CXCR4-Using HIV-1 Variants Evolve In The Presence Of And Co-Exist With CCR5-Using Variants

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BACKGROUND

- HIV-1 uses either CCR5 (R5 virus) or CXCR4 (X4 virus) as a coreceptor to enter host cells.
- X4 variants, usually seen in the late stage of infection, are associated with more rapid disease progression.
- However, the triggering event that allows the evolution of X4 variants and the dynamics of X4 and R5 variants following the emergence of X4 variants are unclear.

METHODS

- We identified 21 women with HIV in the Women's Interagency HIV Study (WIHS) whose:
  - 1) CD4 T+ cell counts declined from >600 to <100 cells/μl in the **absent of effective antiviral therapy** while in the study, and
  - 2) plasma samples were available during the period of CD4+ T cell decline with HIV-1 RNA quantification.
- Multiplexed Primer ID NGS targeted HIV-1 gag, pol and env (V1/V3) of longitudinal specimens collected every 6 months.
- X4 variants were inferred using the Geno2Pheno coreceptor algorithm; X4 lineages were defined as having a false positive rate below 2% and comprising at least 0.3% of the intra-host viral population.

We propose that the emergence of X4 viruses serves as a biomarker for a state of virus-specific immunodeficiency, allowing the virus to proliferate in inactivated CXCR4+ CD4+ T cells, leading to a more rapid loss of CD4+ T cells.

RESULTS

- A median of 4 years follow-up were studied for each participant.
- X4 variants were identified in 16 participants, with a median CD4+ T cell level of 620 cells/μL at the time of detection. (Fig.1)
- At the time point when X4 first emerged, these variants constituted a median of 11% of the intra-host population. X4 variants co-existed with the R5 variants in longitudinal follow-up. At the final time point, the X4 population made up a median of 19% of the intra-host quasispecies. (Fig.2)
- The emergence of X4 variants accelerated disease progression, evidenced by an increased CD4+ T cell decline rate of 206 cells/μl/year (95% CI: 31 to 382, p=0.025) following their emergence.
- The X4 Env V3 sequences were linked with specific Env V1/V2 lineages, suggesting genetic compartmentalization of X4 variants. In some participants, multiple X4 lineages with distinct V3 sequences were identified at the same time point, suggesting diverse origins of X4 variants. (Fig.3)
- X4 and R5 variants continued to evolve over time. The emergence of X4 did not increase the viral diversity in Env V1/V3.

CONCLUSIONS

- X4 variants can emerge as minor variants early during the course of HIV-1 infection.
- X4 viruses co-exist with CCR5-using viruses, suggesting that the evolution of X4 variants is not driven by the lack of CCR5+ CD4+ T cells.
- We propose that the emergence of X4 viruses serves as a biomarker for a state of virus-specific immunodeficiency, allowing the virus to proliferate in inactivated CXCR4+ CD4+ T cells, leading to a more rapid loss of CD4.

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Fig. 1 CD4 cell count and X4 virus detection in the study participants.

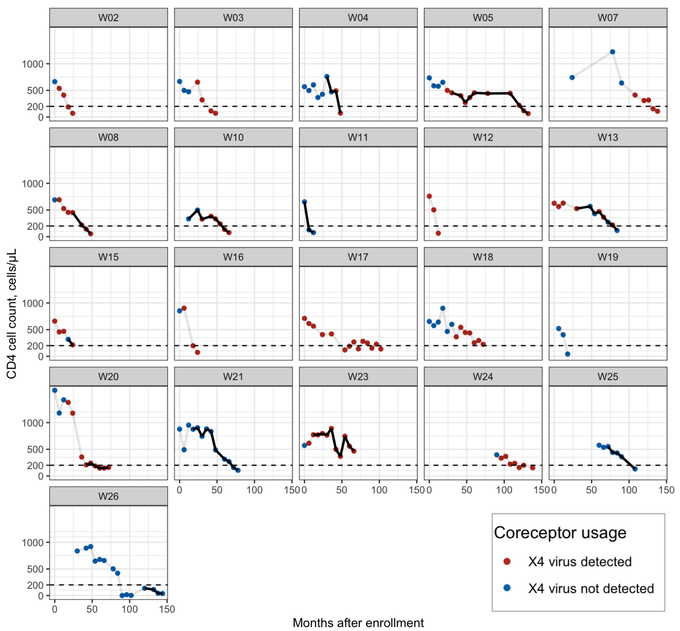


Fig. 2 Change of X4 and R5 viral load across the disease course in the study participants.

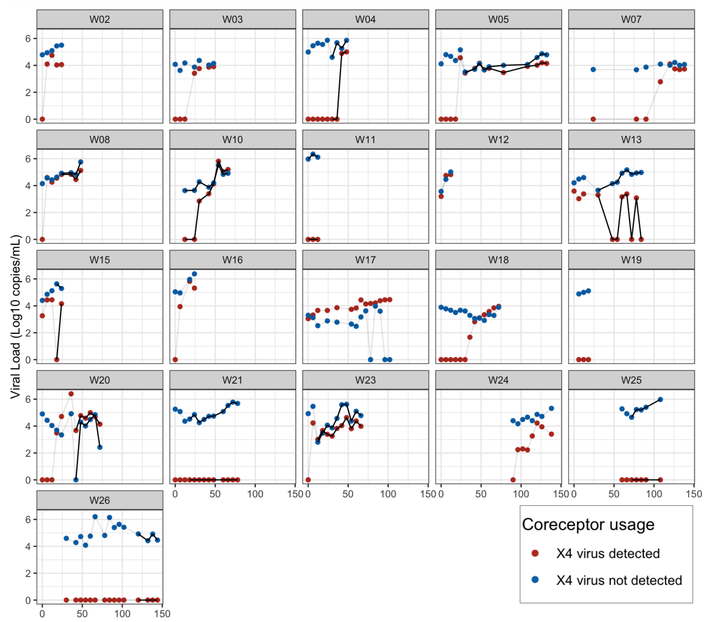


Fig.3 Phylogenetic analysis of X4 and R5 lineages of participant W02

