To the Editor—In their commentary regarding our recent study examining the preferential selection of previously transmitted strains in sexual transmission of human immunodeficiency virus type 1 (HIV-1), Wertheim et al offer a reanalysis of a portion of the data we presented in our article and conclude from this that the “data do not support the conclusion by Redd et al” [1]. They came to this conclusion by reexamining only 2 of the 4 sections of data that we presented to support the conclusions in our study.

Wertheim et al reanalyzed the phylogenetic analysis of our next-generation sequence data, using a molecular clock in a Bayesian Markov chain Monte Carlo framework. They legitimized the need for this reanalysis by comparing our data to the great ape lineage. This comparison is misleading since it implies that we sampled 3 different populations at the same time. Instead, we have dated samples from 1 population at 2 time points and a new population that arose from the first population within a given time frame. In contrast to the arguments given by Wertheim et al, with this sampling regimen, the “most related”
populations are not necessarily those that share the most recent common ancestor. For example, suppose we sample a viral population and then a selective sweep subsequently spreads through the population, after which some virions are stored as provirus in latently infected CD4+ T cells. If we then sample the stored and circulating viral populations ≥1 year later, the stored and circulating viral populations will share a common ancestor, but the stored virus will be genetically more similar and more closely related to the ancestral virus. The results presented by Wertheim et al rely solely on their narrow definition of "most related" and ignore other data and associations that better explain the likely biological relationships between the donor and recipient viral strains. Importantly, their phylogenetic analysis also assumes that the data are clocklike, thus implicitly assuming a priori that contemporary sequences are transmitted. However, if ancestral sequences are transmitted, the data will be anything but clocklike, thus breaking their assumptions of method and producing results that are not interpretable.

Interestingly, their reanalysis of our findings in many cases agreed with our own phylogenetic analyses that used a maximum likelihood approach. In couples 1, 8, 11, and 14, our phylogenetic analyses and their Bayesian approach identified the donor late (or contemporaneous) sequence as the source for the transmitted strain. In couples 6 and 15, there were sequences from the donor at the early time point and at the time of transmission that were identical to the most prominent strain found in the recipient at the time of transmission. These were classified by Wertheim et al as being "indistinguishable" by their Bayesian approach; however, this ignores the fact that the donor late sequences inherently came from the donor early population. Therefore, a more likely biological explanation for this situation is that the donor early sequences have been "preserved" within this host and have subsequently been transmitted. This may seem like a semantic argument; however, one of the advantages of using deep sequencing in this context is that it allows you to observe these preserved variants in some cases. Couples 9 and 10 are examples in which the data are not clocklike and, therefore, the Bayesian analysis used by Wertheim et al is likely to be misleading, as mentioned above. The neighbor-joining tree that we show for couple 10 (Figure 3C [1]) highlights another problem with their analysis. In this case, the viral population in the donor at the earlier time point consists of 2 distinct clades, whereas at the later time point, the majority of sequences are in only 1 clade and 1 minor variant remains in the other clade. Interestingly, this minor variant is the most closely related sequence to the recipient viruses. We believe that, taken together, these findings indicate that the transmitted strain was preserved in the donor and then subsequently transmitted. Couple 12 is similar to couple 10 in that the most prominent virus in the later donor sample is in a separate clade, which is why we listed this as preserved. However, if you remove this clade, the transmitted strain is identical to variants in the later donor samples, as highlighted by Wertheim et al.

The authors also reanalyzed our analysis of 22 couples who were examined by bulk polymerase chain reaction sequencing. They highlight that, because of the limited sampling available for the individual couples, one cannot determine whether the early or later donor sequences are statistically more closely related to the recipient strain. However, we examined these couples as a population by estimating the slope of the difference between the d_n and d_0 time points for the 22 couples, using a mixed-effects linear model with the least Akaike information criterion (spatial power structure; Figure 1A [1]). The model demonstrated a positive slope between the d_n and d_0 time points (0.19/ year; 95% confidence interval,.02%–.36%; P < .05), indicating that, in this population of couples, the recipient strains are genetically more similar to donor viruses present prior to as compared with near the time of estimated transmission.

We would like to point out that we presented 2 additional collections of data (interhost and intrahost diversity analysis, as well as a detailed clonal analysis of 3 couples) that also supported our conclusion that there is a preferential transmission of ancestral strains during sexual transmission. Wertheim et al do not comment on these data. In addition, an in-depth modeling analysis of HIV-1 evolution within a population indicated that the preferential transmission of ancestral HIV-1 strains through a possible "store and retrieve" type mechanism is the most likely scenario for explaining why HIV-1 evolves faster within an individual than in a population as a whole [2].

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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