our prevention efforts, particularly for these population groups most at risk of HIV acquisition.

Combined with robust individual patient care, understanding HIV at a population level is important for identifying trends and needs for targeted community-led intervention, prevention programs, education and further research.[5] Australia currently works under a model that incorporates collection and management of a wide range of data from HIV and AIDS notifications, notifications for other sexually transmitted infections, and behavioral and clinical information, which allows estimates and projections on epidemic growth via mathematical modelling and that can be used to inform public health responses.[6] The Kirby Institute publishes HIV population level data in an annual report – including national and jurisdictional rates of new diagnoses, HIV incidence, exposure routes, risk behaviors and testing prevalence.[7–9] However, in order to eliminate HIV, by identifying and treating new infections early, and ensuring regular testing and health checks, a deeper and near real-time characterisation of HIV transmission is needed.

Molecular epidemiology is the term for this more in-depth characterisation of HIV, and is a valuable epidemiological tool that will strengthen current efforts,[10–13] by enabling a more effective and efficient public health response, and improved patient care. This will benefit both individuals and the community by ensuring early diagnosis and treatment for those living with HIV and reducing new HIV diagnoses. However, the use of molecular epidemiology has been met with concern and unease from community. This is understandable when stigma, discrimination, and attempts at criminalisation have pervaded the lives of those living with HIV. HIV transmission is a prosecutable offence in many countries, including Australia, and genomic data has been used incorrectly as evidence in criminal cases already.

CRIMINALISATION

One of the most serious concerns involves criminalisation of HIV and the misuse of genome data to support prosecution. HIV criminalisation laws were enacted when little was known about HIV and can include non-disclosure, misrepresentation of one's status when asked, and potential or perceived exposure and transmission. None of these are based on scientific soundness and they all cause unnecessary harm and hinder public health intervention by increasing stigma and fear around HIV.[14] Decriminalisation of HIV is complicated as HIV prosecution is possible and has occurred also under non-HIV specific laws. For example, there have been over 200 HIV-related prosecutions in Canada for aggravated sexual assault. Efforts to remove HIV-specific criminalisation laws are crucial for the safety of the community. UNAIDS notes that criminalisation may only be justifiable in very rare cases where transmission has occurred and intent of transmission can be proven.[15]

Australia has had no HIV-specific criminal laws since 2014 but all states and territories have public health laws which ask for individuals to take reasonable precaution to prevent transmission. The jurisdictional public health management can impose public health orders but unlike criminal laws, public health acts include protection of privacy and individuals cannot be named publicly. Of note, such public health orders are also very rare.[16]

An Australian consensus statement outlined the damage of criminal prosecution of HIV, not only to individuals but to the population overall.[17] The authors point out the limitations of any method, including phylogenetics, to be used as evidence of linked acquisition, as these methods use a statistical approach for determining similarity. However, legal interpretations do not need to show the scientific soundness of the method used, instead phylogeny output is misinterpreted to provide support for prosecutions or civil suits.[18] Thus, a clear understanding on how molecular epidemiology has been used for prosecutions in the past is needed and efforts must be taken to minimise the accessibility of HIV data to law enforcement and prosecutors, as well as hold both accountable about using scientific fact to present findings. The HIV Justice Network[16] has documented 53 cases of HIV prosecution in Australia. A report by Health Equity Matters (formerly AFAO) notes that only a small number of prosecutions have included molecular epidemiology or genome data as evidence. In the three examples given, the output from molecular epidemiological analysis was misinterpreted. The report highlights that despite this small number of cases, the risk around the use of molecular epidemiology is increased due to stigma surrounding HIV transmission.[19] Hence, the benefits of using this method for public health purposes need to outweigh the risk of prosecution.

The use of genome data in criminalisation of HIV is possible but not probable. Regardless, measures to safeguard access to genetic data need to be set before it can be used for prevention by public health.

PHYLOGENY AND MOLECULAR EPIDEMIOLOGY AND WHAT WE HAVE LEARNED.

Molecular epidemiology studies can be divided into three main types. The first type involves studying drug resistance mutations, including measuring different subtypes and recombination events, and understanding their global distribution. The second type involves using large-scale population-level models to analyse how epidemics grow. The third type focuses on understanding viral clusters within populations and identifying where a public health response is needed. All three types of research methods can link their outcomes to public health interventions and evaluate success or failure at different levels.

