Estimating HIV-1 Viremic Time From Reservoir Sequence Diversity With Uncertainty Quantification

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BACKGROUND

Research Question: Can we predict pre-ART viremic time (with confidence intervals) using diversity in on-ART reservoir sequences?

Importance: Accurate estimation of HIV viremic time, or the duration between infection and viral suppression, is valuable for:

- ✓ understanding HIV epidemiology,
- ✓ reservoir dynamics, and
- ✓ informing cure trials.

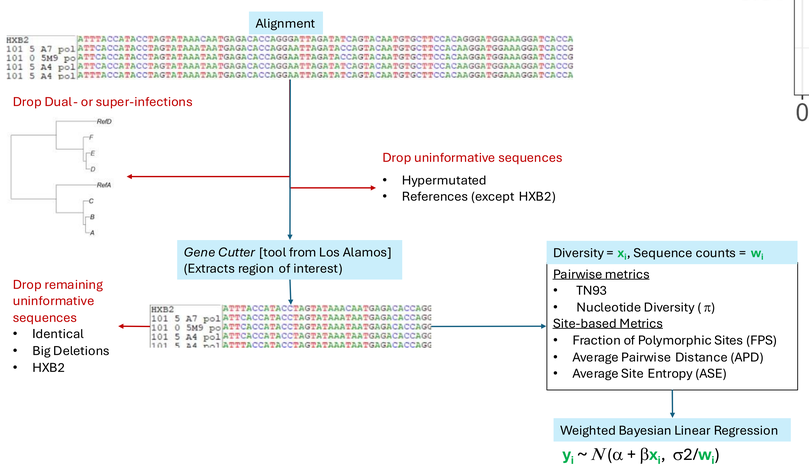
Gap: Traditional approaches rely on:

- Serological assays or CD4 counts, which can lack quantitative precision.
- Sequence-based estimates using diversity in pre-treatment plasma RNA address this limitation, but are increasingly limited in the era of immediate ART initiation.

METHODS

Participants and Sequences: Cohorts with:

1. Available reservoir proviral DNA or viral outgrowth sequences (1 or more timepoints).
2. Individuals with known viremic times (y_i), collectively spanning ≥ 2 years.



We developed and validated an approach that uses simple diversity metrics to estimate HIV Viremic Time, with confidence intervals.

RESULTS

- ✓ Rakai HIV Reservoir Cohort, Uganda: gp41 sequences (n = 22 participants) and RT (n = 21)
- ✓ Swedish HIV cohort, Brodin et al, *Elife*, 2016 [PMC5201419]: Matrix p17 (n = 10)

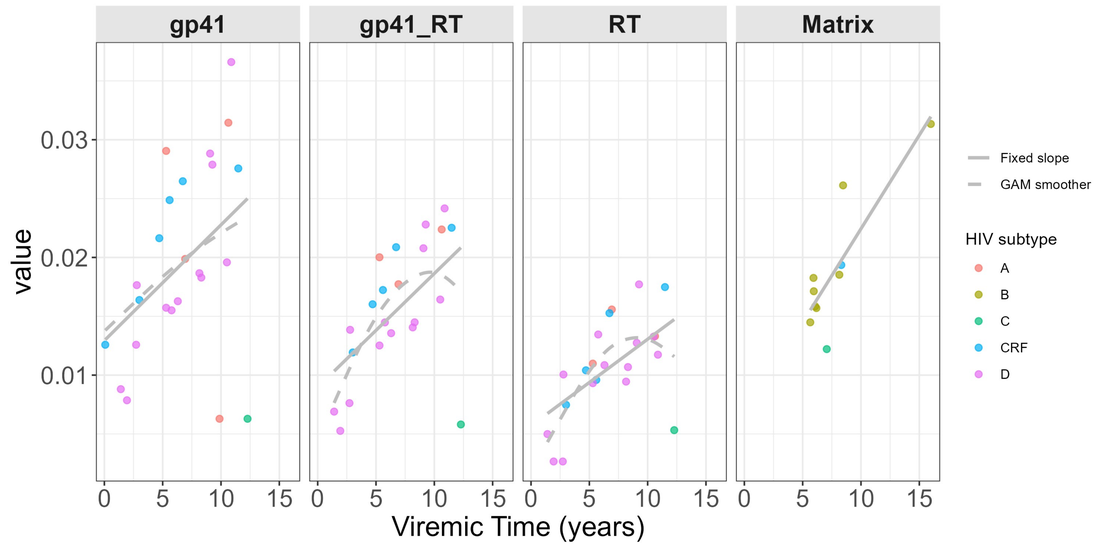


Figure 1: HIV-1 reservoir diversity and Viremic Time in years for participants in the training dataset. Diversity metric = π, similar trends for other Diversity metrics.

RESULTS (CTD)

- ➢ **Patterns**: Diversity increased with viremic time, across all metrics.
- ➢ **Best metric**: Nucleotide diversity (π) and TN93 distance (simple diversity metrics).
- ➢ **Best regions**: Average diversity in RT and gp41, followed by RT, the gp41. p17 showed weaker performance
- ➢ **Best weights:** log-transformed sequence counts (increased the precision of prediction)

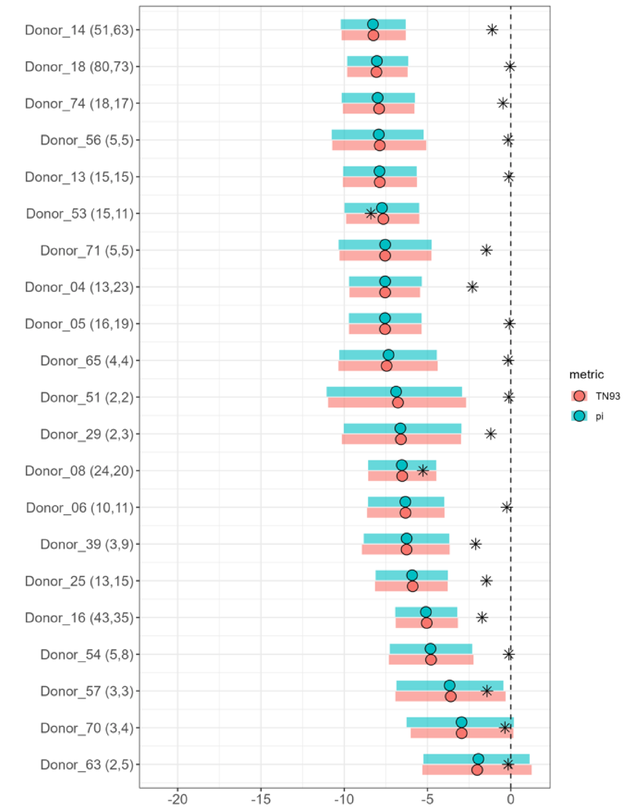


Figure 2: Validation of the best performing model on Rakai participants with known HIV diagnosis dates. X-axis is years relative to ART initiation. HIV diagnosis dates are marked with an asterisk (*).

CONCLUSIONS

- ✓ This new Bayesian approach can estimate viremic time from reservoir sequences, with credible intervals.
- ✓ Works across subtypes and chronic infection
- ✓ Uses simple diversity metrics

ADDITIONAL KEY INFORMATION

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PLAIN LANGUAGE SUMMARY:

By recovering and comparing hidden copies of HIV in the body, we can estimate how long someone was infected before treatment. This information can guide cure research.