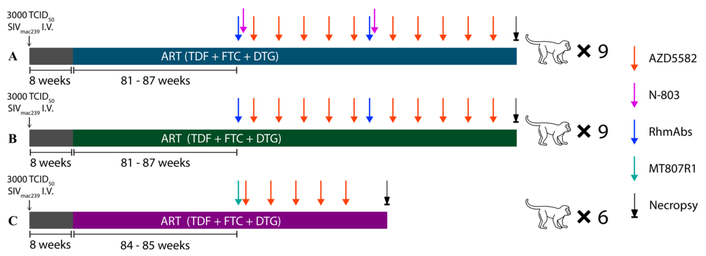
Modeling reveals AZD5582-reactivated cells differ from productively infected cells

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BACKGROUND

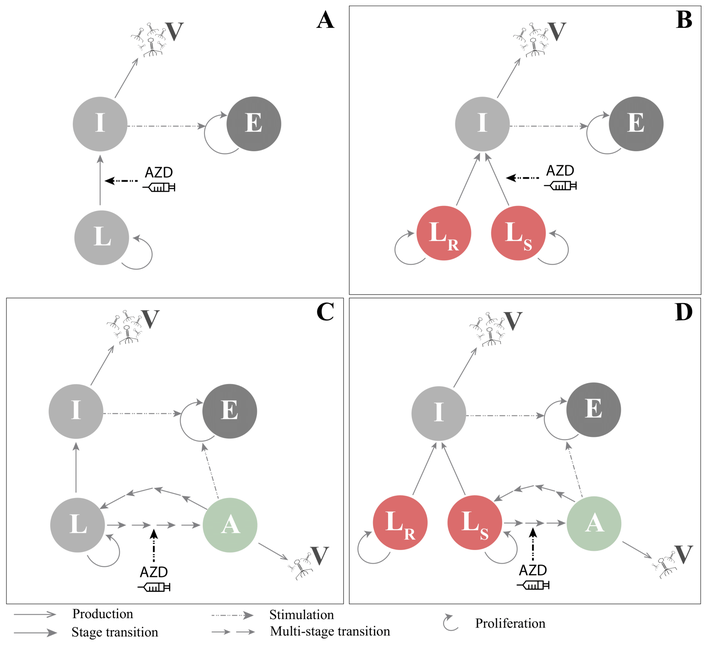


Experimental Design from Dashti et al. and Mavigner et al.

Observation: AZD5582 (AZD) reactivates latently infected cells, leading to a 2–3 log increase in on-ART viral load; however, the reduction in SIV CA-DNA is typically less than 1 log.

Hypothesis: AZD5582-reactivated cells differ from productively infected cells.