Historically, HIV-1 subtypes and drug resistant strains have been associated with specific parts of the world and with particular modes of transmission.[20–27] However, the distribution of different subtypes and recombinant forms is becoming more heterogeneous globally because of population mobility and contact between different population groups.[7,28–30] In Australia, subtype B has been dominant among MSM but in recent years new non-B diagnoses have appeared, which follows a global trend. HIV-1 mutates at an extremely fast rate,[31] and the longer a strain has been established in an area, the greater the time available for mutation to permit evolution into different strains. These strains can differ by way of replication fitness, rate of disease progression, transmissibility, accuracy of current diagnostic assays, and importantly, response to therapy and development of drug resistance mutations.[7,28,32–36]

Methods using genome data allow for modelling rates in transmission over time. The Covid-19 pandemic has popularised the measure of basic reproductive number R, that is an estimate of pandemic growth - <1: the spread is slowing down, >1: the pandemic is growing. A reduction in R can be a measure for the success of a public health measure in reducing transmission.[37] These methods are also used for estimating the virus diversity present, i.e., how much mixing there is among populations, and link that back to the positive effect of prevention measures. Several studies have used this approach to verify the success of different interventions. A study from Portugal calculated a reduction in HIV transmission following the introduction a harm-reduction program for people who inject drugs.[38] Another study from Ukraine showed how the reproductive number decline between 2013 to 2019 in the city Odessa, where a targeted public health program was implemented.[39]

HIV is more prevalent among certain population groups; in Australia and many other countries, MSM have the highest burden of acquisition. In some low to middle income countries, people who inject drugs and sex workers are at very high-risk of acquiring HIV, and in sub-Saharan Africa HIV is most commonly acquired via heterosexual sex. In the past 20 years, hundreds of studies have used molecular epidemiology to explain the patterns of HIV acquisition in different populations. Models have been used to predict epidemic growth and suggest how molecular epidemiology could be used for targeted prevention efforts.[40] It was quickly noted that for HIV, the use of molecular epidemiology could improve focused public health responses.[41] The strengths and benefits of molecular epidemiology lie in the technology being a valuable addition to enhance existing public health measures.

In Australia to date, there has been one national peer-reviewed study using molecular epidemiology, to determine subtype prevalence and understand how HIV was moving between state and territory borders. [32] This study by the Australian Molecular Epidemiology Network (AMEN), examined 4873 sequences from South Australia, New South Wales Victoria, Western Australia, and Queensland. The authors found a marked increase in HIV genetic diversity over time, with a higher prevalence of non-B subtypes emerging nationally. State-specific studies from Western Australia,[33] South Australia,[34] Victoria ,[35] and New South Wales[36] have also found an increase in non-B subtype prevalence over time, including an increase in recombinant strains. These studies showed that this increase in non-B subtypes is predominantly due to local acquisition of the now endemic CRF01_AE subtype, rather than an increase in HIV strains from overseas.[44 45–47]

The HIV epidemic is becoming more diverse with increased subtype diversity and new recombinant variants appearing. Understanding their impact on treatment outcome is crucial for patient care.

MOLECULAR EPIDEMIOLOGY IN THE PUBLIC HEALTH RESPONSE

Canada was the first country to apply molecular epidemiology as a pillar in their public health response, with Poon and colleagues using molecular epidemiology to monitor HIV transmission in near real-time in 2016.[48] They used HIV genomic data in an automated monitoring system for cluster detection in Canada, and found a growing cluster of viruses that contained transmitted drug resistance mutations. This triggered a timely and enhanced public health follow-up response consisting of thorough contact tracing efforts and enhanced linkage to care and early treatment, which successfully reduced community transmission.[48] A recent study from the same group showed that by modelling transmission they identified clusters most at risk of growth (i.e. uncontrolled transmission), and thus, would benefit most from immediate intervention measures.[49] This allowed public health units to selectively allocate their resources for prevention to those clusters, utilising resources effectively.

