Longitudinal Evaluation of Viral Tropism in Archived Intact DNA Genomes in Acute HIV-1 Infections

#465

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Viral Tropism

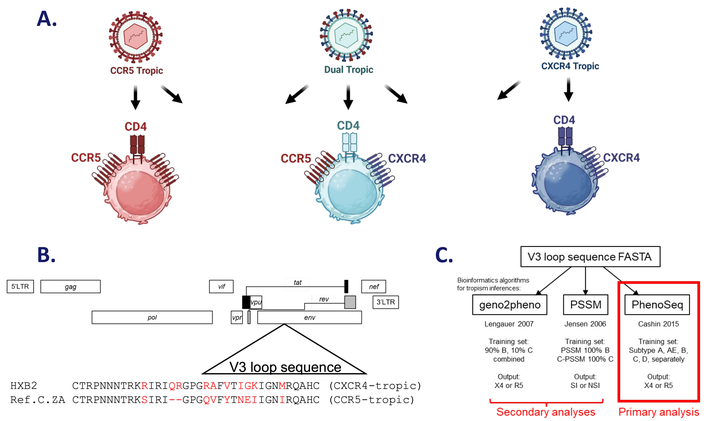


Figure 1: (A) HIV-1 tropism refers to the ability of the virus to infect CCR5- and/or CXCR4-expressing CD4+ cells. Since CXCR4 expression is associated with naïve T cells, whereas CCR5 is associated with memory T cells, viral tropism has direct implications in the composition of the persistence viral reservoir. **(B)** HIV-1 Env V3 loop sequence is a major determinant of viral tropism. HIV-1 subtype C have been predominantly associated with CCR5-usage. **(C)** V3 sequences can be analyzed for viral tropism using bioinformatics algorithms such as geno2pheno (g2p), PSSM and PhenoSeq. PhenoSeq was chosen as the primary analysis method for this study as it was trained with subtype-specific CCR5/CXCR4-usage-phenotype data.

The FRESH Cohort



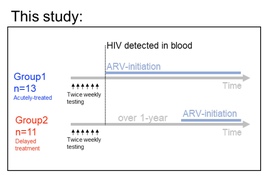


Figure 2: The FRESH cohort in Durban, South Africa enrolls young women at high risk for acquiring HIV infection who undergo HIV-1 RNA testing twice per week for 9-months. We studied 24 women who were detected during acute HIV-1 infection and followed for up to 1,102 days; 11 initiated treatment >1 year after detection and 13 initiated treatment 1-3 days post-detection.

Objective

In this study, we evaluated viral tropism longitudinally using V3-loop sequences derived from archived viral DNA genomes in an acute infection cohort.

The prevalence of X4-tropic viruses associated with archived intact HIV-1 DNA in subtype C acute infections is unexpectedly high. The extent and role of X4-tropic variants in intact viral DNA genomes needs to be further assessed as they may represent potential sources of viral rebound.

Near-full-viral-genome sequencing (FLIP-seq)

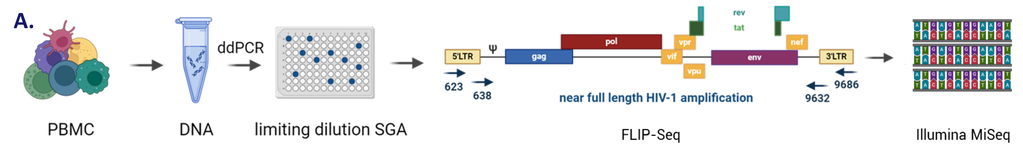
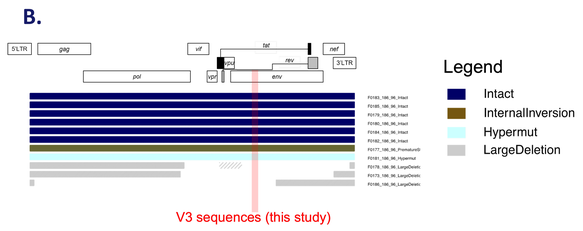
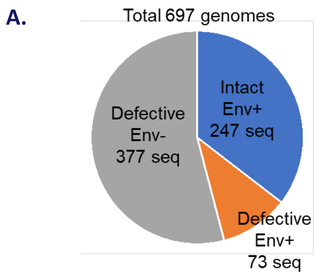


Figure 3: (A) Near-full-length single-genome HIV-1 DNA sequencing (HXB2 638-9632) was performed on longitudinal PBMC samples, and genomes were classified as intact or defective using HIVSeqinR. **(B)** HIV-1 genome landscape from a representative donor. Viral subtyping was performed with RIP 3.0. Viral tropism was inferred using V3-loop sequences with PhenoSeq.



Results



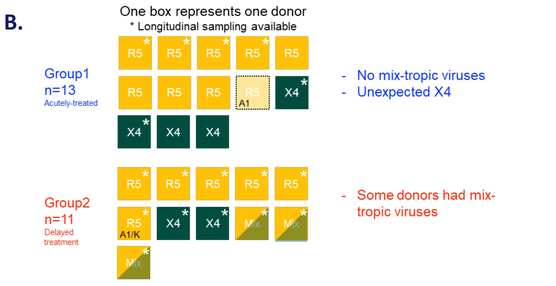


Figure 4: (A) We obtained 697 viral DNA genomes, of which 320 (46%) contained full-length Env (247 intact and 73 defective) representing all 24 donors. Intact viral DNA genomes were detected in 23 out of 24 donors. **(B)** Among intact genomes and pooling all time points available, V3-loop analysis using PhenoSeq revealed that 61% donors were entirely R5-tropic (n=13 subtype C, n=1 A1/K), 26% donors were entirely X4-tropic, (n=6, all subtype C), and 13% donors had a mix of R5- and X4-tropic viral DNA genomes (n=3 all subtype C). Mixed-tropic populations were observed only in donors who were untreated during acute infection (n=3). For the one donor who had no intact genome detected (subtype A1), tropism results from defective genomes were shown with dotted lines around the box.

Results



Figure 5: Tropism remained stable in 82% (14/17) of donors who had longitudinal data. Delayed treatment in Group2 was due to historic treatment guidelines and who remained viremic for a median of 332 days (IQR 330-441). All participants were detected at Fiebig staging I except 198 (Fiebig III) 442 (Fiebig V).

Conclusions

- We detected a higher than expected prevalence of X4-tropic archived intact HIV-1 DNA in acute infections in FRESH by PhenoSeq, confirmed by geno2pheno[coreceptor] and C-PSSM (results not shown).
- Given that previous studies have associated subtype C and acute infections with mostly R5-tropic variants, our results suggest phenotypic studies are needed to further assess the extent and roles of archived X4-tropic variants in intact HIV-1 DNA genomes, which may have implications in the types of cells that would fuel virologic rebound during treatment interruptions.

Additional Key Information

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