Quantifying Mechanisms of HIV Immunotherapy Using Models of Post-Treatment Viral Rebound

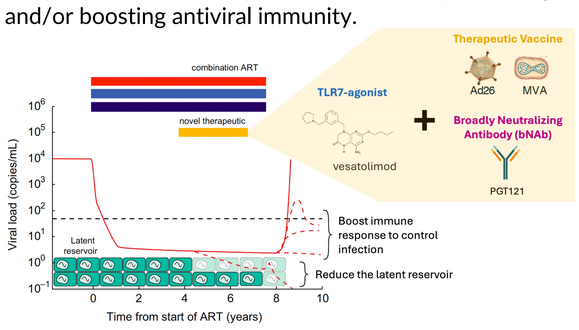
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Introduction

HIV can be treated but not cured with cART

The current standard of care for HIV, combination antiretroviral therapy (cART), must be taken life-long: if stopped, viral rebound typically occurs within weeks due to an ineffective immune response against re-activated latently infected cells. HIV cure strategies therefore focus on immunotherapies that delay or prevent rebound by reducing the latent reservoir and/or boosting antiviral immunity.

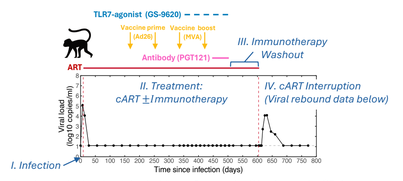


Preclinical studies have demonstrated induction of SIV or SHIV remission by immunotherapy

Three immunotherapies have previously been evaluated in non-human primate (NHP) models of HIV[1-4]:

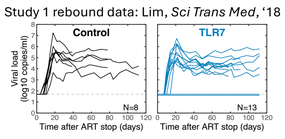
- TLR7-agonist (vesatolimod), which activates the innate antiviral immune response
- Therapeutic vaccine, which is given during infection
- Broadly neutralizing antibody (bNAb) PGT121, which neutralizes diverse HIV strains

Rhesus macaques infected with SIV (studies 1&2) or SHIV (studies 3&4) received cART ± single/combination immunotherapy, and viral rebound was monitored after treatment washout. Many animals showed altered rebound kinetics, and a subset achieved remission:

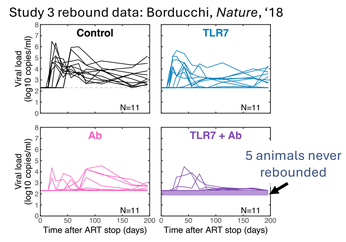


Time from infection to cART start (I→II): 9 weeks for S1, ~1 week for S2-4

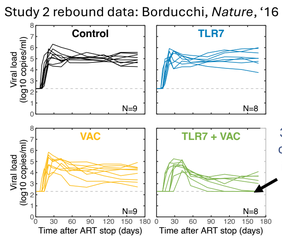
Study 1 rebound data: Lim, *Sci Trans Med*, '18



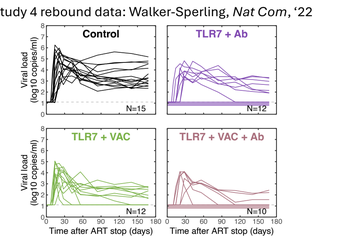
Study 3 rebound data: Borducchi, *Nature*, '18



Study 2 rebound data: Borducchi, *Nature*, '16



Study 4 rebound data: Walker-Sperling, *Nat Com*, '22



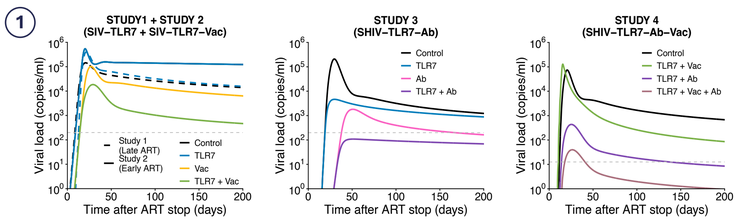
Objectives:

