LR Rodger 16-7507 edited

9/12/16

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In Reply:

Dr Goldman and colleagues highlighted aspects of the phylogenetic analyses used to investigate HIV transmission events in the PARTNER study. Previous studies have taken advantage of the now discontinued Roche 454 deep sequencing platform to obtain sequence reads of sufficient length to allow reliable phylogenetic analyses of minority viral species.1  We have been conducting work to optimize the Illumina deep sequencing platform in order to perform an analysis of minority species in couples in our study. The reconstruction of HIV haplotypes presents notorious technical and interpretative challenges when applied to the short sequence reads that are currently obtained by Illumina. We are also using conventional limiting dilution techniques to obtain single and near full-length genomes using established methods.2 These further analyses will be published once completed and peer reviewed..

Also, Goldman and colleagues propose that some *env* pairwise genetic distances in samples from the PARTNER study were similar to those of samples found to be linked in another study.3 The proposed comparison of genetic distances is complicated by the fact that the sequences in the PARTNER study were considerably longer (2,000 bp) than those reported in the other study (~516 bp). Nonetheless, as shown in the article’s supplement(eTable 2), the median pairwise distance of *env* control sequences was at least 5 times lower than the median pairwise distance of the partners’ *env* sequences. When considering sequences falling in the upper limit of the previously reported range,3 the *env* phylogeny did not support linkage. Detailed analyses of the *env* sequences were made available to selected expert reviewers from JAMA and deemed robust. All phylogenies will be published in full once the study is completed.

Goldman and colleagues are correct that phylogenetic analyses of putative transmission events should include control sequences drawn from epidemiologically relevant settings and take into account time since seroconversion.4 These factors were taken into account in the PARTNER study. The study design was such that patients were sampled never later than 6-8 months from seroconversion. Constraints dictated by the terms of the ethical approvals and need to protect patients’ confidentiality mean that the phylogenetic investigations must not reveal the geographical origin of the specimens undergoing analysis. While we recognize the importance of disclosing to public scrutiny our detailed analyses, the confidential data we hold in this respect are entirely consistent with the reported conclusions of the PARTNER study.

We are confident that clinicians are able to interpret the data and counsel patients appropriately taking into account individual circumstances and tolerance of any risk, however small.

Anna Maria Geretti, MD, PhD

Institute of Infection & Global Health

University of Liverpool

Liverpool, United Kingdom

Alison J. Rodger, MD

Research Department of Infection & Population Health

University College London

London, United Kingdom

Jens Lundgren, MD

Department of Infectious Diseases

Rigshospitalet/CHIP

Copenhagen, Denmark

**Corresponding Author:** Alison Rodger, MD, Research Department of Infection & Population Health, University College London, Rowland Hill St, London, NW3 2PF, United Kingdom ([alison.rodger@ucl.ac.uk](mailto:alison.rodger@ucl.ac.uk)).

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Geretti reported receiving consultancy and speaker’s fees from Abbott Diagnostics, Abbvie, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Pfizer, and ViiV and serving as a principal investigator for studies for which the University of Liverpool received grant income from Bristol-Myers Squibb, Gilead, Janssen, and Viiv. No other disclosures were reported.

1. Eshleman SH, Hudelson SE, Redd AD, et al. Analysis of genetic linkage of HIV from couples enrolled in the HIV Prevention Trials Network 052 trial. *J Infect Dis*. 2011;204:1918-1926.
2. Foster GM, Ambrose JC, Hué S, Delpech VC, et al. Novel HIV-1 recombinants spreading across multiple risk groups in the United Kingdom: the identification and phylogeography of Circulating Recombinant Form (CRF) 50\_A1D. *PLoS One*. 2014;9:e83337.
3. 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.
4. Bernard EJ, Azad Y, Vandamme AM, Weait M, Geretti AM. HIV forensics: pitfalls and acceptable standards in the use of phylogenetic analysis as evidence in criminal investigations of HIV transmission. *HIV Med*. 2007;8:382-387.