




Advancing the course of HIV genomics research in Africa

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INTRODUCTION

The Human Heredity and Health in Africa (H3Africa) initiative aims to enhance genomics research in Africa while fostering a sustainable research enterprise led by African scientists for the benefit of African people and the global community. The H3Africa hosted a workshop in Nairobi, Kenya, focusing on HIV genomics. The workshop provided numerous insights within five major themes on HIV genomics research in Africa: (1) HIV across the lifespan, (2) non-communicable diseases (NCDs) among people living with HIV (PLWH), (3) HIV and coinfections, (4) HIV vaccine development and (5) ethical and social issues related to the use of genomics methods for HIV prevention.

HIV ACROSS THE LIFESPAN

As of 2023, an estimated 39.9 million people globally were living with HIV, with 1.3 million new infections and 630 000 deaths recorded that year.¹ While global efforts have significantly reduced both incidence and mortality since the epidemic's peak, HIV remains a major public health challenge. Sub-Saharan Africa (SSA) bears the highest burden, home to nearly 26 million PLWH, accounting for over two-thirds of the global total.² Eastern and Southern Africa alone account for 20.8 million cases, with countries like Eswatini, Lesotho and South Africa reporting adult prevalence rates exceeding 15%.³

Over 70% of new childhood HIV infections occur in SSA despite advances in prevention and treatment. Prevention of mother-to-child transmission programmes have achieved notable success, reducing paediatric HIV infections by 75% since 2000 in countries

SUMMARY BOX

- ⇒ The use of genomics methods and technologies for HIV research and public health holds potential in reducing the HIV burden in sub-Saharan Africa.
- ⇒ Continued innovation, improved access to care and strategies to reduce health inequities are essential to ensure better outcomes for children, adolescents and adults living with HIV globally.
- ⇒ Continued research into the biological and behavioural factors, as well as studies on immune changes, antiretroviral therapy toxicity and multiomics, will be essential for developing effective preventive and therapeutic intervention.
- ⇒ There is an urgent need for research on genetic factors underlying susceptibility to HIV and other coinfections and potential avenues for optimised HIV-coinfection treatment strategies.

implementing comprehensive three-drug antiretroviral therapy (ART) programmes during pregnancy. Despite these achievements, barriers to access to care and ART for all pregnant women persist, alongside maternal health, foetal exposure risks and birth outcomes, which require ongoing attention. Nonetheless, Botswana's commitment to eliminating mother-to-child transmission of HIV serves as a beacon of hope, earning the country a certification by the WHO for its progress and surpassing UNAIDS's 95-95-95 targets ahead of schedule.⁴

Community engagement, patient-centred care and community-led monitoring have proven essential in advancing elimination of mother-to-child transmission, with innovations such as point-of-care infant HIV testing and viral load monitoring contributing to more timely interventions. Increased viral load monitoring and the use of Point-of-care



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Immuno-Monitoring Analyser (PIMA) machines for early infant diagnosis have improved access to care for pregnant and breastfeeding women, providing results within 24 hours. Despite these advances, retention in care remains a challenge, and efforts to bring mothers and babies back into care, such as Uganda's 'Bring Back Mother and Baby' campaign, have shown promise in improving retention rates.⁵

Adolescents encounter unique challenges in HIV treatment, experiencing disparities in incidence and treatment outcomes compared with adults. Among children and adolescents, only 41% achieve the 95-95-95 targets for viral suppression, in contrast to 70% of adults. Adherence to ART is a critical determinant of treatment success, yet barriers such as side effects, mental health issues, stigma, medication formulations and complexity of regimens often hinder adherence. Simplifying ART regimens for children, with fewer pills and less frequent dosing, is essential for improving outcomes. Moreover, as children born with HIV survive longer, they continue to face the complexities of managing a chronic condition into adulthood. The transition from paediatric to adult care involves not only medical considerations but also teaching self-management skills. Additionally, addressing the interplay between HIV treatment and NCDs is increasingly important as PLWH age.