The United States has also included molecular epidemiology into their HIV public health response - known as the HIV Cluster and Outbreak Detection and Response Program.[50] This program was designed following multiple studies showing the benefits of using molecular epidemiology in containing outbreaks in North America. This program helped detect outbreaks among people who inject drugs and demonstrated reduced harm by applying targeted prevention steps such as syringe exchange programs.[51] In 2019, a local West Virginian health unit identified a sudden increase in new HIV cases among people who inject drugs.[52] Analysis of genome sequences revealed a rapidly growing transmission cluster, and with help from the CDC a response plan was implemented. First, demographic, and behavioural data for the clusters were summarised to identify gaps in the prevention response. A lack of comprehensive testing availability was identified, and increased testing support was promptly implemented, leading to a 173% increase in HIV testing in the community. This led to an overall improvement in early diagnoses and linkage to health care.[52] The program has allowed North America to improve HIV care overall by identifying and resolving gaps in prevention. Testing and access to care has increased and this has resulted in a reduction in the HIV rate.

Canada and the US have successfully demonstrated the benefit of using molecular epidemiology to understand how HIV moves and grows among populations. It is important to note that these models are based on probability and estimate connections based on available data. These models can exclude possible transmission links based on probability, but they cannot definitively prove direct transmission between two or more individuals. Additionally and most importantly, the models cannot determine the direction of transmission.[53]

The use of transmission models is to understand cluster dynamics and respond in a near real-time way, NOT to prove direction of transmission.

COMMUNITY FEEDBACK ABOUT MOLECULAR EPIDEMIOLOGY

In the United States, people living with HIV have raised concerns about the lack of community engagement in research and public health activities using molecular epidemiology data.[54] These concerns were heard, and what followed was multiple workshops and working groups to address them, and to identify ethical and legal issues and possible solutions. Following the HIV Cluster and Outbreak Detection and Response Program by the CDC, the Presidential Advisory Council on HIV/AIDS (PACHA) group published a report and proposed solutions for the proper use and implementation of an HIV molecular epidemiology program in the US.[54] The main recommendations were to establish collaborations between community members and states/jurisdictional units to ensure adequate education and explanations to affected individuals, and also to educate governments on the harm and stigma around HIV criminalisation.

A study was then conducted, interviewing people living with HIV and those at risk of acquisition. The study found that there was general support for the use of molecular epidemiology and the majority of those interviewed believed that the benefits of using molecular epidemiology for public health support outweigh the risks to the individual if used correctly.[55,56] However, interviewees expressed concerns regarding data privacy and how public interpretations of research outcomes could potentially increase discrimination against those living with HIV. People living with HIV had more concerns about data privacy and subsequently expressed mistrust in digital health systems compared to the general population. This highlights the importance of consent and community engagement, accountability, and education around digital health systems, particularly for vulnerable communities.[55,56]

WHAT IT MEANS FOR AUSTRALIA

Australia has been at the forefront globally with HIV public health interventions. The immediate community engagement from the first HIV cases reported triggered a rapid and thorough response which allowed for timely transmission control. This included community action to design and implement safe sex interventions for MSM communities and sex workers, and the implementation of needle syringe programs, first in Sydney in 1986 and implemented nationally in 1988.[57] Needle and syringe programs have been extremely successful in preventing HIV through injecting drug use, virtually eliminating new cases, as have prevention efforts for sex workers and mother-to-child-transmission. Virtual elimination refers to the absence of sustained local transmission (endemic) in that population, with large outbreaks not expected to occur again.[58] In addition, community education campaigns on safe sex, facilitated access to testing, and timely antiviral therapy has allowed Australia to reduce the overall prevalence of HIV to below 0.2%, one of the lowest rates globally. More recently, Australia's rollout of PrEP programs has assisted in further reducing the number of new diagnoses to the lowest ever recorded.[59] However, Australia faces challenges with the epidemic affecting a more diverse population. Thus, a better understanding of the changes in the epidemic could assist to successfully implement more targeted interventions within populations. Molecular epidemiology has potential to improve our understanding on the transmission risks and subsequently support the public health response in reducing transmission.