METHODS



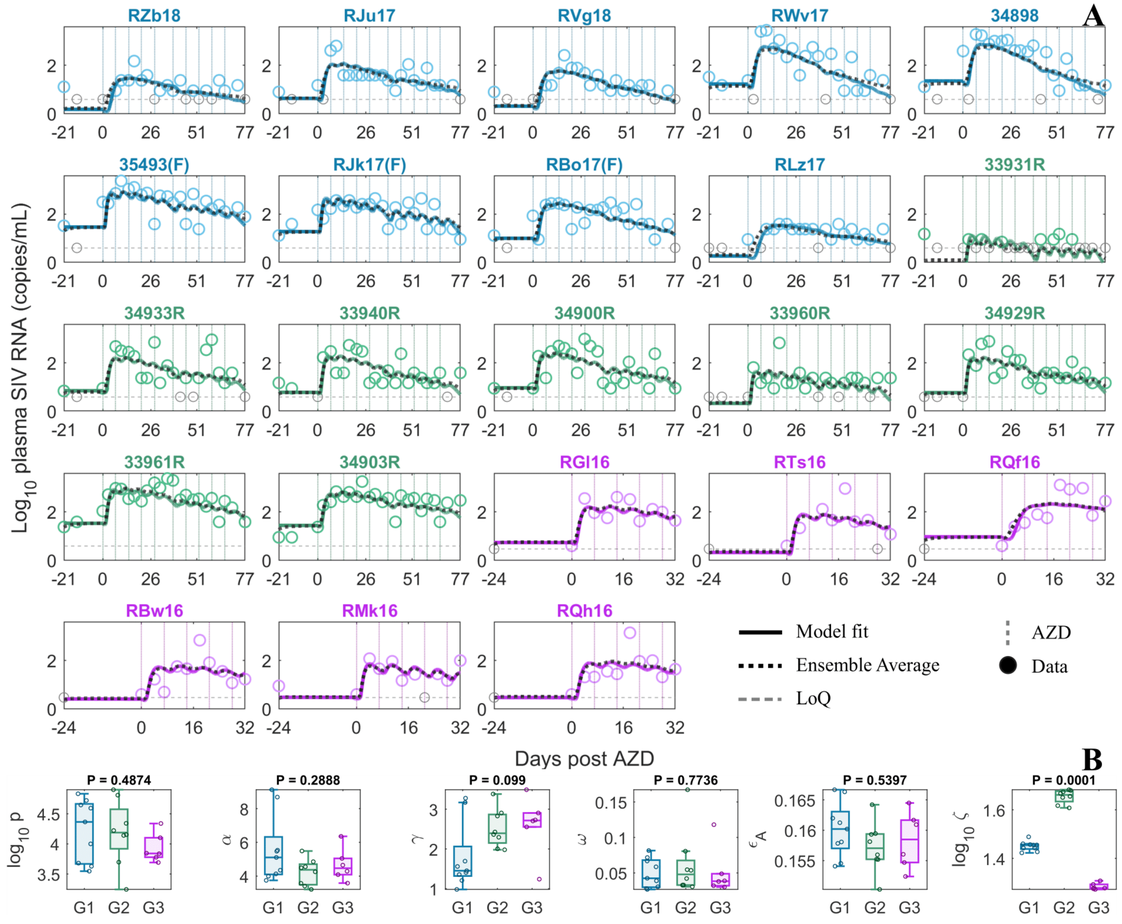
Baseline Model Variations

Build **an ensemble of models** to test hypothesis.

Data fitting uses nonlinear-mixed effect model (Monolix).

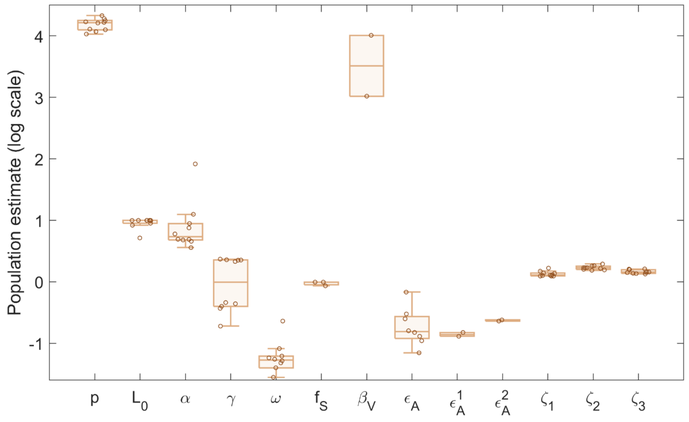
Mathematical models predict AZD5582-reactivated cells exhibit reduced virion production and lower death rate by 32 - 89%.

RESULTS



Best Model Fit and Group Parameter Estimates

A model based on variation **C (Baseline Model Variations)** is the best fit model.



Ensemble population parameter estimates

CONCLUSIONS

- AZD5582-reactivated cells produce virus, die, and stimulate immune response at a lesser rate than productively infected cells.
- AZD5582-reactivated cells may return to latency.
- Such cells may be temporarily refractory to AZD5582.
- Results robust across models in the ensemble.

ADDITIONAL KEY INFORMATION

1. Dashti, Amir, Sophia Sukkestad, Anna M. Horner, Margaret Neja, Zain Siddiqi, Chevaughn Waller, Jordan Goldy et al. Nat Med 29, no. 10 (2023): 2535-2546.
2. Mavigner M, Liao LE, Brooks AD, Ke R, Mattingly C, Schoof N, et al. CD8 Lymphocyte Depletion Enhances the Latency Reversal Activity of the SMAC Mimetic AZD5582 in ART-Suppressed Simian Immunodeficiency Virus-Infected Rhesus Macaques. J Virol 2021;95:e01429-20.

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PLAIN LANGUAGE SUMMARY

Mechanistic modeling explains the limited reservoir reduction despite robust AZD5582-mediated latency reversal. Models predict that AZD5582-reactivated cells produce virus, die, and stimulate immune response at a lesser rate than typical productively infected cells.