- Determine how each therapy alters rebound kinetics (i.e., by reducing the latent reservoir and/or boosting the antiviral immune response)
- Identify synergistic drug effects
- Predict single/combination immunotherapy efficacy for preventing or delaying rebound in people with HIV

Mechanistic Insights into HIV Immunotherapies

We identified significant differences in biological processes (②-⑦) that can explain treatment-group differences in rebound kinetics following immunotherapy (①)

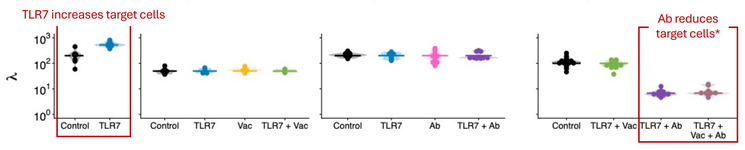
①



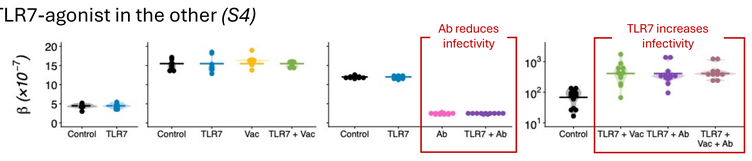
Individual agents can act on both the latent reservoir and immune response and can influence early viral growth

Distribution of individual parameter estimates by treatment group:

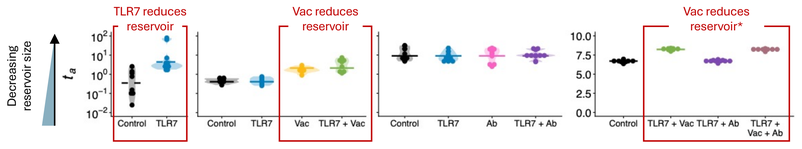
② **Target cell availability (λ):** ↑ 2.6-fold by TLR7-agonist in cohort with late ART initiation *(S1)* and ↓ 15-fold by bNAb in one of the SHIV studies *(S4)**



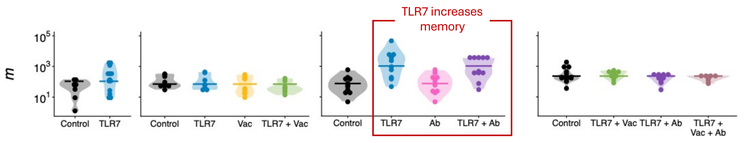
③ **Viral infectivity (β):** ↓ 5-fold by bNAb in one of the SHIV studies *(S3)* and ↑ 6-fold by TLR7-agonist in the other *(S4)*



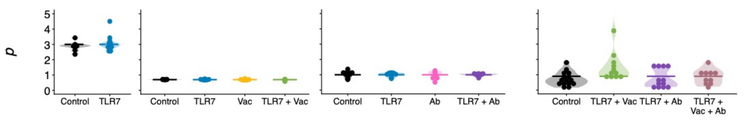
④ **Latent reservoir size ($\propto t_a^{-1}$):** ↓ 13-fold by TLR7-agonist in cohort with late ART initiation *(S1)*. ↓ by Vaccine 5-fold in SIV *(S2)* and 1.2-fold in SHIV *(S4)**, not meaningfully affected by bNAb



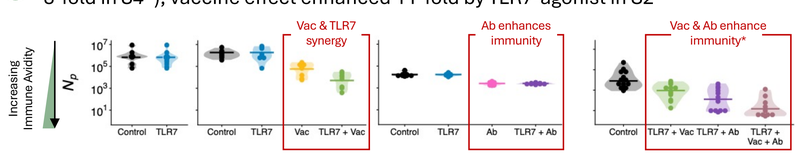
⑤ **Immune memory precursors (m):** ↑ 14-fold by TLR7-agonist in one SHIV cohort *(S3)*



