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The PANGEA-HIV Consortium: Phylogenetics and Networks for Generalised HIV Epidemics in Africa

Deenan Pillay[a,b], **Joshua Herbeck**[c], **Myron S. Cohen**[d], **Tulio de Oliveira**[a,b], **Christophe Fraser**[e], **Oliver Ratmann**[e], **Andrew Leigh Brown**[f], and **Paul Kellam**[g] **on behalf of the PANGEA-HIV Consortium**

[a]Wellcome Trust-Africa Centre for Health and Population Studies, University of Kwazulu-Natal, ZA

[b]Division of Infection and Immunity, University College London, London, UK

[c]Department of Global Health, University of Washington, Seattle, WA

[d]Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC

[e]Department of Infectious Disease Epidemiology, Imperial College London, London, UK

[f]Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, UK

[g]Wellcome Trust Sanger Institute, Cambridge, UK

There have been notable increases in coverage of antiretroviral treatment (ART) in Africa in the last decade. More HIV-infected individuals are receiving treatment, and life-expectancy of infected individuals has increased.[1] However, the HIV epidemic continues and overall prevalence of HIV will increase.[2] HIV burden remains highest in sub-Saharan Africa: with 75% of all HIV infections and adult prevalence at 5%.[3] The use of ART to reduce individual viral loads and viral transmission rates has emerged as a promising approach to further slow the epidemic.[4] Yet, it is unclear how to implement treatment as prevention (in combination with pre-exposure prophylaxis or behavioral change interventions) in the most effective and efficient ways. One possibility is to target individuals most at risk of transmitting HIV, thus decreasing resources needed and potentially increasing impact.[*e.g.*5-7]

Such targeted methods require fine scale understanding of HIV transmission dynamics, particularly in generalized epidemics where the conditions that drive epidemics can be unknown. Novel phylogenetic analyses can help to provide this understanding.[8] These methods involve estimating epidemic and evolutionary parameters from gene sequence data, with each sequence linked to clinical, demographic or geographic data. These methods can: 1) identify the source of emerging epidemics or assess putative transmission partnerships;[*e.g.* 9, 10] 2) identify the stage of individual infections that is the most frequent source of transmissions (*e.g.* early HIV infection);[*e.g.* 11, 12] 3) assess historical changes in epidemic size and growth rate;[*e.g.* 13, 14] and 4) identify individual traits associated with high relative infectiousness.[*e.g.* 15, 16] Phylogenetic studies of HIV in concentrated epidemics have largely involved *post-hoc* use of HIV drug resistance test datasets. Sizeable datasets like this are not found in Africa, given the paucity of such routine testing. One exception is the Southern African Treatment and Resistance Network (http://www.bioafrica.net/saturn/), with a growing database of >7,000 HIV sequences (although sampled from a large HIV-infected

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population, and therefore representing a smaller sample fraction than datasets found in concentrated epidemics).[17]

The Phylogenetics and Networks for Generalized HIV Epidemics in Africa consortium (PANGEA-HIV) is an international partnership to use viral sequence analyses to assess the transmission of HIV in Africa. PANGEA HIV aims include: 1) to sequence 20,000 total HIV genomes from multiple African study sites, with each genome sequence linked to clinical, demographic and epidemiological data; and 2) to direct the development of phylogenetic methods to address key challenges and opportunities in measuring, understanding and controlling HIV transmission in generalized epidemics.

The sequencing workload is divided between the Wellcome Trust Sanger Institute (United Kingdom), and the genomic facility of the Africa Centre at the University of KwaZulu-Natal (South Africa). Participating African HIV cohorts include the Rakai Community Cohort Study (Uganda), multiple cohorts from the Medical Research Council/Uganda Virus Research Institute (Uganda), the Mochudi Prevention Project and the Botswana Combination Prevention Project (Ya Tsie) (Botswana), the Africa Centre for Health and Population Studies (South Africa), and PopART/HPTN 071 (South Africa, Zambia). PANGEA-HIV includes scientists focused on the application of phylogenetics to HIV transmission dynamics. These consortium analysts, which includes scientists from Africa, Europe and North America, is tasked with assessing current methods, developing new approaches, and fostering the participation of interested outside investigators. Currently ongoing is a molecular epidemiological methods comparison exercise, using simulated data that model distinct scenarios of generalized HIV epidemics.

Analyses of HIV sequences linked to clinical and epidemiological information must balance the public health benefit of understanding ongoing transmissions with the potential impact of disclosure on the individuals concerned[18]. PANGEA-HIV will proceed with careful consideration of the ethical requirements that are critical for such analyses.

PANGEA-HIV is funded primarily by the Bill and Melinda Gates Foundation (BMGF), but builds on existing infrastructure, cohorts, and clinical trials that are funded independently by the BMGF, Centers for Disease Control and Prevention, French Agence National de Recherches sur le Sida et les Hépatites Viral, Medical Research Council (UK), National Institutes of Health, Wellcome Trust, World Bank STI Project, Henry M. Jackson Foundation, and Fogarty Foundation.

Both BMGF and the Wellcome Trust Sanger Institute are committed to open access data. To this end, PANGEA-HIV has a policy for open access that follows similar policies established by previous large-scale genetic and epidemiological collaborations (*e.g.* the UK Drug Resistance Database (http://hivrdb.org.uk/), and the International HapMap Project (http://www.hapmap.org)). Participating African cohorts and study sites will have full and immediate access to the data generated from their own samples. After 5 years, there will be public release of a basic dataset including sequences and minimal demographic data. Perhaps most importantly, PANGEA-HIV will facilitate new collaborations among scientists

and public health professionals in industrial and developing countries with the shared goal of ending the HIV/AIDS pandemic.

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