NCDS AMONG PLWH

Despite long-term ART and viral suppression, PLWH experience persistent endothelial dysfunction, an instance where endothelial cells do not work the way they should, causing blood vessels to constrict, which increases their risk for NCDs.⁶ The interplay between HIV, residual persistent inflammasome (innate immune system receptors/sensors that induce inflammation in response to infectious), endothelial dysfunction, cardiovascular risk, metabolic syndrome (MetS) disorders, related chronic health outcomes among ART-treated PLWH, highlight the need for continued research, early detection and intervention strategies.⁷

A notable emerging relationship exists between albuminuria and cardiovascular disease (CVD) risk, particularly concerning low-grade albuminuria (LGA) below the microalbuminuria threshold.⁸⁻⁹ LGA is associated with elevated rates of atherosclerosis, cardiometabolic disease and mortality among people with hypertension (HTN) and diabetes mellitus (DM),^{8,9} making it a potential marker of subclinical cardiovascular damage and risk. However, data on albuminuria among PLWH in Africa remain scarce. A study involving 1537 PLWH on ART studied for 12 months revealed an estimated 20% prevalence of albuminuria.¹⁰ Notably, the findings showed a concerning link between LGA and CVD risk, stressing the importance of recognising albuminuria as a marker for subclinical cardiovascular damage. Key predictors of albuminuria included male gender, higher waist-hip ratio, DM, diastolic HTN and longer ART duration. This

showed that PLWH experienced an increase in albumin-to-creatinine ratio over time, necessitating larger longitudinal studies to evaluate the impact of ACEs and angiotensin receptor blockers on albuminuria.

Additionally, emerging evidence suggests that the risk of MetS disorders and other NCDs may be higher among PLWH as compared with the general population.¹¹⁻¹² This increased risk has been attributed to factors such as accelerated ageing, chronic immune activation and ART-associated toxicity.¹³⁻¹⁴ Preliminary findings from a cohort study involving 440 PLWH and 232 persons without HIV (PWoH) in Nigeria revealed a significantly higher prevalence of MetS disorders (30.7% vs 22.8%). The prevalence estimates were higher among PLWH for pre-diabetes (33.8% vs 21.1%), DM (20.5% vs 8.2%), low High-density lipoprotein (HDL)-cholesterol (51.1% vs 41.4%) and high triglycerides (24.5% vs 17.2%). Although the incidence of high blood pressure (22.3% vs 20.3%) and abdominal obesity (38.4% vs 37.1%) did not differ by HIV status, both were at the high range of estimates reported by other studies from SSA. Alarmingly, many individuals with DM or HTN in the cohort were previously undiagnosed. Significant correlations were observed between MetS and some of its components with traditional risk factors, including older age, female sex, alcohol use and duration on ART. These findings indicate excess metabolic risks among PLWH, with an alarmingly high level of undiagnosed prevalent cases, which could lead to adverse cardiovascular outcomes.¹⁵

HIV AND COINFECTIONS

The discussion on paediatric HIV management in Africa emphasises the critical need to address genetic susceptibility and coinfections within the context of syndemics—synergistic epidemics arising from underlying social and health disparities. The concept of syndemics recognises that epidemics and pandemics occur in the context of pre-existing social and health conditions, warranting complex, comprehensive and coordinated solutions for effective outcomes.¹⁵ This approach becomes even more relevant now as the paediatric HIV epidemic approaches maturity and consequently suffers from the 'last mile syndrome'. As efforts near epidemic control, identifying the remaining 5% of patients is more difficult and costly, particularly amidst persistent stigma, mental health issues and recent pandemics like COVID-19. Moreover, societal stressors like poor economic performance, high youth unemployment, gender-based violence, discrimination in access to care for the lesbian, gay, bisexual, transgender, queer or questioning, intersex and asexual (LGBTQIA) community, neurocognitive disorders and cognitive dissonance remain a challenge. For this reason, a call for innovative approaches based on the syndemic theory, special focus on coinfections, innovative diagnostics for paediatric tuberculosis, and above all, not letting paediatric HIV become a neglected disease, as this may reverse gains made against the pandemic.

