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ESTIMATING EVOLUTIONARY PATHWAYS TO CXCR4 USAGE FROM CROSS-SECTIONAL DATA

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BACKGROUND: Coreceptor usage of HIV-1 is mainly determined by the V3 loop of gp120. Mutations outside V3, most notably in the bridging sheet, have also been described to be correlated with X4 viruses. So far, however, it is not understood if these mutations prepare for the coreceptor-switch, or if they act as compensatory mutations for fitness losses induced by 11/25 mutations (306R/ K/H and 322R/K/H). In this work, we wanted to study this question with the help of mutagenetic trees, which have previously been used to model HIV resistance pathways in presence of drug pressure.

METHODS: Sequence data containing the V3 loop ($n=9,557$) as well as one of the gp160 regions V2 ($n=2,656$), C4 ($n=2,098$) or GP41 ($n=827$) were downloaded from the Los Alamos Sequence Database. Only subtype B sequences and at most one sequence per patient were analyzed. Samples with experimentally determined phenotype were used to detect mutations associated with X4 viruses (Fisher's exact test). Mixture models of mutagenetic trees containing the most significant mutations were then generated using the R-package Rtreemix.

RESULTS: Mutations at 13 positions within V2, 23 in V3, 2 in C4 and 15 in GP41 were significantly ($P<0.05$) associated with X4 viruses. In almost all generated trees, the mutations 306R/K/H and 322R/K/H appeared in two different arms of the tree suggesting that these are two independent pathways to evolve to X4. 306R/K/H was generally preceded by mutations at positions 306 and 316 while 322R/K/H was selected by I424V and mutations at position 317. Other mutations usually came afterwards. GP41 mutations including the highly predictive insertion A/I/V after position 515 in GP41 were all seen as successors of 306R/K/H. Mutations disrupting the N-glycosylation motif of V3 followed this pathway

too. By contrast, V2 mutations, such as the well known X4 mutation S195H, commonly appeared after 322R/K/H. Another mutation in C4 (S440D/E) previously been described as highly correlated with CXCR4 usage evolved independently from 306R/K/H and 322R/K/H.

CONCLUSIONS: Since 11/25 mutations predominantly appeared as one of the first mutations in our trees, it can be assumed that most other mutations associated with X4 viruses are compensatory mutations following after the coreceptor switch and that there is no ongoing evolution towards X4 viruses over time.

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14

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