Role of donor genital tract HIV-1 diversity in the transmission bottleneck

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AUTHOR SUMMARY

According to the Joint United Nations Program on HIV/AIDS, an estimated 2.6 million new HIV infections occurred in 2009, with heterosexual transmission as the primary driving force. Sexually transmitted HIV-1 infection requires the passage of virus across a mucosal barrier; in general, a genetically unique viral variant establishes infection in the newly infected individual despite a genetically diverse viral swarm in the transmitting partner (1, 2). The mechanistic basis of this genetic bottleneck is unknown, and it is important to determine whether it is driven simply by chance or whether particular variants are selected during transmission. To address this question, we compared the genetic composition of the virus population present in the genital tract (GT) of the transmitting partner with the particular virus initiating infection in the recipient partner. We found that although discrete viral populations dominate in the GT of the transmitting partner, the transmitted variant that established systemic infection was genetically distinct from this dominant population. These results suggest that particular viruses are chosen for transmission, further suggesting the possibility of targeting these viruses for prevention (Fig. P1).

In sub-Saharan Africa, heterosexual HIV-1 transmission between partners of discordant couples (in which one partner is infected) is recognized as the major contributor to the epidemic (3). Counseling and HIV testing decrease but do not completely eliminate transmission in such couples. Thus, following two large HIV-prevention intervention cohorts of discordant couples in Zambia and Rwanda, we identified new infections close to the time of transmission and sampled virus in the blood and GT of the transmitting partner, which would mean it was most likely transmitted by chance. Thus, in the current study, we compared the genetic composition of the virus in the GT of eight transmitting partners with that in their blood and that in the blood of their newly infected partners. The results demonstrated that in seven of eight of the transmitting partners, there were discrete virus variants in the GT, and in most cases, these represented a majority of the virus present. Statistical analyses of the genetic relatedness among these viruses (their phylogeny) confirmed that these GT subpopulations were compartmentalized from those in the blood. In several individuals, multiple identical sequences were present in the GT, consistent with the hypothesis of a locally replicating subpopulation. Because localized virus replication from a limited subset of cells raised the possibility that these discrete GT populations may be transient, we analyzed the GT viruses in four chronically infected women over time and observed a distinct and relatively stable GT population in two of the four individuals studied.

We next compared the virus in each newly infected partner with that in the GT of the transmitting partner for the eight pairs. Remarkably, in each case, the transmitted variant was genetically distinct from the predominant variants in the GT at the time of sampling. Therefore, with the limitation that the exact genetic composition of the virus population at the time of transmission cannot be unequivocally defined, these findings

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![Fig. P1. Heterosexual transmission across a mucosal barrier. (A) GT-derived virus population at the time of sampling contains a large subpopulation of virus (red virions), as well as numerous other variants. In this study, only one of these variants, distinct from the large variant population, successfully crosses the mucosal epidermis barrier of the genitals (B) to generate an infection capable of spreading to all lymphoid tissues of the recipient (C).](image-url)

The authors declare no conflict of interest.

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point to the selection of a minor GT variant with properties favoring transmission.

Understanding the viral factors that facilitate heterosexual transmission of HIV-1 is critical to the development of preventative approaches, including vaccines, which could curtail the epidemic. Previous studies have shown that the viruses present in newly HIV-1–infected subjects have traits distinct from those in chronically infected individuals (1), consistent with a selective, rather than a random, process of determining the particular infecting viral variant. The results presented here provide further support for this selective process and, by extension, the possibility of targeting this transmission bottleneck to prevent infections.