Including new prevention measures for HIV is not straightforward. It can be a long wait between first reports showing efficacy, to overall acceptance and wide-range implementation. Clinical trials are needed to test for the efficacy of new drugs or new drugs combinations. The potential benefit of a pre-exposure pill was first reported in 2010,[60] numerous pilot and implementation studies followed. The largest one in Australia was the EPIC-NSW study from 2016 – 2018. It immediately showed significant reductions in HIV acquisition and subsequently PrEP was approved by the Pharmaceutical Benefits Scheme.[59]

In 2008, the Swiss National AIDS Commission issued a statement for doctors in Switzerland saying that individuals who are HIV positive and on effective antiretroviral treatment cannot sexually transmit HIV to other individuals. What is now known as the 'Swiss statement' was the first reporting of Undetectable viral load equals Untransmittable, or U=U.[61] The statement led to initial criticism and controversy, but what followed was numerous studies supporting the statement and showing the effectiveness of treatment to suppress viral loads. In 2018, the Opposites Attract study led by the Kirby Institute, UNSW recruited a large cohort of MSM and found no transmission of HIV linked to those with suppressed viral load.[62] Only by using molecular epidemiology has it been possible to provide evidence that individuals with undetectable viral load do not transmit the virus to others. Studies like this were critical for changes in HIV guidelines with recommendations of immediate treatment commencement known as 'treatment as prevention', and 'test-and-treat.[63]

Contact tracing, also known as partner notification, was first introduced to tackle the syphilis epidemic in the 1930s.[64] Later, it was used for other sexually transmitted infections like gonorrhoea and chlamydia and eventually HIV.[65] Contact tracing consists of efforts to locate and notify any person who may have been exposed to a pathogen. This is usually done by trained sexual or public health employees and involves thorough but sensitive interviewing of the patient, about sexual relationships, potential drug use and other behaviours. Studies have shown that contact tracing is highly effective in identifying undiagnosed individuals.[66,67] However, contact tracing can be challenging as it requires participants to reveal intimate details and can feel intrusive, and thus, increase fear and stigma surrounding HIV acquisition. It is also challenging in cases where the diagnosis happened years after infection and thus the potential place and time of exposure is unknown.

Molecular epidemiology is an additional tool to assist clinicians and public health responses, to ensure timely diagnosis and treatment, and evolving community-led prevention efforts.

COST-EFFECTIVENESS

Demonstrating the cost-effectiveness of prevention and intervention measures has its challenges. In Australia, the annual health care cost for all people living with HIV, including antiviral medications, was approximately $600M (estimate based on 27,545 Australians living with HIV in 2017). The CSIRO estimates a life-time cost of HIV treatment per person of $280,000 in Australia.[68] Thus, prevention of new HIV acquisition is a high government priority. The field of molecular epidemiology is growing rapidly with an increasing number of online data repositories for molecular sequences and a growing number of sophisticated tools to analyse this data.[53,69,70] Sequencing techniques are becoming more and more innovative allowing for faster and larger sequencing outputs; this means that instead of one genome output per assay these new technologies can generate hundreds to thousands of genome outputs from one assay, and subsequently allowing for faster and broader testing (and that was used during the Covid-19 outbreak). The cost and efficiency of genome sequencing has improved markedly. However, in the development of this paper community organisation members identified the argument that if the other parts of the HIV response are funded appropriately, the use of molecular epidemiology may not be needed. Thus, it is important that a cost-benefit analysis is conducted to ascertain whether adding molecular epidemiology to our current surveillance efforts will result in improved outcomes for people living with HIV, reduced overall cost burden, a reduction in new diagnoses, and an eventual elimination of transmission of HIV in Australia. Despite substantive literature on the efficacy of pathogen genomics in public health microbiology, there are very few cost-effectiveness analyses of pathogen genomics in public health.[71] Thus, community-led and informed pilot projects need to be conducted to evaluate the economical and epidemiological benefit of molecular epidemiology.

