

Several lines of evidence suggest that a selective “bottleneck” contributes to the restricted diversity at HIV-1 transmission. If the homogeneity in the transmitted virus reflected stochastic selection of 1 or a few variants for transmission, we would expect that the transmitting virus would most frequently resemble the predominant species in the source. Although limited by infrequent sampling that can skew the relative frequency of the different variant populations detected, many transmission studies demonstrate differences between the transmitted virus and the predominant variant in the blood [5, 6, 14, 15] or genital tract [16] of the source subject. In addition, HIV-1 transmission is characterized by the strict selection for variants that use the C-C chemokine receptor type 5 (CCR5) coreceptor, despite C-X-C chemokine receptor type 4 (CXCR4) variants in the partner [6, 17–19]. Finally, recently transmitted variants of HIV-1 subtypes A and C, though not necessarily subtype B, typically have shorter envelopes and/or fewer potential N-linked glycosylation sites than chronically infected subjects [14, 15, 20–24]. Together, these data suggest that the limited viral diversity during HIV-1 transmission is not simply a stochastic event, but rather that it may also involve selective pressure for particular envelope features.

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In 1993, Zhu et al proposed that HIV-1 selection is reset at transmission, with evolution starting over in newly infected individuals [6]. More recently, several investigations have suggested that transmitted and/or early variants are more closely related to the donor’s ancestral sequences. In an examination of HIV-1–infected subjects followed longitudinally, Herbeck et al found that HIV-1 interhost genetic diversity and divergence are significantly less during early infection, suggesting evolution toward an ancestral state following transmission [20]. Sagar et al directly examined the characteristics of viruses selected during transmission by examining 13 linked heterosexual transmission pairs from the Rakai Community Cohort Study (RCCS) [14]. The transmitted variants differed from the donor sequences and were more closely related to the computed most recent common ancestor of the donor virus than they were to the majority of contemporaneous viruses, suggesting that variants with ancestral features were favored for transmission [14]. These studies left open the question of whether early donor viruses are archived and favored for retransmission or whether the virus evolves immediately after transmission in the absence of the selective forces driven by a robust immune response [20, 25].

2

Rewrite

When HIV-1 is sexually transmitted, only one virus variant is typically transmitted from the index to the previously uninfected partner. If the transmitted variant was selected randomly, we would expect the index partner’s predominant viral variant to be transmitted most commonly. But this predominance is not observed. Instead, transmitted variants pass through a bottleneck; certain variants with specific characteristics are transmitted more often. Characteristics that enhance transmission include the use of the C-C chemokine receptor type 5 (CCR5) coreceptor and, for HIV-1 subtypes A and C, shorter envelopes and/or fewer potential N-linked glycosylation sites.

Transmitted variants are closely related to ancestral HIV-1 variants, suggesting an adaptation for transmission. Among people with early HIV-1 infection, viral genetic diversity is considerably less between persons. Furthermore, in the Rakai Community Cohort Study, the viruses in the newly infected partners resembled the most recent common ancestral virus among the couples more than contemporaneous circulating viruses in the transmitting partners. This observation supports the hypothesis that ancestral variants have a transmission advantage. Alternatively, the virus could evolve rapidly after transmission to the ancestral state given the absence of a robust immune response during early infection.

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