

proven by a new upsurge of incidence since the end of November, 2014.⁵ That R_0 was not increased in a dense urban population as compared with the overall epidemic might be explained by the fact that most (81%, 95% CI 80–82) community transmissions took place within families. Families in the city are not larger than families in the rural areas. The downside of the family focus is that transmission rates from non-hospitalised cases were barely reduced since the initial outbreaks in March. Here is the biggest challenge for intervention. The description of the epidemic in Conakry by Faye and colleagues³ might provide realistic targets for control programmes in other areas.

The study also provides one of the first analyses of the effect of viral load on transmission. Results suggest that a 1 \log_{10} increase of plasma viral load in the first week of symptoms doubles the transmission rate. However, transmission might be via body fluids other than blood, wherein viral load kinetics are not synchronous but delayed after plasma viraemia.^{1,6} Because viraemia only increases during the first week of symptoms, it is conceivable that blood viral loads were lower in some patients simply because they were admitted early to treatment centres, reducing infections by isolating patients from the family context. Although viral load is probably correlated with outcome,^{7,8} it will need larger datasets to prove a direct effect on transmission, particularly during the first week of symptoms. The time a patient spends in the community after symptom onset, particularly beyond the fourth day of illness, is crucial for transmission.¹ According to simulations made in the study, a 10% increase of rates of hospital admission (from 81% to 91%) would have reduced the lengths of transmission chains by 26% (95% CI 4–45).

The focus on community and family transmission suggested by results from this study provides independent support for a new strategy promoting self-sequestration through the establishment of small community care centres instead of fewer but larger treatment units.⁹ Passive case finding could help to overcome the logistical challenge of case identification in a dispersed epidemic in Sierra Leone, the current Ebola hotspot.¹⁰ Patients need to be admitted as early as possible to halt transmission in families.

Christian Drosten

Institute of Virology, University of Bonn, Bonn 53105, Germany
drosten@virology-bonn.de

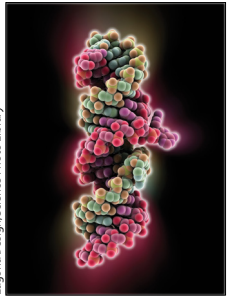
I declare no competing interests.

- 1 Yamin D, Gertler S, Ndeffo-Mbah ML, et al. Effect of Ebola progression on transmission and control in Liberia. *Ann Intern Med* 2015; **162**: 11–17.
- 2 WHO Ebola Response Team. Ebola virus disease in west Africa—the first 9 months of the epidemic and forward projections. *N Engl J Med* 2014; **371**: 1481–95.
- 3 Faye F, Boëlle P-Y, Heleze E, et al. Chains of transmission and control of Ebola virus disease in Conakry, Guinea, in 2014: an observational study. *Lancet Infect Dis* 2014; published online Jan 23. [http://dx.doi.org/10.1016/S1473-3099\(14\)71075-8](http://dx.doi.org/10.1016/S1473-3099(14)71075-8).
- 4 Pandey A, Atkins KE, Medlock J, et al. Strategies for containing Ebola in west Africa. *Science* 2014; **346**: 991–95.
- 5 WHO. Ebola response roadmap situation report, Dec 17, 2014. Geneva: World Health Organization, 2014.
- 6 Kreuels B, Wichmann D, Emmerich P, et al. A case of severe Ebola virus infection complicated by Gram-negative septicemia. *N Engl J Med* 2014; **371**: 2394–401.
- 7 Towner JS, Rollin PE, Bausch DG, et al. Rapid diagnosis of Ebola hemorrhagic fever by reverse transcription-PCR in an outbreak setting and assessment of patient viral load as a predictor of outcome. *J Virol* 2004; **78**: 4330–41.
- 8 Schieffelin JS, Shaffer JG, Goba A, et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N Engl J Med* 2014; **371**: 2092–100.
- 9 Whitty CJ, Farrar J, Ferguson N, et al. Infectious disease: tough choices to reduce Ebola transmission. *Nature* 2014; **515**: 192–94.
- 10 Lewnard JA, Ndeffo Mbah ML, Alfaró-Murillo JA, et al. Dynamics and control of Ebola virus transmission in Montserrado, Liberia: a mathematical modelling analysis. *Lancet Infect Dis* 2014; **14**: 1189–95.