LEGAL AND ETHICAL CONCERNS

The purpose of molecular epidemiology is to improve population-based prevention and intervention measures. However, we are aware that without proper safety measures to protect from misuse of data – intentional or otherwise – the inclusion of genome data is vulnerable to violations of privacy, community mistrust, and exacerbation of stigma and discrimination. Steps must be taken to ensure privacy and confidentiality is maintained at all times. Careful and considered reporting of HIV information is crucial.[72,73] The focus of molecular epidemiology is on understanding characteristics of populations, not identifying individuals. The HIV Justice Network has published a detailed review on the uses of molecular epidemiology for public health interventions and the risks to the individuals.[74] The risks included in the review relate to consent, lack of community consultation and engagement, stigma, privacy and data protections, “proving” direct transmission, and criminalisation. The review includes recommendations for researchers, public health practitioners, legal experts, and the community, and highlights the importance of reducing harm (in research studies, prevention measures, and legal acts) whilst increasing knowledge and producing tools most useful to the community. Other significant concerns identified by community organisation members in the development of this paper included the potential for technology, regulations and laws to change in the future. This included concerns that even with appropriate protections in

place for current use, the laws and regulations could be changed in the future to reduce these protections or allow potential of misuse of the technology. This also included concerns that although the direction of transmission cannot be proven currently, that changes in technology may enable this in the future. Thus, data security and restrictive access is key.

These themes have been confirmed through our work thus far with community members, and current efforts in designing molecular epidemiology programs for Australia are done in consultation and collaboration with community representatives, as well as specialist legal and data privacy advisors. Key aspects include data encryption, storage, and sharing and access to ensure the protection of personal and health data use at present and the future.

This, and the crucial work by the AMEN group in Australia over the last decade, has led to the creation of H2Seq, a near real-time program that aims to identify trends in virus transmission and new infections and enhance the already highly effective public health response to these increasingly dispersed epidemics. The H2Seq system is being developed in partnership with peak community bodies to ensure patient privacy is a primary consideration, and that any systems developed are acceptable to affected communities.[77,78] The ability to conduct molecular epidemiological analyses in near real-time has the potential to improve Australia's already world-class response to HIV, by finely mapping the effectiveness of current public health strategies and optimising efforts by identifying areas where more targeted campaigns are necessary.

The Kirby Institute in NSW, and the Doherty Institute in Victoria are tackling these important topics, developing pilot projects to test the possibilities and usefulness of molecular epidemiology in our public health response. Both the Kirby and Doherty Institutes have long-established and trusted relationships with the Australian community, including the HIV-community. A project currently led by the Doherty is investigating ethical and legal aspects of using molecular epidemiology for ending HIV transmission.[75] The project leads have conducted rigorous survey methods to understand community concerns and viewpoints, H2Seq are working in collaboration with them. The Kirby Institute has an ongoing program for drug resistance mutation transmission modelling (NSW Resistance Database), which was formed from community consultation with organisations including ACON, ASHM and PositiveLife, as well as public health units and pathology laboratories.[76] Under this research program, molecular epidemiology studies have been conducted safely for the past five years.

LEGISLATION OF GENOME DATA AND CONSENT

Any study involving molecular epidemiology makes use of data already available; the *HIV genome data* that is collected and stored by pathology laboratories and *HIV demographic data (notifications)* that is collected by state public health units that exists under the auspices of the *National Health Security Act 2007* and *Public Health Acts* of each jurisdiction. Currently, at time of diagnosis, a blood sample is taken to create a viral sequence for each patient and to check for the virus subtype and to see if the virus the patient is carrying has any pre-existing resistance to antiviral drugs being used as first line treatment. These drug resistance mutations can reduce the efficacy of antiretroviral therapy and while most subtypes display similar drug sensitivity, some may have greater propensity to develop certain mutations.

The use of combined public health and laboratory data for HIV transmission modelling raises complex ethical considerations because it sits at the intersection of two different branches of ethical reasoning – clinical ethics and public health ethics. In Australia, HIV is a notifiable condition and thus mandatory data collection and use falls under each state's Public Health Act. ASHM has detailed information on the Privacy Acts and Laws in place to protect individuals.[79] Genome data is not clearly defined within these acts and laws and the wording around personal and health data varies across states and territories. However, the legislations

do state that institutions can only *"collect health information about a patient with the patient's consent, and for a use to which that consent relates"*. For HIV this means that HIV genome data is originally collected for routine clinical care to the individual and currently informed consent for its use beyond this purpose (research and public health use) is not sought. In clinical ethics, the focus is on the individual patient, and consent is a fundamental requirement.[80] In public health ethics, the focus is on the population, and in some cases it is justified to override or restrict individual liberties such as consent to protect the health of the population. Thus, the use of genome data for research requires exemptions and a waiver of consent to be approved by Human Ethics committees.

