Genetic characterization of HIV-1 subtype C Gag and Env sequences derived from transmitted/founder and rebound viruses from participants in a treatment interruption clinical trial

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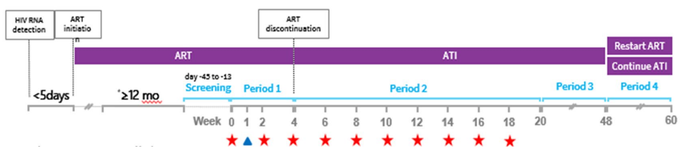
BACKGROUND

Combination approaches using antiretroviral therapy (ART) and immunological interventions such as broadly neutralizing antibodies (bNAbs) are showing promise in inducing antiretroviral-free HIV control, but the underlying mechanisms are not well understood. This study aimed to investigate the diversity and immune-driven evolution of Env and Gag sequences in rebound viruses from participants who initiated ART during acute infection and subsequently underwent an analytical treatment interruption (ATI) after receiving an immunotherapeutic intervention with two bNAbs.

METHODS

Virus sequences were analysed from 7 of 20 early treated South African women enrolled in an ATI-inclusive clinical trial that assessed two bNAbs (VRC07-523LS and CAP256V2LS) plus vesatolimod (NCT05281510). Full-length HIV-1 *env* and *gag* single genome amplicon (SGA) sequences were generated from plasma collected at TF and viral rebound during ATI. Rebound virus was obtained within 18 days of initial viremia, with the exception of participant 10005 from whom virus was obtained 336 days post-rebound.

Clinical trial study design



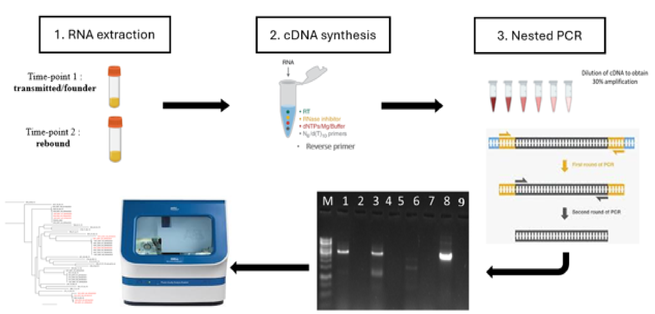
Rebound timelines

Early ART restart (<16 weeks in ATI)
- 19991001-10002
- 19991009-10007
- 19991010-10008

Delayed ART restart (16-44 weeks in ATI)
- 19991003-10003
- 19991005-10004

Post treatment controllers (> 44 weeks in ATI)
- 19991006-10005
- 19991013-10010

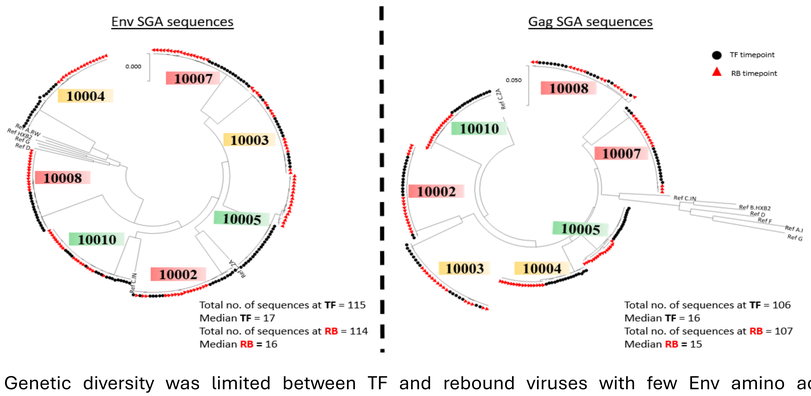
Single genome amplification



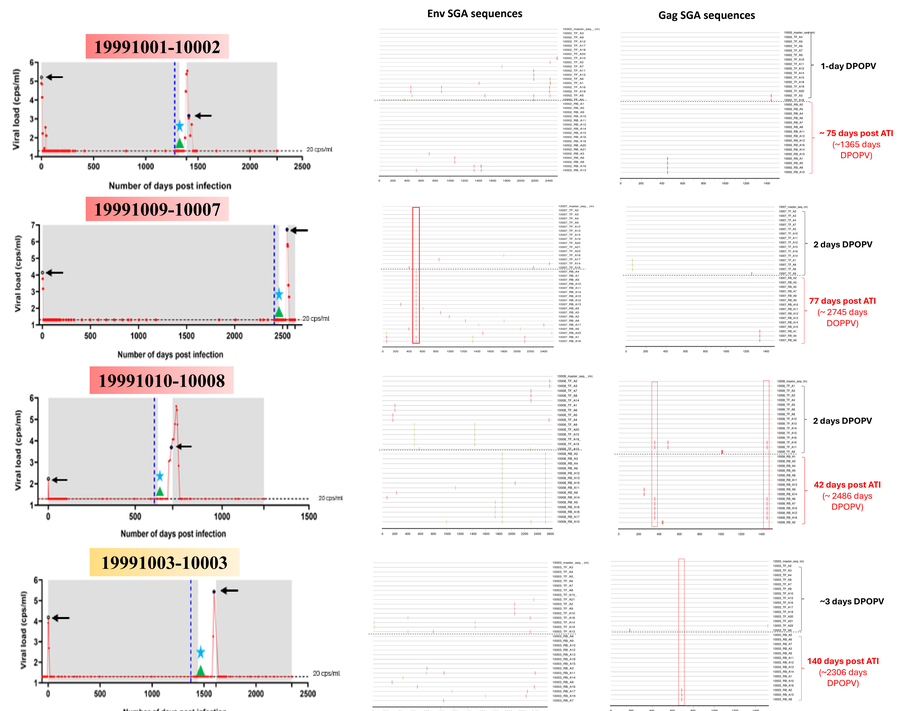
The viral rebound following ATI was not as a result of emergence of bNAb resistance or CTL escape