PANGAEA-HIV: phylogenetics for generalised epidemics in Africa

Notable increases in coverage of antiretroviral treatment (ART) have been made in Africa in the past 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 The burden of HIV 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, how to implement treatment as prevention (in combination with pre-exposure prophylaxis or behavioural change interventions) in the most effective and efficient ways



Laguna Design/Science Photo Library

is unclear. One possibility is to target individuals most at risk of transmitting HIV, thus decreasing resources needed and potentially increasing effect.^{5,6}

Such targeted methods require fine scale understanding of HIV transmission dynamics, particularly in generalised epidemics where the conditions that drive epidemics can be unknown. Novel phylogenetic analyses can help to provide this understanding.⁷ These methods involve estimation of epidemic and evolutionary parameters from gene sequence data, with every sequence linked to clinical, demographic, or geographical data. These methods can identify the source of emerging epidemics or assess putative transmission partnerships,⁸ identify the stage of individual infections that is the most frequent source of transmissions (eg, early HIV infection),^{9,10} assess historical changes in epidemic size and growth rate,^{11,12} and identify individual traits associated with high relative infectiousness.¹³ 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, in view of the paucity of such routine testing. One exception is the Southern African Treatment and Resistance Network, which has a growing database of more than 7000 HIV sequences (although sampled from a large HIV-infected population, and therefore representing a smaller sample fraction than datasets found in concentrated epidemics).¹⁴

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

The sequencing workload is divided between the Wellcome Trust Sanger Institute (UK), 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 (Botswana), the Africa Centre for Health and Population Studies (South Africa), and PopART/HPTN 071 (South Africa, Zambia). PANGAEA-HIV includes scientists focused on the application of phylogenetics to HIV transmission dynamics. These consortium analysts, which include scientists from Africa, Europe, and North America, are 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 generalised 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 effect of disclosure on the individuals concerned.¹⁵ PANGAEA-HIV will proceed with careful consideration of the ethical requirements that are critical for such analyses.

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

Both the Bill & Melinda Gates Foundation and the Wellcome Trust Sanger Institute are committed to open access data. To this end, PANGAEA-HIV has a policy for open access that follows similar policies established by previous large-scale genetic and epidemiological collaborations (eg, the UK Drug Resistance Database, and the International HapMap Project). 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, PANGAEA-HIV will facilitate new collaborations between scientists and public health professionals in

For more on the Southern African Treatment and Resistance Network see <http://www.bioafrica.net/saturn/>

For the UK Drug Resistance Database see <http://hivrd.org.uk/>

For the International HapMap Project see <http://www.hapmap.org>

industrial and developing countries with the shared goal of ending the HIV/AIDS pandemic.

*Deenan Pillay, Joshua Herbeck, Myron S Cohen, Tulio de Oliveira, Christophe Fraser, Oliver Ratmann, Andrew Leigh Brown, Paul Kellam, on behalf of the PANGEA-HIV Consortium

Wellcome Trust-Africa Centre for Health and Population Studies, University of Kwazulu-Natal, Durban, South Africa (DP, TdO); Division of Infection and Immunity, University College London, London, UK (DP, TdO); Department of Global Health, University of Washington, Seattle, WA, USA (JC); Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA (MSC); Department of Infectious Disease Epidemiology, Imperial College London, London, UK (CF, OR); Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, UK (ALB); and Wellcome Trust Sanger Institute, Cambridge, UK (PK)
d.pillay@ucl.ac.uk

We declare no competing interests. We acknowledge the contributions of the PANGEA-HIV Consortium Steering Committee.

