A reservoir-coupled therapeutic interfering particle can assist immune-mediated HIV-1 post-treatment control: a within-host modeling study

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Illustrative within-host modeling study / hypothesis generation — not validated experimental or clinical findings, and not medical advice. Preprint: Zenodo DOI 10.5281/zenodo.20801699.

Abstract

Background. Therapeutic interfering particles (TIPs) are engineered, conditionally-replicating defective HIV-1 genomes proposed as single-administration antivirals. Existing within-host models treat active infection; Dodd & de Boer (2025) found that an immune response *reduces* the parameter range over which a TIP is effective. Whether a TIP helps or hurts the immune-mediated cure — durable ART-free remission, governed by the latent reservoir and post-treatment control (PTC) — has not been modeled. **Methods.** We add a latent replication-competent reservoir and an ART → analytical treatment interruption (ATI) schedule to a within-host TIP model, with stochastic (tau-leaping) dynamics, calibrated to clinical rebound timing and PTC fractions (A5345, ACTG pooled, CHAMP, RIO). We introduce one coupling parameter, χ, the fraction of reservoir reactivations that co-introduce the TIP, and test across three structurally distinct immune models. **Results.** A non-coupled TIP (χ=0) is neutral to PTC and recovers the de Boer active-infection limit. A TIP coupled to reservoir reactivation raises durable control monotonically in χ, helps most for marginal controllers, and shows no systematic backfire — robust across global parameter sampling and all three immune models, and protective even under active immune exhaustion. A derived effective reproduction number, $R\_eff = R_0 \cdot d/(d+\kappa)$, explains the effect: coupling lowers the immune threshold for control. **Conclusions.** We predict that a reservoir-co-residing TIP could assist immune-mediated PTC, testable in an ATI animal model. This is an illustrative hypothesis conditional on the coupling assumption.

1. Introduction

Antiretroviral therapy (ART) suppresses HIV-1 but does not eliminate the latent reservoir, so treatment is lifelong and the virus rebounds on interruption. A leading cure goal is durable ART-free remission — *post-treatment control* (PTC), in which the reservoir persists but rebound is contained after ART interruption. Its mechanism is multifactorial and not settled: PTC has been associated with a smaller reservoir, cytotoxic CD8 responses, NK-cell activity, and humoral immunity, with the dominant correlate differing between individuals and settings (Mesquita & Li 2024; Blazkova et al. 2021). CD8 control is one contributor — clearest under early ART and

antibody/combination immunotherapy (Passaes et al. 2024) — but the canonical spontaneous-PTC cohort (VISCONTI) controls with *weak* CD8 responses, and broadly-neutralizing-antibody trials such as RIO act substantially through antibody and reservoir effects (the "vaccinal" effect; Tipoe & Fidler 2022). We therefore model the immune axis generically, as cytotoxic-effector killing of antigen-expressing cells (CD8 and/or NK/ADCC), not a CD8-specific pathway.

A therapeutic interfering particle (TIP) is an engineered defective HIV-1 genome that replicates only in cells co-infected by wild-type (WT) virus, diverting WT packaging to itself; a single dose reduced SHIV viremia by >3 $\log_{10}$ (>1000-fold) in non-human primates, the TIP conditionally replicated for

> 6 months, and "TIP-treated animals exhibited significantly improved immune responses, with no evidence of increased inflammation" (Pitchai et al., *Science* 2024) — an empirical hint of TIP–immune interplay that has not been modeled. *In vitro*, the same study found that upon ART cessation the TIP reactivated together with HIV and interfered with its outgrowth — a non-clinical hint of the reservoir co-reactivation this model formalizes as the coupling χ (the in vivo NHP work included no ART-interruption arm).

Within-host TIP theory has, to date, treated active infection only. Dodd & de Boer (2025, *J Theor Biol*) derive the TIP basic reproduction number and show that an immune response against infected cells "drastically decreases the range of parameter values for which therapy is effective" — i.e. immunity hurts the TIP's suppression of active virus. Their model contains no latent reservoir and no treatment interruption. The cure-relevant question — does a TIP help or hurt *immune-mediated post-treatment control*? — therefore remains open. We address it.

2. Model and methods

We use a Perelson-class within-host model (target cells T; WT-only, TIP-only, and dually-infected productive cells; quasi-steady free virus), with WT basic reproduction number $R_0 = b \cdot T_0 \cdot p/(d \cdot c) = 8.70$. To this we add (i) a latent replication-competent reservoir L_lat that reactivates to a productive cell, (ii) a defective antigen-presenting clone (Simonetti-type) that primes CD8 independently of active WT, and (iii) an ART → ATI schedule (chronic infection → ART suppression → interruption). Dynamics are stochastic (tau-leaping); durable post-treatment control is defined as active-infection extinction with the reservoir persisting (functional, not sterilizing).

