Viral Genetic Traits of Durable Control in Dual Immunotherapy-treated SHIV-infected Rhesus Macaques

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BACKGROUND

- Antiretroviral therapy (ART) does not cure HIV, and viral rebound occurs after ART interruption due to long-lived cellular reservoirs.
- A recent study demonstrates that combination immunotherapy with the N-803 IL-15 superagonist and dual broadly-neutralizing antibodies (bNAbs) leads to sustained ART-free viral remission(1).
- Understanding the viral genetic features associated with viral fitness and natural ART-free immune-mediated virologic control is critical to the development of effective HIV cure strategies.

METHODS

- Plasma was collected during analytical treatment interruption (ATI) from SHIV-AD8-infected ART-suppressed rhesus macaques (RM) treated with N-803 and the 10-1074 and 3BNC117 bNAbs (N=8) and untreated control animals (N=8).

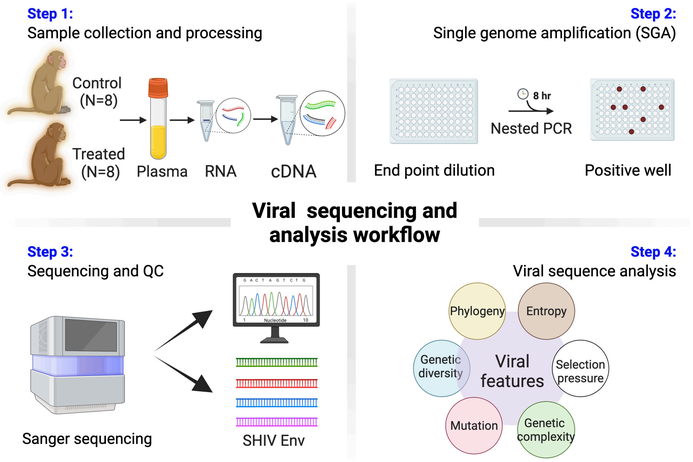


Fig. 1. Schematic framework of methodology

RESULTS

- SHIV *env* sequences from each animal clustered together in phylogenetic analysis (Fig. 2). Viral sequences did not form clusters with respect to immunotherapy treatment status, and low levels of intra-host viral genetic diversity were observed.

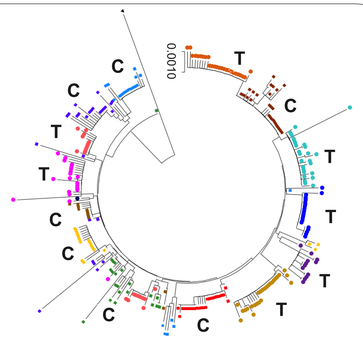


Fig. 2. Maximum likelihood phylogenetic tree. Color coding represents individual animals and scale bar represents genetic distance. T=treated group and C=control group.

- The treated group showed significantly greater viral genetic diversity and genetic divergence than the control group ($p<0.0001$ and $p=0.0038$, respectively), reflecting significant effects of the dual immunotherapy on viral variation (Fig. 3A-C).

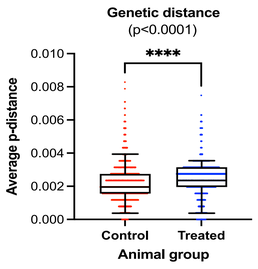


Fig. 3A

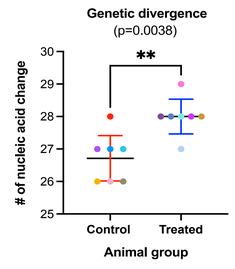


Fig. 3B

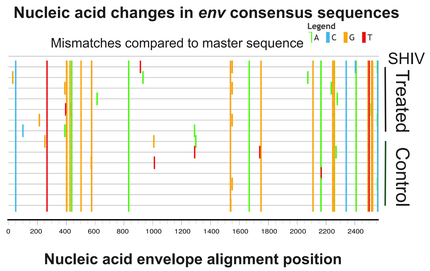


Fig. 3C

Fig. 3. Impact of dual immunotherapy on SHIV population genetics post-ATI.

- Viral genetic evidence of selection pressure did not vary substantially between treatment groups. A small number of non-synonymous mutations were observed in the *env* gene in dual immunotherapy-treated animals potentially reflecting immune escape. None of these sites were under selection in the control group (Fig. 4A-C).

