HIV Rapid Intra-Host Evolution Allows Evasion From VRC01 Infusion via Positive Selection

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Adaptive mutations in HIV *env* after VRC01 infusion were identified separately with evolutionary (phylogeny + dN/dS) and population genetics (selective sweeps + SAFE) approaches. While these approaches agreed in two cases, they also identified distinct mutations as adaptive in other individuals. In vitro assays confirm that mutations identified by both methods decrease neutralization by VRC01.

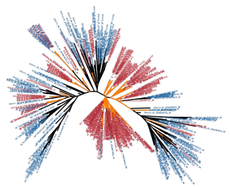
BACKGROUND

- The objective of this study is to identify positions in the *env* gene of HIV that facilitate escape after infusion of the VRC01 bNAb.

HIV is highly diverse between and within individual, due to its high mutation rate, neutral evolution and ongoing positive selection. In a clinical trial published in 2015[1], infusion of the VRC01 bNAb to eight people living with HIV (PLWH), resulted in diverse virological responses, including (1) no reduction in viral load (2) reduction and rapid recovery of viral load (3) reduction and delayed recovery of the viral load. While changes were observed within and outside the VRC01 epitope, it was challenging to determine which of the changes was adaptive to escape VRC01, and which changes were passenger mutations linked to the adaptive mutation.

METHODS

- High-Throughput SGS[2] was applied to samples from the original study to determine full length *env* sequences before and after infusion.
- Panmixia analysis[3] was used to determine shifts in population sequence composition.
- Codon-based positive selection analysis (dN/dS > 1) was applied to the phylogeny before and after infusion using FUBAR[4].

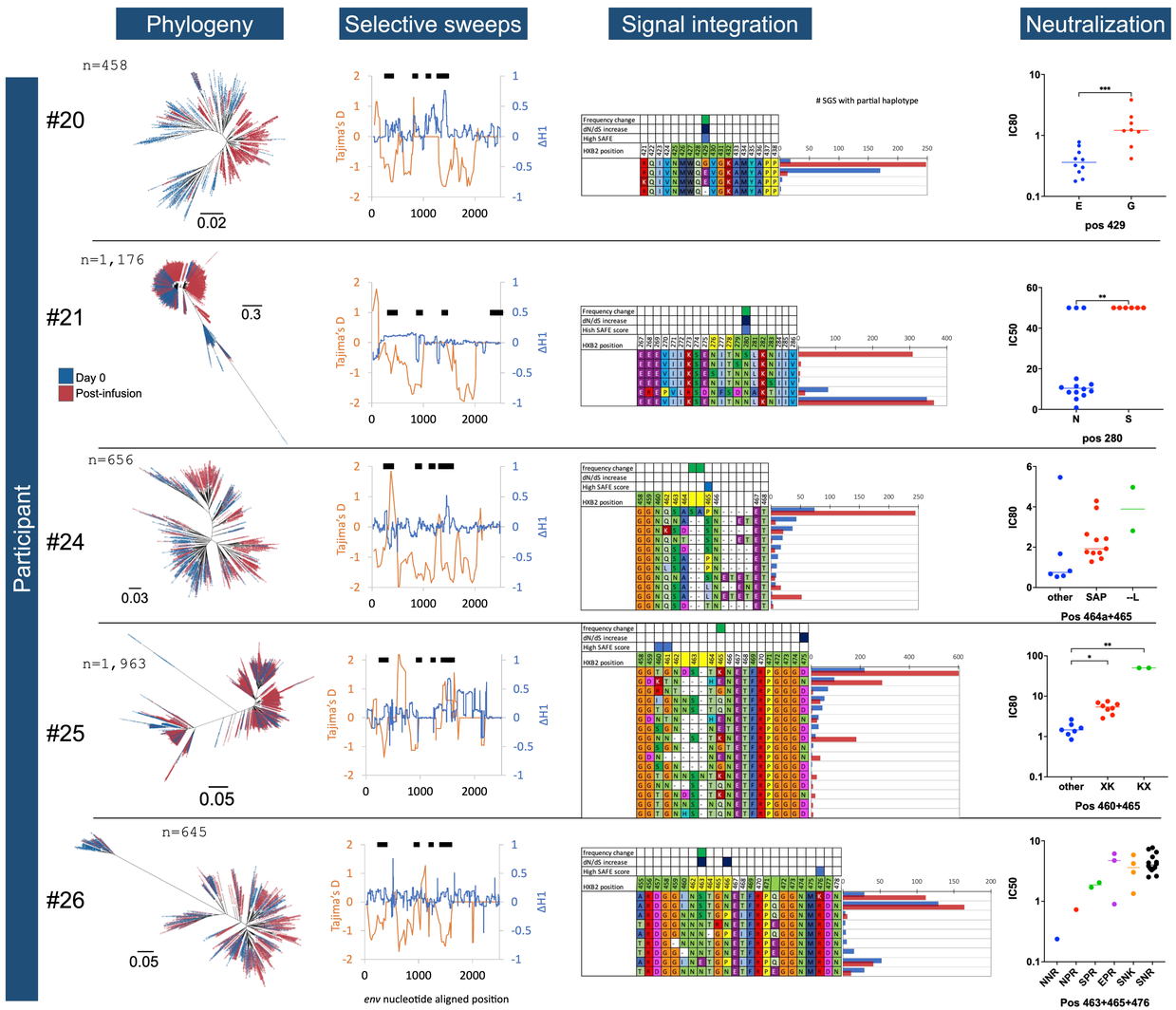


$$\text{Selection fold change} = \frac{\frac{dN}{dS}Post}{\frac{dN}{dS}day_0}$$

Day 0
Post-infusion
Branches leading to Glycine at position 429

- Population genetics methods[5-7] were used to identify selective sweeps and the adaptive mutations in them.

$$D = \frac{d}{\sqrt{Var(d)}} \qquad SAFE(e) = \frac{\phi - k}{\sqrt{f(1-f)}}$$



RESULTS

- Significant shifts in the sequence populations were identified in six out of the eight participant including the groups of (1) no change in viral load and (2) Rapid recovery of viral load.
- Both dN/dS and SAFE scores in selective sweeps identified the same positions within the epitope for two participants (#20 and #21), in two different positions.
- Selective sweeps and highest SAFE scores were identified in the VRC01 epitope in additional four individuals.
- dN/dS increase was also identified in three of the remaining individuals in different positions than the highest SAFE score.
- Neutralization values differ between envelope sequences with amino acids changes at the positions identified as adaptive after VRC01 infusion.

CONCLUSIONS

- dN/dS can be used to identify positive selection in HIV *env* intra-host data. However, lack of a signal could be due to limitations of the method and cannot be interpreted as absence of positive selection.
- Selective sweeps identification is limited in cases of sub-population structure, like dual-infection or predicted co-receptor associated sub-populations.
- Identification of different positions by dN/dS and SAFE is likely due to several adaptive solutions intra-host.
- In cases of subpopulation structure, each sub population can be analyzed separately to identify adaptive positions.
- The study's findings are instrumental for future endeavors to understand intra-host arms race by associating between neutralization fingerprinting in autologous serum and positions under positive selection in the HIV *env*.

References

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