The central new parameter is the **coupling** $\chi \in [0,1]$: the fraction of reservoir reactivations that emerge as TIP-carrying (dual) cells rather than pure WT cells — i.e. how well an engineered TIP co-resides in / co-reactivates with the reservoir. $\chi=0$ reproduces a non-interacting (de Boer-limit) TIP; $\chi=1$ is a fully reservoir-coupled TIP.

We test robustness across three structurally distinct immune models: quasi-steady killing with a maintained antigen floor; a dynamic waning effector memory (no floor); and an actively-exhaustible memory (burden-driven degradation). In all three, the killed compartment is antigen-expressing productive cells, so the killing rate κ denotes cytotoxic-effector pressure generically — CD8 and/or NK/ADCC — which keeps the result independent of the unresolved question of which effector dominates post-treatment control (a deliberate generalization; κ is antigen-driven, fitting adaptive CD8 best). The rebound clock and PTC fractions are calibrated to clinical data (untreated/placebo ATI median ~16–22 d; ACTG rebound-by-week-4/12; CHAMP spontaneous PTC ~4–13%; RIO bNAb durable control ~24% — the 7/29 ATI sub-analysis, vs ~21% (7/34) by the trial's primary endpoint, HR 0.09). Parameters and equations are documented in `analysis/METHODS.md`; all code is open and a single script (`analysis/verify_claims.py`) re-derives every headline number, including a reproduction of the Dodd & de Boer result.

3. Results

3.1 A non-coupled TIP is neutral; coupling flips it to helpful. With the reservoir modeled but the TIP decoupled ($\chi=0$), a TIP does not change post-treatment control — recovering the de Boer "immunity decides" outcome. Coupling the TIP to reservoir reactivation makes control rise **monotonically** with χ: at a marginal immune level, durable control climbed 22% → 32% → 40% → 45% → 58% as χ went 0 → 0.25 → 0.5 → 0.75 → 1, with CD8 maintained throughout (the coupled TIP intercepts the rebound without starving immunity).

3.2 The benefit is robust across immune structure, with no systematic backfire. The result holds across all three immune models. Under a wear-down-able memory, a coupled TIP still helped (7/9 regimes) and did not harm control. Under active, burden-driven immune exhaustion combined with a stealthy (low-visibility) TIP — the configuration most likely to backfire — there was still no backfire: the TIP helped *most* there (e.g. 17% → ~65% control), because by suppressing the rebound it keeps the antigen burden low and **spares the immune response from exhaustion**. (Across the broader phase scans, occasional small negative nudges of ≤1 point appear within stochastic noise — see `analysis/AUDIT2.md` — but no configuration showed a systematic backfire.)

3.3 Phase boundary and reduction to prior work (Fig. 1). As a continuous function of χ and immune strength, the TIP effect reduces to the de Boer limit at $\chi=0$ and grows with χ; the benefit is concentrated at *intermediate / marginal* immune strength (where control is on a knife-edge) and requires substantial coupling ($\chi \gtrsim 0.6$).

3.4 Global sensitivity. Across 30 Monte-Carlo draws varying all six key parameters jointly, the coupled-TIP effect helped (63%) or was neutral (37%) and **harmed in 0%** — no backfire across the sampled space. The dominant driver is immune strength (the TIP helps where immunity is marginal); the reservoir's reactivation timing barely matters.

3.5 A derived criterion (Fig. 2). Post-ART, a reactivating WT lineage has effective reproduction number **$R_{eff(WT)} = R_0 \cdot d/(d+\kappa)$** ($\kappa$ = immune killing rate); control corresponds to sub-criticality, $R_{eff} < 1$, i.e. $\kappa > \kappa_{crit} = (R_0 - 1)d = 7.70$/day. A coupled TIP shifts the effective control threshold *down* by $\Delta(\chi) \geq 0$. This single inequality explains all three empirical findings: the benefit is concentrated just below threshold (marginal immunity), widens with coupling, and — since $\Delta \geq 0$ — never raises the threshold (no backfire). In a static-κ model where R_{eff} is exact, the TIP effect is large in the sub-/near-threshold band and ceilings out once $R_{eff} < 1$, exactly as predicted.