In recent times, a major consideration for PLWH is their ability to mount clinically relevant levels of humoral responses to SARS-CoV-2 vaccines to protect from severe infection. PLWH have a 3.2-fold higher likelihood of testing positive for SARS-CoV-2, which increases their risk of severe COVID-19 outcomes and mortality.^{16 17} Additionally, due to their compromised immune systems, PLWH may serve as reservoirs for the emergence of SARS-CoV-2 variants of concern, as their ability to clear the virus is diminished.¹⁸ Fortunately, the pandemic did not have the devastating impact on PLWH as was expected; instead, encouragingly, was the ability of PLWH on ART to mount comparable levels of neutralising (or blocking) antibodies in response to COVID vaccination.¹⁹ Despite this, African PLWH exhibited delayed humoral responses. However, those on ART demonstrated comparable magnitude of responses to PWOH, highlighting the importance of prioritising ART rollout and SARS-CoV-2 vaccination for PLWH.²⁰

THE HIV VACCINE DEVELOPMENT SPACE: IT IS TIME FOR AFRICA

The generation of broadly neutralising antibodies (bNAbs) against HIV is crucial for vaccine research, as these antibodies could potentially offer protection against infection by most circulating HIV strains. However, only a small proportion of HIV-infected individuals generate bNAbs during natural infection.^{21 22} So far, no HIV vaccine candidate has successfully elicited antibodies with sufficient breadth and potency. Traditionally, empirical approaches for vaccine design were employed with the hope that one of the immunogens tested would elicit protective responses and guide the identification of a correlate of protection. However, there is much to be excited about in the African context; the development of a WHO-sponsored mRNA vaccine technology platform and such recent investments as the BRILLIANT consortium has bolstered the ability of Africa to produce and test an HIV vaccine on the continent.

Lessons learnt have informed the current approaches used to design new generation immunogens. One potential approach is the use of germline targeting (GT) immunogens that aim to expand and diversify rare clones of bNAb precursors that would then be shepherded towards acquiring neutralisation breadth using a series of related antigens at critical points.^{23 24} The eOD-GT8 immunogen is the most advanced among these germline-targeting immunogens and has proven to successfully prime VRC01 bNAb precursors in an American population.²⁵ However, knowledge of the human naïve B-cell repertoire is sparse, and more so among African populations where HIV prevalence is high. The recently completed IAVI-G003 clinical trial seeks to determine if eODGT8 can prime the VRC01 class of antibody responses in African populations. This trial will reveal whether African populations share the same frequency of specific gene precursors (eODGT8)

as observed in high-income countries.²⁶ Additionally, it will evaluate the potential presence of precursors associated with a powerful antibody response (VRC01), characterised by the VHI-2 gene paired with a short 5-amino acid L-CDR3 region (manuscript under review, Science).

ETHICAL ISSUES RELATED TO THE USE OF GENOMICS METHODS FOR HIV PREVENTION

The use of genomic methods for HIV research and public health interventions raises complex ethical questions that require careful consideration for just, equitable and socially acceptable implementation. These questions may emerge during planning, conceptualisation and implementation stages of a research project.

A central question for research activities during disease outbreaks or public health emergencies is: 'Is the proposed research indispensable?' If affirmative, then the key ethical considerations include: (1) informed consent, (2) risk-benefit assessment, (3) privacy and confidentiality, (4) equity and fairness, (5) community trust and engagement, (6) ethical oversight and review and (7) ethical guidance and frameworks for responsible and ethical conduct of research.

