

## CO-RECEPTOR UTILIZATION AND *env* SEQUENCE IN RECENT CXCR4-TROPIC HIV-1 INFECTION

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**Background:** CCR5-tropic variants of human immunodeficiency virus type 1 (HIV-1) predominate in early stages of infection. Late infection is frequently characterized by the appearance of CXCR4-tropic strains and their emergence has been associated with accelerated immunodeficiency and disease progression. The origin(s) of CXCR4-using variants remains unclear and may have clinically important implications. In this study, we have analyzed the co-receptor usage, V3 sequences and gp160 sequence phylogeny of *env* clones from seven individuals who were recently infected with subtype B CXCR4-using viruses.

**Methods:** Multiple *env* clones were isolated from the plasma virus of seven patients (MSM) newly infected with CXCR4-using HIV-1. Co-receptor tropism was evaluated using the Trofile™ assay (Monogram Biosciences) and *env* nucleic acid sequences were determined using conventional chain termination methods.

**Results:** Analysis of *env* clones from seven patients who harbored CXCR4-using virus demonstrated that both X4- and dual-tropic variants were presented in recent HIV infection, either alone, or as mixed populations containing R5-tropic variants. Phylogenetic analysis indicated that new infections can be characterized by either relatively homogeneous or heterogeneous virus populations. Dual-tropic variants differed in their abilities to infect CD4+ target cells expressing either the CXCR4 or CCR5 co-receptors. Dual-tropic variants that inefficiently used CXCR4 shared V3 sequences with R5-tropic clones, whereas dual-tropic variants that efficiently used CXCR4 had V3 sequences that more closely matched X4-tropic variants in the same sample. The prediction of CXCR4 use based on V3 sequence algorithms was insensitive. Clinical history was available for two of the seven patients (X4-tropic, D/M-tropic) and both experienced rapid losses in CD4+ T-cells after infection.

**Conclusions:** CXCR4-using variants of HIV-1 were identified in seven recently infected patients. Based on clonal analysis, these virus populations differed both qualitatively and quantitatively with respect to their ability to use CXCR4. The diversity of CXCR4-tropic variants in the virus populations of recently infected subjects resembles that of subjects with late stage disease. These observations broaden our understanding of virus transmission and may have important implications for the origin of CXCR4-tropic variants, co-receptor switching, response to treatment with co-receptor inhibitors, pathogenesis and vaccine design.