Linking inducible HIV-1 reservoir to rebound after treatment interruption

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Background

The origin of viral rebound remains elusive as only a few links between proviral sequences and rebound plasma viruses have been described. Here we characterized the translation- and replication-competent reservoirs of three individuals under ART and compared it to rebound plasma viruses detected during analytical treatment interruption (ATI).

Methods

Peripheral blood CD4 T cells were collected from 3 ART-treated individuals right before ATI. P24-expressing cells were single-cell sorted following latency reversal and near full-length proviral sequencing was performed. Replication-competent viral sequences were isolated from supernatant of positive quantitative viral outgrowth assay (qVOA) wells. During ATI, plasma was collected at the first detectable viral load (>1000 copies/mL) and either 5'- or 3'-half viral RNA genomes were isolated through single genome amplification.

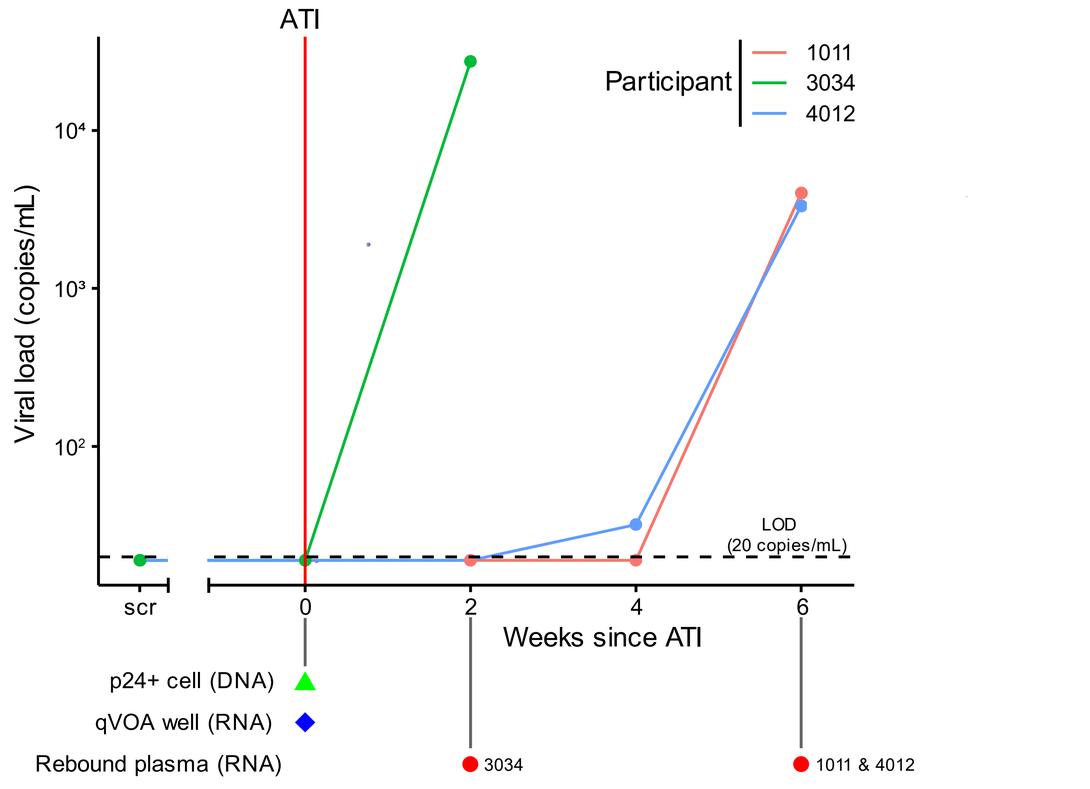

Figure 1: Viral loads measured during sample collection (screening timepoint and during ATI) and performed analysis of HIV-1 populations in plasma and CD4 T cells for all three participants.

Results

- We retrieved 20 sequences from positive qVOA wells, 30 proviral genomes from p24+ cells, 89 (median=32) 5'-half and 94 (median=32) 3'-half rebound plasma sequences acquired during ATI.
- Among distinct sequences retrieved from p24+ cells, 88% displayed defects in the packaging signal (PSI) region and/or major splice donor (MSD) site. Interestingly, among all qVOA and rebound sequences, none had PSI/MSD defects, suggesting their minor role in viral rebound and replication.
- One overlap between the translation- and replication-competent reservoir was observed, notably between the only p24+ cell with an intact PSI/MSD and one genome-intact qVOA sequence. Moreover, two overlaps were observed between viruses from qVOA wells and 5'-half rebound plasma sequences.