Responsible sample and data sharing poses complex ethical challenges, impacting national and global health security, decision-making and access to new interventions. While cross-border sharing of samples and data during epidemics has been extensively discussed, questions of equity and fairness in relation to bioexploitation and intellectual property continue to top the agenda of global health organisations. Equally important is to shift our gaze towards the dynamics of intragovernmental data sharing practices during public health emergencies. This is pivotal because data sharing for public health decision-making within a country can inadvertently lead to stigmatisation or discrimination against specific groups, including the LGBTQIA community. For example, there is in the use of phylogenetic data for HIV surveillance and social and public health implications of the results for vulnerable populations²⁷

Advocating for the adoption of mechanisms for expediting research ethics approvals during epidemics, without compromising the fundamental principles of research ethics, is another area of priority. Initiatives such as the EDCTP-funded African Coalition for Epidemic Research, Response and Training have proffered recommendations to streamline ethics review during outbreaks²⁸ and which could be harnessed by ethics committees to streamline the review process. Furthermore, the WHO has model standard operating procedures for RECS for the review of research during public health emergencies.²⁹ Collectively, these resources provide a foundation to develop standards and guidance for ethics review of HIV genomics research in the case of an outbreak of public health concern.

NEXT STEPS

The recent, successful application of genomics in combating the COVID-19 pandemic, which led to the discovery of variants such as Omicron,³⁰ offers valuable insights into integrating genomics into African health-care systems. This achievement signifies the maturity of these technologies and their promise for improving healthcare in Africa, which are well-documented and involve significant investments in training platforms, research capacity and technological infrastructure across the continent.^{31–33} This existing capacity can be applied to other areas of genomics, such as disease surveillance and pharmacogenomics, extending utilisation to include NCDs and rare diseases. Harnessing these resources, potentially augmented by artificial intelligence and predictive modelling, could improve healthcare delivery at both individual and community levels. Collaboration between key stakeholders, including but not limited to national ministries of health, the Africa Centres for Disease Control and Prevention, the WHO, academic institutions and industry partners, is essential to support this endeavour.^{34 35}

CONCLUSIONS

Genomics can significantly enhance public health and clinical care for viral diseases of great concern such as HIV and AIDS by enabling more precise and cost-effective monitoring, treatment and prevention strategies. Through viral genetic sequencing, health systems can track the spread of HIV, understand the genetic diversity of the virus circulating across different populations, monitor drug resistance mutations and tailor antiretroviral therapies to individual patients or populations. For instance, the veSEQ-HIV platform has been successfully applied to leftover blood from routine tests to generate full HIV genomes, providing insights into viral load, resistance patterns and transmission networks at a fraction of traditional costs in Zambia.³⁶ This integration allows for more responsive and informed public health interventions, especially in resource-limited settings. Moreover, genomics supports the development of personalised medicine approaches, ensuring that patients receive the most effective treatments based on their genetic and viral profiles. As genomic technologies become more accessible, their integration into HIV programmes across Africa holds promise for improving outcomes, reducing transmission and ultimately advancing the goal of epidemic control. Furthermore, community engagement in genomic research can enhance trust and participation, leading to more comprehensive data collection and ultimately informing public health policies and interventions that are culturally and contextually relevant. By harnessing the power of genomics, Africa can move towards more equitable and effective health outcomes in the fight against diseases such as HIV and AIDS.

The H3Africa Genomics and HIV Infection Workshop not only revealed the extraordinary advancements in

HIV and genomics research in Africa and how the continent has made progress in building and conducting ethical HIV research, but also identified priorities for HIV genomics research during public health emergencies in Africa. Critical areas include the development of HIV vaccines, understanding the impact of other communicable and NCDs to improve the lives of PLWH, stakeholder and community engagement in relation to data sharing, expedited ethics review during public health emergencies. Genomics and the enormous diversity we continue to uncover within African populations needs to be at the forefront of future interventions for disease.

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