⑥ **Immune effector proliferation (p):** Not meaningfully influenced by therapy



⑦ **Immune avidity (N_P):** ↑ by bNAb (7-fold in *S3*, 63-fold in *S4**) or Vaccine (33-fold in *S2*, 8-fold in *S4**), vaccine effect enhanced 11-fold by TLR7-agonist in S2



** Experimental design of Study 4 prohibits separating the effect of Ab or Vac from their interaction with TLR7-agonist*

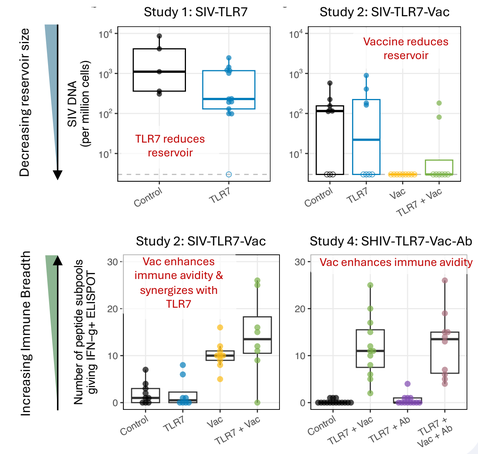
Independent measurements of reservoir size and immune response support several inferred treatment effects

SIV DNA in PBMCs following therapy:

- Lower in TLR7-treated *(S1)* and vaccinated animals *(S2)*, consistent with inferred drug effects reducing reservoir ④

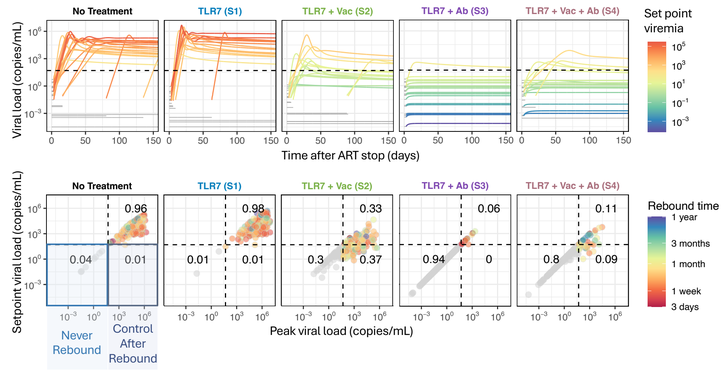
Total breadth of the immune response to SIV/SHIV Gag, Pol and Env peptides:

- Elevated in vaccinated animals, consistent with inferred vaccine effects increasing immune avidity ⑦
- No difference in bNAb-treated animals, suggesting an alternative mechanism for its effect on immune avidity ⑦



Translating NHP-Derived Effects to Predict Efficacy in Humans

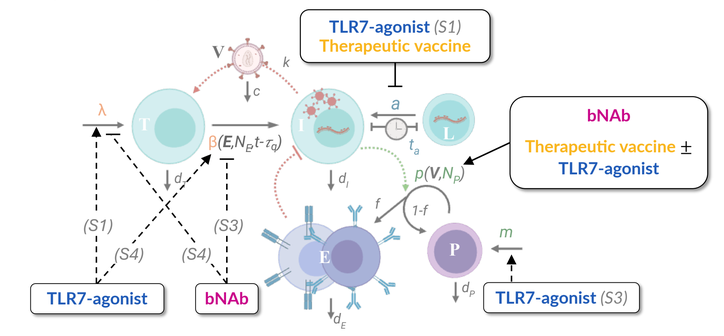
We simulated human trials by fitting the model to HIV rebound data from untreated patients, sampling parameters from the posterior, and applying NHP-derived treatment effects.



