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Phylogenetic Relatedness of HIV-1 Donor and Recipient Populations

To the Editor—A recent article by Redd et al [1] reported preferential transmission of human immunodeficiency virus type 1 (HIV-1) most closely related to strains sampled at least 2 years prior to transmission (ancestral), compared with strains sampled just after transmission (contemporary), in heterosexual couples in Rakai, Uganda. Characterization of the viral population in the recipient is essential when determining both the source of the transmitted virus in the donor and establishing the viral characteristics that may favor successful transmission. We contend that the data do not support the conclusion by Redd et al because of a common misinterpretation of relatedness in an evolutionary framework [2] and statistical issues associated with computing genetic distances between short, highly similar sequences.

The closest relative of a given taxon—whether it be nucleotide sequence, strain, or species—is the taxon (or taxa) with which it shares a most recent common ancestor. Once a phylogeny has been inferred, genetic distance is inconsequential when determining relatedness. For example, humans are more closely related to both chimpanzees and bonobos than we are to gorillas, because we share a common ancestor with chimpanzees and bonobos more recently than we share a common ancestor with gorillas (Figure 1*A*) [3]. Furthermore, even though the genetic distance separating gorillas and chimpanzees (0.245 substitutions/site) is shorter than the distance between gorillas and humans (0.282 substitutions/site), gorillas are equally related to both humans and chimpanzees.

When using phylogenetic analysis to determine the source of HIV-1 transmission, these points are essential. The viral source population in the donor (ancestral vs contemporary) can be identified by determining which donor viruses share the most recent common ancestor with virus in the recipient. We reanalyzed viral sequences from the 9 couples subjected to 454 next-generation sequencing (Figures 3 and 4 in the article by Redd et al [1]), before and after transmission, using a molecular clock in a Bayesian Markov chain Monte Carlo framework [4].

In 4 couples (couples 8–11), viruses from the recipient were monophyletic and shared a most recent common ancestor with contemporary viruses from the donor (posterior probability, ≥ .98; Figure 1*B*). In 3 couples, (couples 1, 12, and 14) viruses from the recipient were intermixed

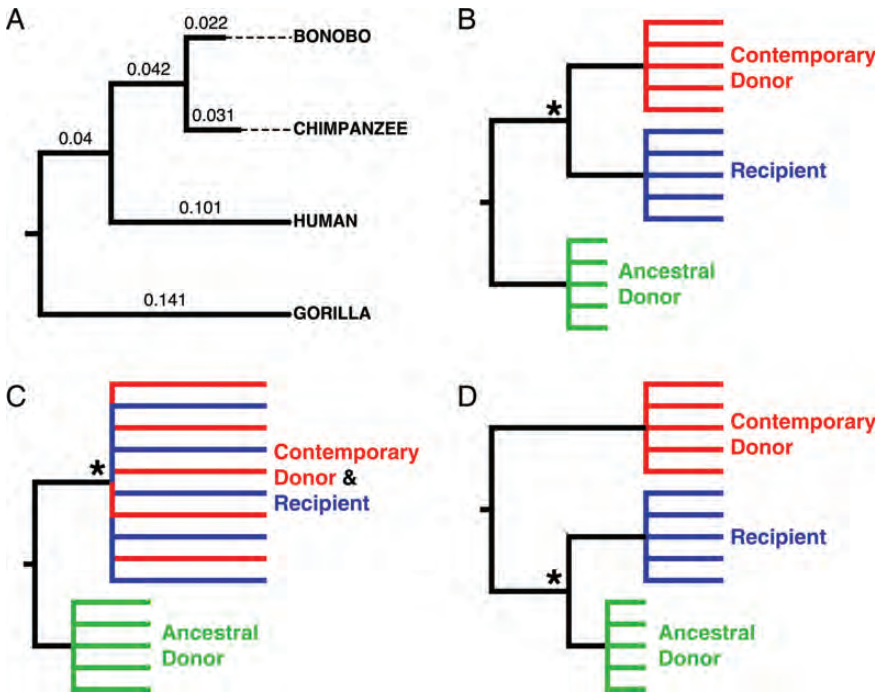

Figure 1. Depictions of phylogenetic relationships. (A) Phylogeny of African apes inferred from the coding region of mitochondrial genomes. Nucleotide substitutions per site are shown on each branch. (B) Idealized phylogeny in which recipient viruses are monophyletic and more closely related to contemporary donor sequences than ancestral donor sequences. (C) Idealized phylogeny in which recipient viruses are intermixed with contemporary donor sequences with whom they share a common ancestor more recently than with ancestral donor sequences. (D) Idealized phylogeny in which recipient viruses are more closely related to ancestral donor sequences than contemporary donor sequences. An asterisk indicates the node whose support is relevant to inference; paraphyletic relationships between donor populations and recipient viruses would yield the same conclusions.

with contemporary donor viruses and were therefore more closely related to contemporary donor viruses than ancestral donor viruses (posterior probability, ≥ .99; Figure 1*C*). In 2 couples (couples 6 and 15), the phylogenies were poorly resolved because of insufficient differentiation between the ancestral and contemporary donor viruses. In no couple was there phylogenetic evidence to support recipient viruses being the closest relatives of ancestral donor viruses (Figure 1*D*). Therefore, our analysis finds it unlikely that ancestral viruses were preferentially transmitted from a sequestered, long-lived reservoir or from a population persisting at low levels in the serum, as suggested by Redd et al [1].

In Figure 1 in the article by Redd et al [1], similarity between ancestral donor and recipient sequences was illustrated by plotting point estimates of genetic distances between donor sequences, sampled at different times, and recipient sequences. Genetic distances between 2 sequences are estimated using statistical procedures, and distances inferred from relatively short nucleotide sequences are imprecise and should be compared with care. For example, in 1 couple (F04331 and H50053), the recipient sequence had 1 nucleotide difference from the ancestral donor sequence and 3 nucleotide differences from the contemporary donor sequence. These differences yielded distance estimates (Tamura-Nei 93 [5]) of 0.25% (95% bootstrap confidence interval [CI], 0.0%–1.25%) and 0.76% (95% bootstrap CI, 0.23%–1.8%), respectively. Because of wide overlapping bootstrap CIs, one cannot determine which donor sequence is more genetically similar to the recipient sequence (posterior probability, .51, by the likelihood ratio test [6]). Indeed, we found sufficient signal to assert that the recipient sequence is genetically more similar to the ancestral donor sequence in only 1 of 22 total couples (posterior probability, ≤.05; no correction for multiple testing).

It remains an open question whether viruses in some recipients are genetically more similar to the ancestral donor population, compared with the contemporary donor population. An increase in the evolutionary rate in donor virus later in infection or a slowdown in the rate of viral evolution in the recipient, due to changes in natural selection or demography (ie, bottleneck followed by population expansion), would account for this phenomenon. Alternatively, convergent evolution (ie, reversion to an ancestral genotype/phenotype) is a possible explanation for decreased genetic distance separating recipient sequences from the ancestral donor viruses [7–8]. Nevertheless, none of these scenarios point to the preferential transmission of ancestral viruses.

Notes

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