However, the transparency principle in public health ethics indicates that at minimum there should be clear communication regarding the public health repurposing of samples obtained for use in clinical care. This principle of transparency emphasises that decision-making should be clear and accountable, and involve all legitimate stakeholders, but not that individual informed consent is required. This means that people with HIV should be informed of their samples being used for public health purposes, but they do not need to be given the option to opt out. However, feedback from the community made it clear that 'informed consent' or 'opt out' options are favourable. Without either there is a risk of increased stigma and fear.

NOTIFICATION AND ANONYMISED DATA

As a notifiable condition, new HIV diagnoses are reported to local public health units, including demographic information (notification data = age, gender, region born, risk exposure, etc.) which is used for understanding the characteristic of HIV on a population level. This reporting is done using a person's identifier consisting of the 2x2 (first 2 letters of last and first name), but in some states using the full name. Genome data or any information on drug resistance mutation is currently not collected as part of this reporting. Instead, genotyping is performed by pathology laboratories which report back to the diagnosing clinician. This is also done using either an identifier, a clinic code, or the full patient's name. Genome data and notification data are collected separately in Australia, but either or both may have the full name linked to it.

For research purposes, all data is de-identified so it cannot be linked back to individuals. This means that only the identifiers (2x2) can be used to link the genome data and notification data and never a full name. After linkage the identifiers are removed and replaced by a random number. The same approach should be used if implementing molecular epidemiology for public health response. This means that aggregation of genome data can only occur with anonymised data, and as such is protected from subpoena. Most beneficial would be a system that allows public health units to link clustering outputs to their notifications (that is demographic data reported by notifying clinicians) and subsequently identify the responsible clinicians, sexual health clinics, or local health districts and guide them in their contact tracing. Not having access to individual names will also protect the data from any future changes in laws.

DATA TRANSFER AND STORAGE

To maintain data confidentiality, researchers must submit their study protocol to a rigorous ethics process which includes describing their data security, privacy and usage protocols, such that combining sources of public health data across jurisdictions – including genetic sequence data – does not increase the risk of data breach and re-identification of individuals.[81] This is only possible as HIV data is collected and de-identified. This means the data is stripped from an individual's name and address and a 'patient identifier' code is used instead. As research involving HIV genome data uses retrospective patient-level data, seeking consent is impractical or impossible without breaching patient privacy. Thus, de-identified data is used instead (that is without the individuals name but using an identification code). Protocols can include use of secure encrypted servers and secure methods for electronic data transmission of data; restricting access to essential staff; requiring multifactor authentication steps for entry into data systems; restricting the copying of datasets onto hard drives or servers; prohibiting remote access; providing data security training for research staff; and maintaining limits on data transfers via data use agreements among collaborators.[81]

Another important aspect for using molecular epidemiology safely is data storage and data sharing. Systems for monitoring HIV are very important for identifying trends and targets for prevention programs, education and further research.[5] Australia currently works under a second generation surveillance (SGS) model, which was introduced in 2000.[6] This model incorporates collection and management of a wide range of data from mandatory HIV notifications, STI surveillance, and behavioral and clinical information, which allows creation of HIV incidence and prevalence estimates and projections via mathematical modelling that can be used to inform public health responses.[6] The Kirby Institute publishes an annual HIV surveillance report – including national and jurisdictional rates of new diagnoses, HIV incidence, exposure routes, risk behaviors and testing prevalence.[7–9] However, outcomes from phylogeny data are yet to be included in the Australian SGS, but are included in reports from other countries.[10–13]

LIMITATIONS AND GAPS IN THE PUBLIC HEALTH RESPONSE

As stated above, current studies and reports about HIV use only retrospective data, that are already available through mandatory notification and drug resistance testing. Data are completely deidentified, which means that any potential identifying information is stripped from the data by public health agencies and replaced with a random number. Retrospective data is deemed acceptable for research purposes and increases our knowledge about epidemic characteristics. However, retrospective data does not assist with real-time health responses. Currently, all data and research outputs lag from between twelve months to several years behind public health interventions. This means it is not possible to identify a sudden increase in HIV diagnoses among a population – this could be a shared geographic location or shared risk exposure – which also means we are unable to respond quickly in terms of prevention and intervention measures. Drug resistance monitoring at a national level is not being conducted at all in Australia, this can create a big gap in the HIV response, as, for example, identifying any rising number of transmitted drug resistance mutations is crucial for the evaluations of PrEP effectiveness.