4. Discussion

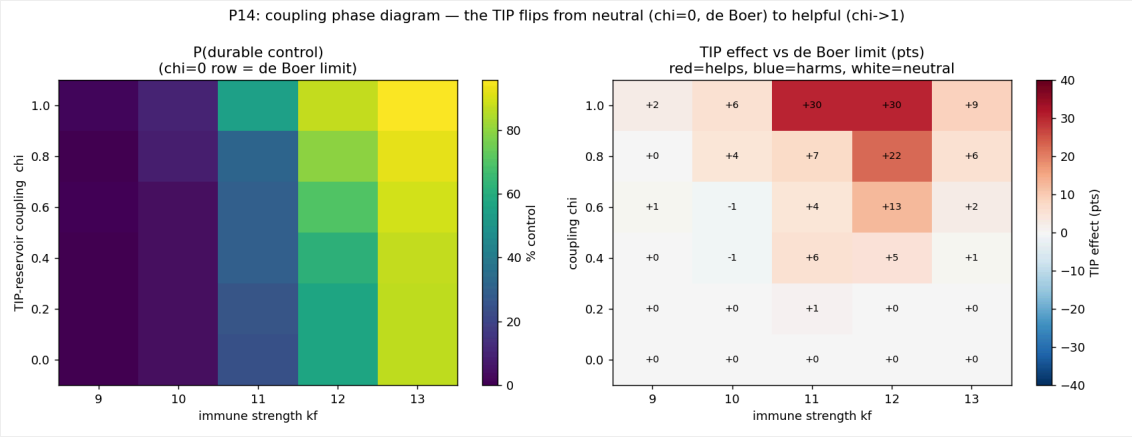
A TIP modeled against the latent reservoir in a post-treatment-control setting is, to our knowledge, new; the existing TIP literature treats active infection, and reservoir/ATI models contain no TIP. Our result does **not** contradict Dodd & de Boer: at zero coupling we reproduce their finding, and the help appears only in a regime (reservoir + ATI) and via a mechanism (TIP–reactivation coupling) their model does not contain. The mechanism is intuitive: on the active-infection axis a TIP and immunity *compete* over the same wild-type, but on the reservoir-control axis a coupled TIP and immunity *cooperate* — the TIP caps each reactivation burst while immunity clears it, and by keeping the burden low it protects immunity from exhaustion.

Falsifiable prediction. A TIP engineered to co-reside in / co-reactivate with the latent reservoir (high χ) should improve durable post-treatment control after ATI, while a non-reservoir-coupled TIP ($\chi \approx 0$) should be neutral; the benefit should be largest in intermediate/marginal controllers and require substantial coupling. Direct test: a humanized-mouse or NHP ATI study comparing (a) no TIP, (b) a standard TIP, (c) a reservoir-targeting TIP, measuring time-to-rebound and control fraction; the model predicts (c) > (b) ≈ (a). A null result in arm (c) would falsify the coupling mechanism.

Limitations. This is an illustrative within-host model: parameters are illustrative beyond calibrated rebound timing; “control” is functional (active-infection extinction with the reservoir persisting), not sterilizing; coupling χ is a coarse single knob, not a mechanistic co-packaging model; $\Delta(\chi)$ is shown ≥ 0 numerically, not in closed form (a full next-generation-matrix treatment of the nonlinear TIP interference is the natural next step). The clinical target is itself uncertain: post-treatment control is multifactorial and its mechanism unresolved — reservoir size, CD8, NK, and humoral immunity are all implicated and vary by individual — so the effector-killing axis here is a deliberate generalization, not a validated CD8 mechanism; whether immunity stays primed through suppression (the antigen “floor” that makes control achievable, modeled via defective-clone antigen presentation) is a further load-bearing assumption; and there is currently no evidence that a therapeutically delivered TIP localizes to the pre-existing replication-competent reservoir, so $\chi > 0$ is an engineering goal, not an established property (see `analysis/AUDIT3.md`). The conclusions are conditional on the coupling assumption. A multi-agent adversarial audit (in the repository) retracted several of the author’s own earlier overclaims and is the reason the framing is “conditional/assist,” not “cure.”

Figures

- **Fig. 1** — Coupling phase diagram: P(durable control) and the TIP effect vs (coupling χ, immune strength).