RESULTS

Figure 1: Phylogenetic tree representing env and gag SGA sequences generated at transmitter found and rebound time points



Genetic diversity was limited between TF and rebound viruses with few Env amino acid differences observed overall (median=1.5). Similarly, Gag sequences at TF and rebound were nearly identical. The virus from participant 10005 was obtained 336 days post-rebound and had diversified notably from the TF timepoint.



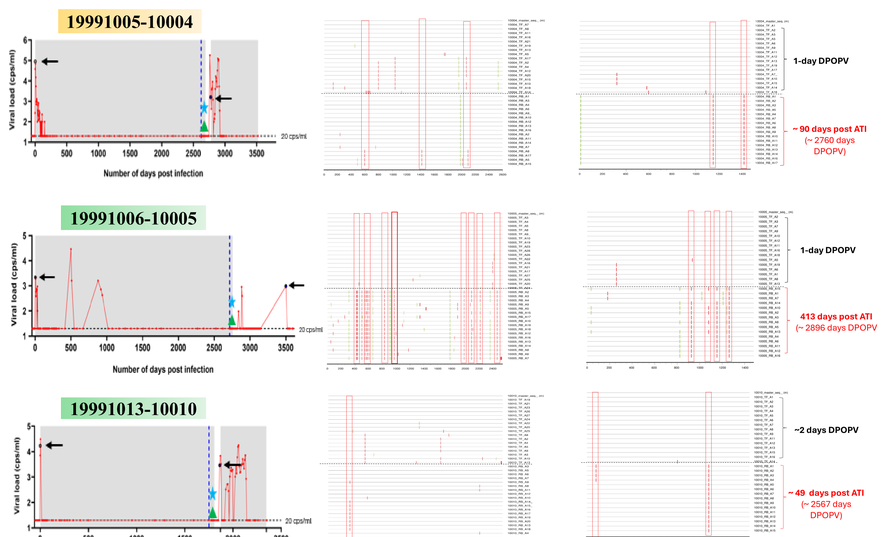


Table 1 and 2 : Bioinformatic analysis on the two bNAb epitopes

V1V2 region- **CAP256-V2LS**

	Timepoint	156 NXT	160 NXT	R166G/T	D167T	K169E/V	Q170K	K171E/R
	Cons.	**N**	**N**	**R**	**D**	**K**	**Q**	**K**
10002	TF	N	.	.	.	R	**K**	.
	RB	N	.	.	.	R	**K**	.
10007	TF	N	.	.	.	.	**K**	.
	RB	N	.	.	.	.	**K**	**V**
10008	TF	N	.	.	.	**E**	R	.
	RB	N	.	.	.	**E**	R	.
10003	TF	.	.	.	.	.	.	.
	RB	.	.	.	.	.	.	.
10004	TF	N	.	.	.	R	R	T
	RB	N	.	.	.	R	R	T
10005	TF	N	.	.	.	.	.	.
	RB	N	.	.	.	**E**	.	.
10010	TF	N	.	.	.	.	.	.
	RB	N	.	.	.	.	.	.

CD4bs region- **VRCO7-523LS**

Timepoint	197 NXT	234 NXT	276 NXT	N279D	R456D	R4766A
Cons	**N**	**N**	**N**	**D**	**R**	**K**
TF	.	.	.	N	.	.
RB	.	.	.	N	.	.
TF	N	.	.	N	.	R
RB	N	.	.	N	.	R
TF	N	.	.	.	.	R
RB	N	.	.	.	.	R
TF	.	S	.	N	.	R
RB	.	S	.	N	.	R
TF	.	.	.	N	.	.
RB	.	.	.	N	.	.
TF	.	M	.	.	.	.
RB	.	M	.	N	.	.
TF	.	.	.	N	.	.
RB	.	.	.	N	.	.

CONCLUSIONS

- Six participants were infected with a subtype C variant, while participant **10004** is infected with a recombinant strain of subtype A and C.
- In participant **10005**, an amino acid change associated with resistance in the V1V2 antibody binding region was observed in the rebound virus present 1 year after rebound.
- We have identified few amino acid changes in the rebound viruses that are not well characterized– these would require further experiments to confirm their influence on the virus's sensitivity to these two antibodies that were administered in the clinical trial.
- In most participants there was no amino acid changes between the two timepoints. CTL scape mutations were conserved between the two timepoints, except for participant **10010**.

PLAIN SUMMARY

- The virus at the rebound is the same as the virus at pre-ART.
- There were no mutations that were associated with the bNAbs that were administered during the clinical trial.

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