The H2Seq project aims to identify ways for the safe inclusion of more data into current surveillance for an enhanced and near real-time response. Legal advice has been sought to ensure that models for implementing molecular epidemiology follow the appropriate guidelines and use protective measures for people living with HIV.[82] A collaborative partnership between researchers and the affected community has been successfully established and discussions between community, public health agencies, health care providers, and health

researchers have identified several aspects that need to be considered for the project conceptualisation. A report was commissioned from the HIV/AIDS Legal Centre to understand the legal obligations related to implementation of molecular epidemiology for HIV in Australia. In doing so, it became evident that numerous aspects need to be considered for the effective implementation of molecular epidemiology for public health. These include criminalisation, data collection and consent, data transfer and storage, data access (subpoena), name notifications and potential changes in laws and public health acts, but also methodological and technological possibilities.

Molecular epidemiology has the capacity to improve the response to HIV by identifying and developing effective treatment strategies, creating targeted prevention efforts and monitoring epidemics in near real-time. It has the potential to be a powerful tool tool for guiding evidence-based interventions, improving public health outcomes, and ultimately helping to work towards the goal of ending HIV transmission. As noted through this paper, there are also a range of concerns about its uses and impacts. These concerns and impacts must be considered and addressed, with protections for appropriate use, if this technology is to be utilised.

Table 1. Addressing community concerns for implementing molecular epidemiology for public health

CONCERNS	AUSTRALIAN RESPONSE
Misuse of data in criminal prosecutions	Safeguards must be implemented including concrete firewalls that protect public health, genome, and surveillance data from access by • Law enforcement • Corporations • Criminal legal courts • Immigration enforcement
Need for informed consent for use of private health information	• Provide information in plain language to inform people on what their data is used for, and the types of surveillance being conducted. • Provide an opt-out option for genotype data to be used for molecular epidemiology.
Data security and privacy	• Develop models for safe data transfer and storage. • Include secure one-way encryption steps. • Exclude patient names or patient named codes.
Potential risk of increasing stigma and inequities for populations already marginalised	Adapt strategies through engagement with stakeholders including people living with HIV for each jurisdiction. • Should molecular epidemiology be implemented at all? • How can it be implemented without causing harm?
Cost of implementation of molecular epidemiology	Continuous review of the effectiveness and benefits of molecular epidemiology compared to other prevention measures.

GLOSSARY

Virus genome data	The genome sequence generated from routine testing in pathology laboratories for the purpose of identifying potential drug resistance mutations present and ensure the most effective antiretroviral therapy can be recommended.
Phylogeny	Phylogeny is the study and predicted ordering of relationships among living organisms based on shared, derived similarities. It assesses how biological sequences are genetically related and estimates hypothetical common ancestors, mostly based on DNA or protein sequences. The original purpose of phylogeny was to classify relationships between different species, however phylogenetic tools have greatly expanded over the years and are now used to assess diversity within species. This provides invaluable insight into how the life form, in this case HIV, has evolved over time, where it originated from, where it has travelled to and by what route.
Molecular epidemiology	The combination of epidemiological studies with phylogenetic analysis, thus, linking demographic factors such as disease severity, geographic location, and behavioural factors to the evolutionary history.
Clusters	When studying evolutionary relationships, a cluster refers to a group of genetic sequences that are very similar to each other. When it comes to HIV, clusters are used to define potential transmission groups, thus transmission among a group of people who are closely connected socially or sexually, or within a specific area, where the viral sequences share genetic similarities.
Surveillance	Here used as only as surveillance of pathogens (HIV). It means the systematic collection and analysis of data. This may include demographic data, genome data, and output reports of different analyses (for example incident).
Demographic / notification data	An individual's personal data is collected for HIV notifications. This includes demographics such as region born, age, and most likely risk of transmissions, but also clinical data like CD4T cell count, viral load, and disease symptoms.

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