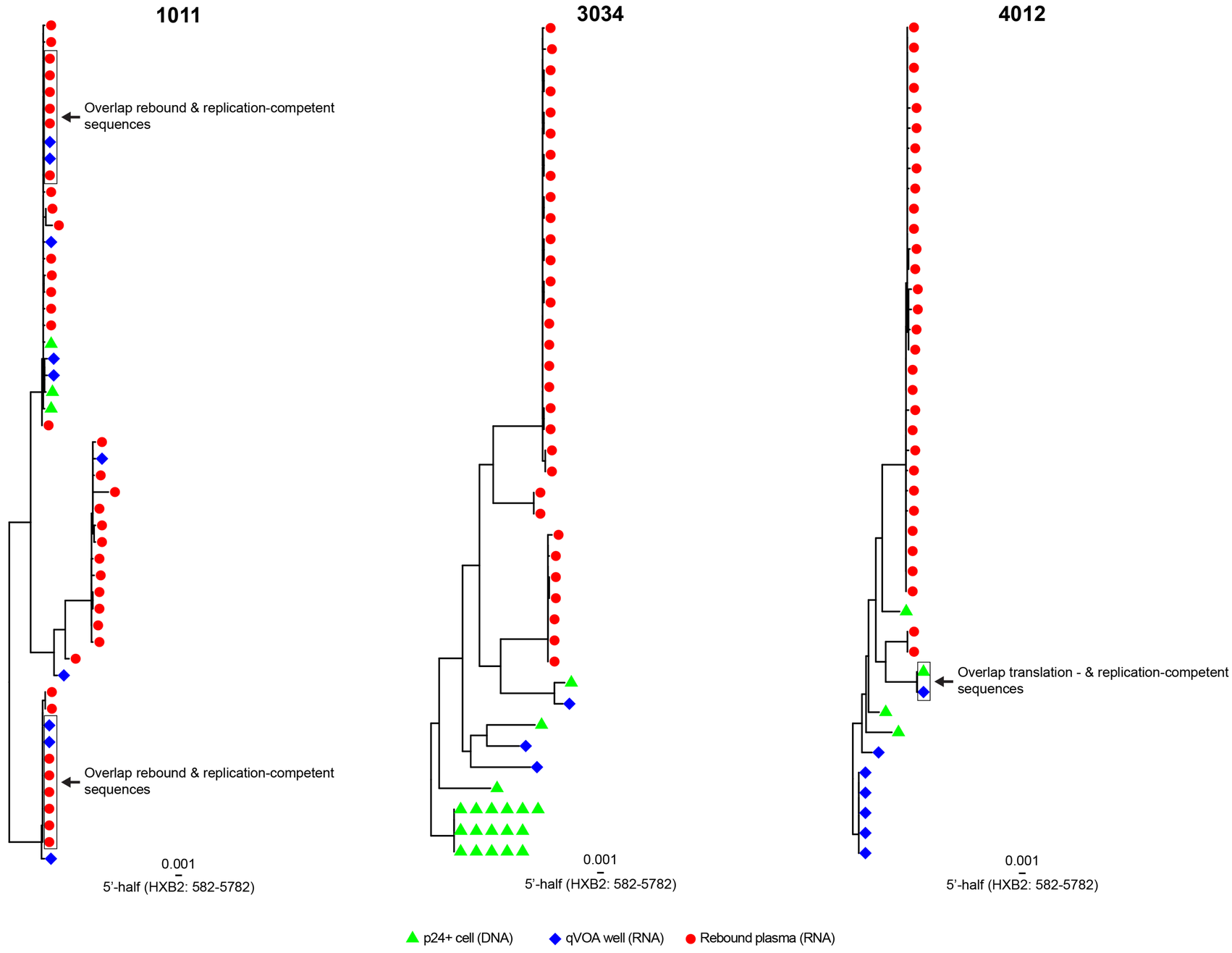

Figure 2: Phylogenetic trees for all three individuals including DNA sequences from p24+ cells and RNA sequences isolated from positive qVOA wells and plasma collected at viral rebound,

Conclusion

The direct origin of rebounding plasma virus remains hard to identify as only few overlaps were detected by comparing the translation and replication-competent fractions to plasma viruses collected during ATI, with no overlap between the three datasets. Yet, we report an overlap between an intact qVOA sequence and a provirus from a p24-expressing cell, confirming that some of the translation-competent proviruses are capable of inducing new cycles of replication.

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