Combination therapy including bNAb induces durable viral control in the majority of virtual patients

Key Findings

Our analysis quantified mechanisms of action for three complementary immunotherapies:



Therapeutic vaccination: **reduces the latent reservoir** ④, and **enhances the immune response** to control infection by ↑ effector activation ⑦

BNAb: **slows the rate of early growth** upon viral rebound by ↓ viral infectivity ③ or target cells ②, **enhances the immune response** by ↑ effector activation ⑦; no significant effect on the latent reservoir ④

TLR7-agonist effects are **context-dependent**, and **may act against its therapeutic potential** by facilitating viral growth:

With late ART against SIV *(S1)*, **reduces the latent reservoir** ④ and **increases target cell availability** ②

With early ART, **enhances the effect of vaccination** on effector activation against SIV *(S2)* ⑦, **increases immune memory** in one SHIV cohort *(S3)* ⑤, and **increases viral infectivity** in another *(S4)* ③

No synergy detected between bNAb & TLR7-agonist on the **latent reservoir** – the hypothesized "kick-and-kill" effect was not supported

Combination therapy may **induce HIV remission in patients**, but **patients may rebound before establishing control:** cure trials may need **altered ART restart criteria to capture remission**

Mathematical Model and Parameter Inference Framework

We fit rebound data from the NHP studies above to a basic viral dynamics model (target cells T, infected cells I, virus V), extended with latent cell (L) reactivation and an antigen-driven immune response: precursor (P) cells expand to effector (E) cells that inhibit new infection.

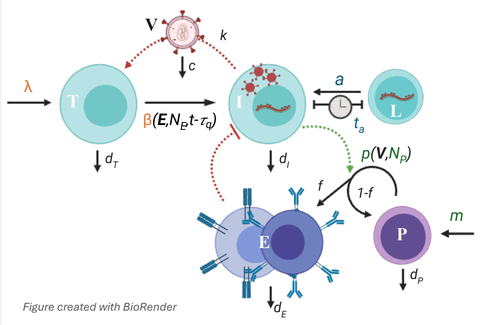


Figure created with BioRender

$$\dot{T} = \lambda - \beta TV - d_T T$$

$$\dot{I} = \frac{\beta}{1+(E/N_E)} T(t-\tau_q)V(t-\tau_q)e^{-d_T \tau_q} + a - d_I I$$

$$\dot{P} = m + p(1-f)\frac{V}{V+N_P}P - d_P P$$

$$\dot{E} = pf\frac{V}{V+N_P}P - d_E E$$

$$V = \frac{k}{c}I, \quad a = f(t_a^{-1})$$

For each NHP study, we used mixed-effects modeling (*Monolix*) to estimate parameter distributions for target cell availability (λ), viral infectivity (β), time to latent reactivation (t_a), and immune effector activation/expansion (m, p, N_P) - **identifying which process each therapy modulates and testing for drug synergies** via mean parameter differences between groups (*treatment effects*).

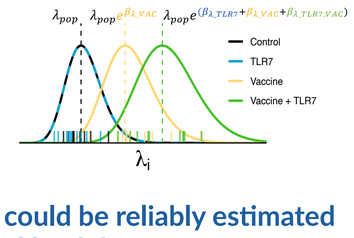
$$\log(\lambda_i) = \log(\lambda_{pop}) +$$

Effect of drug 1: $\beta_{\lambda\_TLR7}[TLR7 = 1] +$

Effect of drug 2: $\beta_{\lambda\_VAC}[VAC = 1] +$

Synergistic effect: $\beta_{\lambda\_TLR7:VAC}[TLR7:VAC = 1] +$

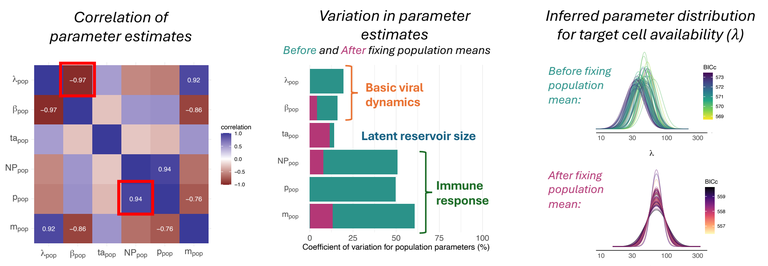
Random Effect: $\eta_{\lambda,i} \quad \eta_{\lambda,i} \sim N(0, \Omega_\lambda)$



