Modeling of the Establishment and Dynamics of the Latent Reservoir During Acute HIV/SIV Infection

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BACKGROUND

A major barrier to curing HIV is the establishment of a latent reservoir early during acute infection. The seeding of the reservoir likely occurs within days after infection [1]. Viral genetic evidence from human cohorts suggests that the half-life of the reservoir during untreated infection may be shorter than the half-life estimated under antiretroviral therapy (ART) [2]. However, our quantitative understanding of the reservoir dynamics and the drivers of the dynamics during untreated infection remain limited.

In this work, we use mathematical modeling to explore the interplay between viral dynamics, host immune responses, and the factors that contribute to reservoir formation and turnover during acute infection.

METHODS

Datasets.

- The non-human primate dataset [3]: Longitudinal viral loads were measured from 32 macaques who were infected by SIV and treated with ART at day 3, 4, 5, 6, 7, 9 and 12 of infection. Reservoir sizes under ART were measured using IPDA.
- The human dataset [4]: Longitudinal viral loads were measured from 26 human participants where ART were initiated within 45 days of estimated infection. Reservoir sizes were measured using VOA.

Mathematical modeling.

Multiple viral dynamics models were developed using ordinary differential equations. They were then fitted to the longitudinal datasets from both NHP and humans using a nonlinear mixed effect modeling approach with Monolix v2024. Best models were selected using the Akaike Information Criterion (AIC).

REFERENCES

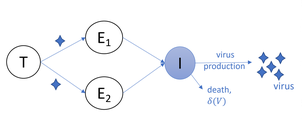
1. Whitney et al. (2014) Nature, 512(7512):74-7.
2. Abrahams, et al. (2019) Science translational medicine, 11(513), p.eaaw5589.
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Mathematical modeling shows that the SIV/HIV reservoir is highly dynamic during untreated acute infection, and the half-life of the reservoir becomes shorter and/or the probability of entering latency becomes smaller as viral load increases.

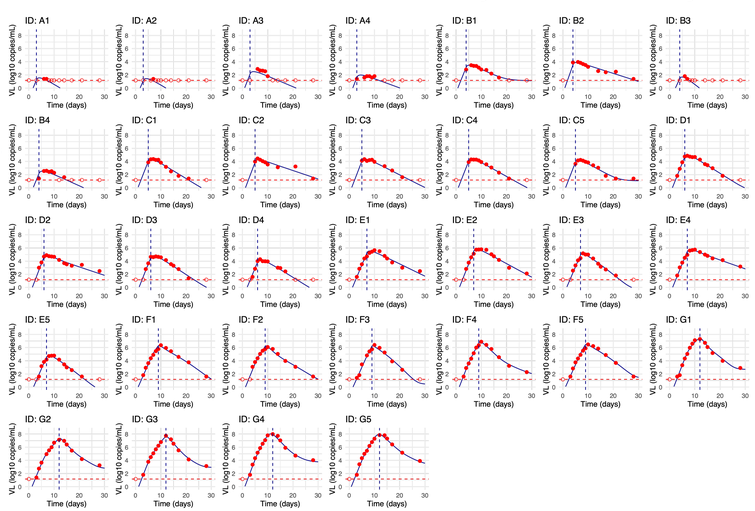
RESULTS

Constructing mathematical models to describe acute infection dynamics accurately

Model schematic

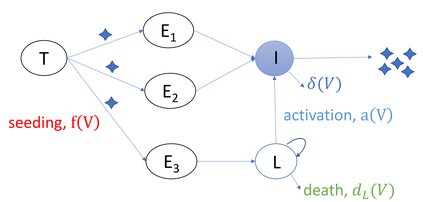


T: Target cells
E_1: Short-lived infected cells in the eclipse phase
E_2: Long-lived infected cells in the eclipse phase
I: Productively infected cells
V: Viruses



Extending the models to test hypotheses of reservoir dynamics

Extending the model with reservoir dynamics



1. VL dependent seeding model: $f(V) = \frac{Km}{Km+V} f_{max}$

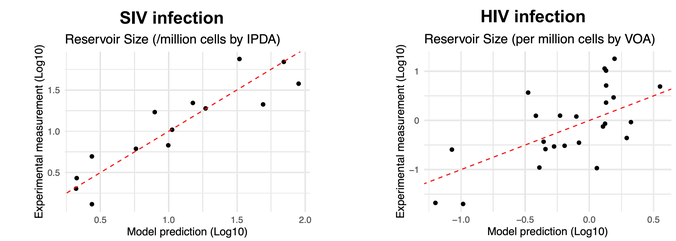
2. VL dependent death model: $d_L(V) = d_{L,0} + \frac{V}{Km+V} d_{max}$

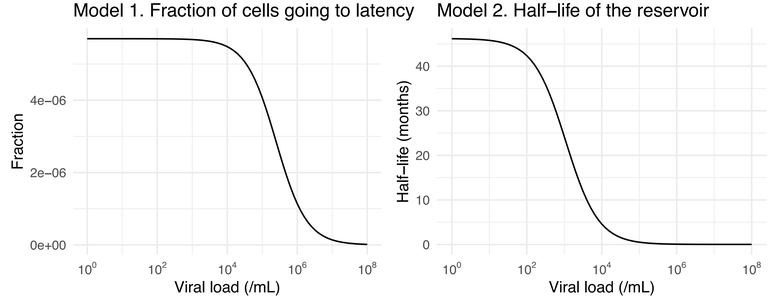
3. VL dependent activation model: $a(V) = a_0 + \frac{V}{Km+V} a_{max}$

Models assuming either VL dependent seeding (1st model) or VL dependent reservoir turnover (2nd and 3rd model) describes SIV/HIV reservoir data well

AIC	VL dependent seeding model	VL dependent death model	VL dependent activation model	VL independent model
NHP data	**541.8**	**542.4**	**539.8**	570.4
Human data	**-23.7**	**-22.4**	**-22.8**	-3.6

Model-predicted reservoir sizes agree well with measured reservoir sizes





CONCLUSIONS

Our results suggest that during untreated acute infection, either the half-life of the reservoir shortens or the probability of entering latency decreases as viral load increases.

ADDITIONAL KEY INFORMATION

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PLAIN LANGUAGE SUMMARY

By fitting mathematical models to viral load and reservoir size data, we found that the SIV/HIV reservoir is highly dynamic during untreated acute infection, and the reservoir is seeded slower and/or turns over faster as viral load increases.