- 1 Bor J, Herbst AJ, Newell ML, Barnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. *Science* 2013; **339**: 961–65.
- 2 Zaidi J, Grapsa E, Tanser F, Newell ML, Barnighausen T. Dramatic increases in HIV prevalence after scale-up of antiretroviral treatment: a longitudinal population-based HIV surveillance study in rural Kwazulu-Natal. *AIDS* 2013; **27**: 2301–05.
- 3 UNAIDS. Joint United Nations Programme on HIV/AIDS. UNAIDS World AIDS Day report. Geneva: Joint United Nations Programme on HIV/AIDS, 2012.
- 4 Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365**: 493–505.
- 5 Tanser F, de Oliveira T, Maheu-Giroux M, Barnighausen T. Concentrated HIV subepidemics in generalized epidemic settings. *Curr Opin HIV AIDS* 2014; **9**: 115–25.
- 6 Anderson SJ, Cherutich P, Kilonzo N, et al. Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: a modelling study. *Lancet* 2014; **384**: 249–56.
- 7 Grabowski MK, Redd AD. Molecular tools for studying HIV transmission in sexual networks. *Curr Opin HIV AIDS* 2014; **9**: 126–33.
- 8 Campbell MS, Mullins JI, Hughes JP, et al. Viral linkage in HIV-1 seroconverters and their partners in an HIV-1 prevention clinical trial. *PLoS One* 2011; **6**: e16986.
- 9 Brenner BG, Roger M, Routy JP, et al. High rates of forward transmission events after acute/early HIV-1 infection. *J Infect Dis* 2007; **195**: 951–59.
- 10 Frange P, Meyer L, Deveau C, et al. Recent HIV-1 infection contributes to the viral diffusion over the French territory with a recent increasing frequency. *PLoS One* 2012; **7**: e31695.
- 11 Hue S, Pillay D, Clewley JP, Pybus OG. Genetic analysis reveals the complex structure of HIV-1 transmission within defined risk groups. *Proc Natl Acad Sci USA* 2005; **102**: 4425–29.
- 12 Hughes GJ, Fearnhill E, Dunn D, et al. Molecular phylogenetics of the heterosexual HIV epidemic in the United Kingdom. *PLoS Pathog* 2009; **5**: e1000590.
- 13 Fisher M, Pao D, Brown AE, et al. Determinants of HIV-1 transmission in men who have sex with men: a combined clinical, epidemiological and phylogenetic approach. *AIDS* 2010; **24**: 1739–47.
- 14 de Oliveira T, Shafer RW, Seebregts C. Public database for HIV drug resistance in southern Africa. *Nature* 2010; **464**: 673.
- 15 UNAIDS. Ending overly broad criminalization of HIV non-disclosure, exposure and transmission: critical scientific, medical and legal considerations. Geneva: Joint United Nations Programme on HIV/AIDS, 2013.

For the list of committee members see <http://www.pangea-hiv.org/Governance/Steering-Committee>

Combination HIV prevention and the battle of the sexes

1.6 million new HIV infections occur every year in sub-Saharan Africa.¹ Transmission is predominantly heterosexual, and women (by comparison with men) are disproportionately infected. The international agencies that propose policy guidelines for control of the HIV pandemic, such as WHO and the Joint UN Programme on HIV and AIDS, have recognised the crucial need to reduce the number of new infections in women and girls and mother-to-child transmission of HIV.²

No intervention is 100% effective at protecting against HIV infection. As a result, a combination of different types of interventions—ie, use of a combination HIV prevention (CHP) approach—is necessary to prevent the maximum number of new infections. Mathematical models that specify the transmission dynamics of HIV have been used to identify which combination of interventions would be the most cost effective at reducing transmission.^{3–7} In these studies, several different combinations of interventions are

compared. The transmission models are used to predict the number of HIV infections that would be prevented by each combination. The cost-effectiveness of each combination is then calculated by dividing the predicted number of prevented infections by the cost of the interventions.

Cost-effectiveness analyses should be used as the foundation for allocation of HIV-prevention budgets. However, these analyses do not always identify the best CHP approach for the control of generalised epidemics in sub-Saharan Africa because the most cost-effective approach—as shown by Anderson and colleagues³—is to spend most of the prevention budget on men. Men will always win in the battle of the sexes in terms of resources for HIV prevention—the reasons for which are two-fold. First, the most cost-effective intervention is medical male circumcision, which reduces a man's risk of infection by about 60%.⁸ Unfortunately, no similar cost-effective intervention exists for women. The second reason is more complex,