We confirmed treatment effects could be reliably estimated from available viral load data

1) *Assessing practical identifiability*

- Repeated fitting from different initial guesses[5-7] revealed mutual non-identifiability between two viral dynamics and two immune parameters
- Fixing one parameter's mean per pair via profile likelihood improved estimate consistency across fits:



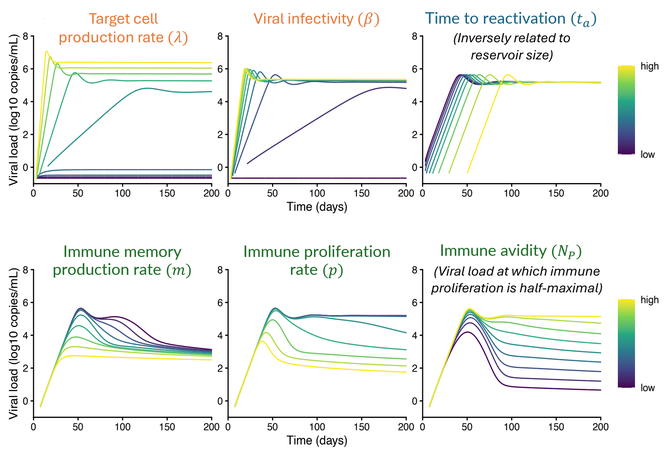
2) *Building the treatment effect model*

Limited statistical power precludes fitting the full treatment effect model. We identified significant effects via covariate model building (SCM) with:

- Safeguards against overfitting
- Comparison of the best-fit model to alternative models defined from intermediate model building steps
- Comparison to pre-defined biological hypotheses



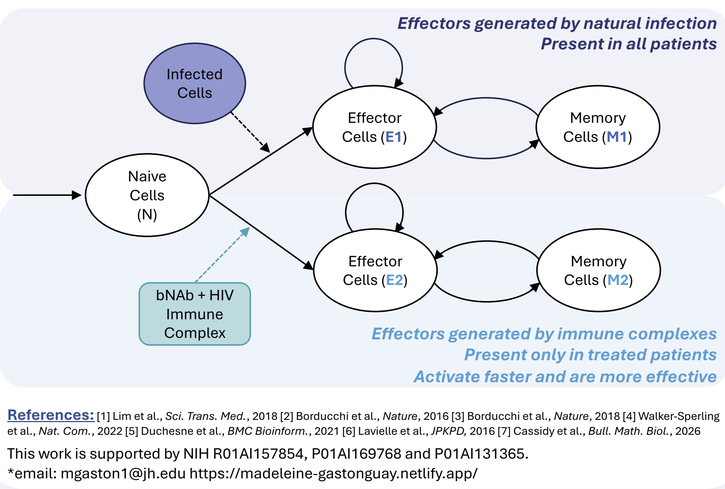
The model recapitulates observed viral rebound kinetics



Univariate sensitivity analysis reveals that target cell availability (λ) and viral infectivity (β) similarly drive early growth and peak viremia. Immune proliferation (p) and avidity (N_P) both influence set-point viremia.

Future Directions

How do bNAbs enhance the antiviral immune response? How should bNAbs be optimally administered?



References: [1] Lim et al., *Sci. Trans. Med.*, 2018 [2] Borducchi et al., *Nature*, 2016 [3] Borducchi et al., *Nature*, 2018 [4] Walker-Sperling et al., *Nat. Com.*, 2022 [5] Duchesne et al., *BMC Bioinform.*, 2021 [6] Lavielle et al., *JPKPD*, 2016 [7] Cassidy et al., *Bull. Math. Biol.*, 2026

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