analysis/p14_coupling_phase.png

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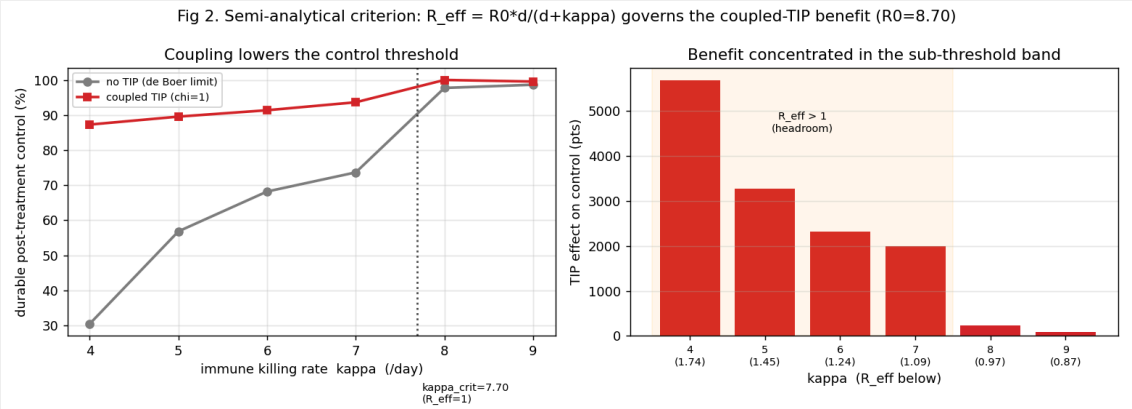
- **Fig. 2** — Semi-analytical criterion: coupling lowers the control threshold (left), and the TIP effect is concentrated in the sub-threshold band where R_eff = $R_0 d/(d+\kappa) > 1$ (right).



analysis/p16_analytic.png

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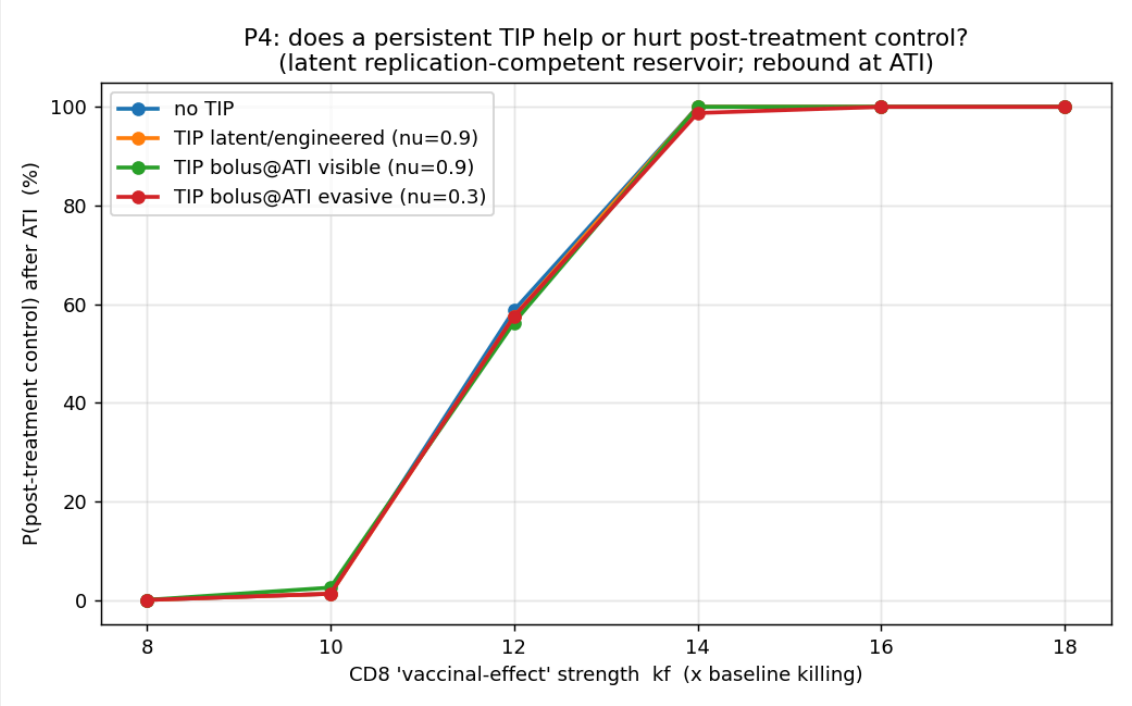
- **Supp.** — ATI rebound / post-treatment-control calibration (



analysis/p4_ati.png

); global sensitivity (`analysis/p15_sensitivity.npz`).

Data and code availability

All code, figures, the literature corpus, the verification harness, and the audit trail are openly available: https://github.com/sethc555/hiv-aids-research (archived at Zenodo, DOI: 10.5281/zenodo.20799761). Running `cd analysis && python3 verify_claims.py` re-derives every headline number (22/22), including a reproduction of Dodd & de Boer.

Disclosures

Status: illustrative within-host modeling / hypothesis generation; not validated experimental or clinical findings, not medical advice. **AI assistance:** this work was developed with substantial help from an AI coding/analysis assistant (Anthropic Claude) for implementation, derivation, audit, and drafting, under the author's direction; AI tools are not authors. **Competing interests:** none. **Funding:** none.

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