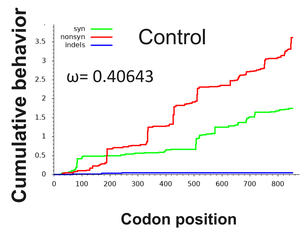


Fig. 4A

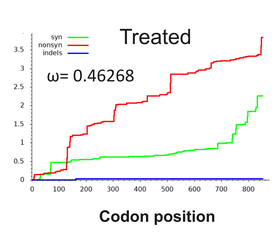


Fig. 4B

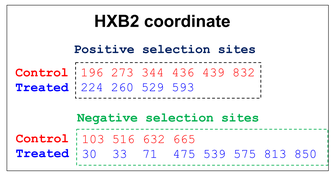
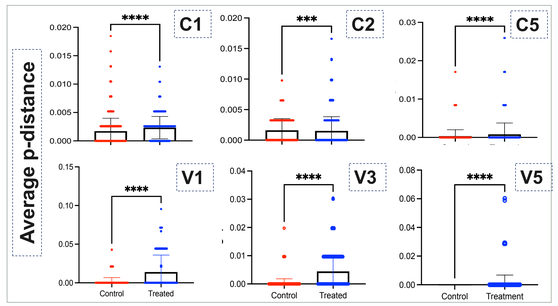


Fig. 4C

Fig. 4. Evidence of selection pressure mediated by the dual immunotherapy on SHIV *env*.

- Nucleic acids in the constant (C1, C2, C5) and variable (V1, V3, V5) regions of *env* show significant changes, suggesting envelope conformation shifts in response to bNAb (10-1074 and 3BNC117) treatment (Fig. 5).



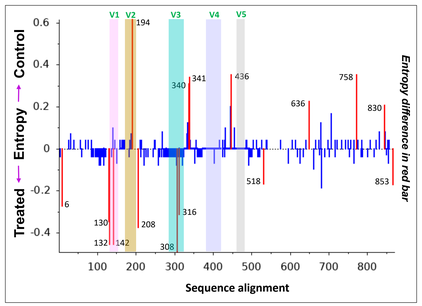


Fig. 5. Diversification at SHIV *env* sites potentially driven by bNAb exposure.

- Dual immunotherapy resulted in unique signatures in CTL epitopes at glycosylation and bNAb interface sites (Fig. 6).

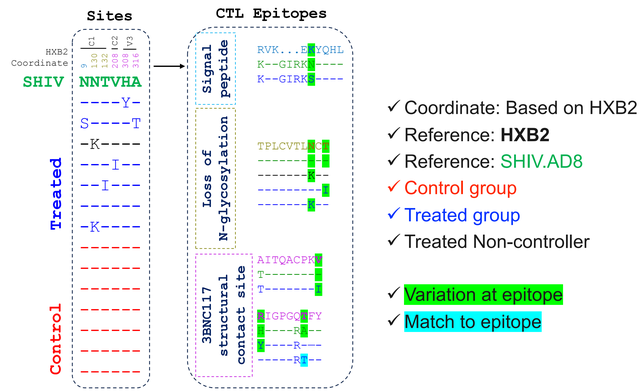


Fig. 6. Functional attributes of dual immunotherapy-induced mutations.

The evolution of select Env features modulating bNAb and CTL susceptibility may contribute to the induction of durable remission by dual immunotherapy in SHIV-infected ART-suppressed macaques.

CONCLUSIONS

- Dual immunotherapy with N-803 and the 10-1074 and 3BNC117 bNAbs induces genetic variation in the SHIV envelope gene, reflecting viral adaptation to immune pressure.
- Unique signature mutations suggest that the dual immunotherapy may drive immune escape through the evolution of key epitopes and structures targeted by bNAbs.
- The observed immune escape mutations may impact viral fitness, contributing to the durable remission induced by dual immunotherapy in SHIV-infected rhesus macaques.

❖ Future studies should focus on monitoring long-term viral evolution, immune escape mechanisms, and fate of induced mutations during viral rebound to ensure sustained viral suppression and long-term treatment efficacy.

REFERENCE

(1) Lim, So-Yon, et al. "Induction of durable remission by dual immunotherapy in SHIV-infected ART-suppressed macaques." *Science* 383.6687 (2024): 1104-1111.

ADDITIONAL INFORMATION

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