Heterogeneity in HIV viral rebound dynamics following treatment interruption

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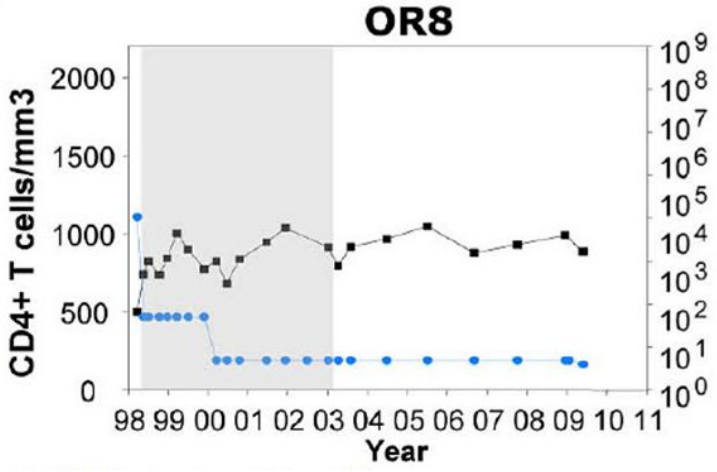
May 19, 2019

HIV/AIDS Research Priorities include

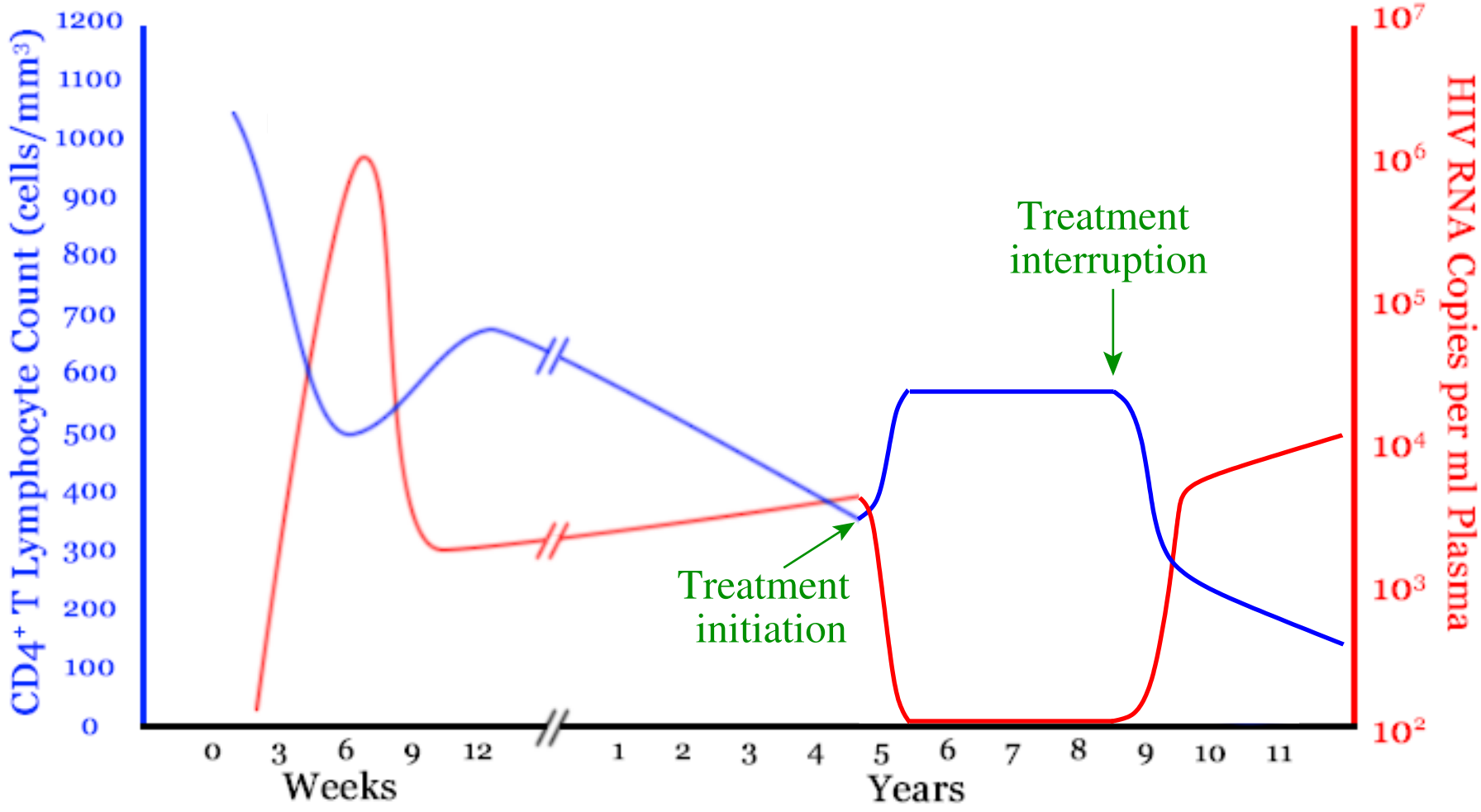
HIV Cure and Functional Cure

- immune checkpoint inhibitors
- gene therapy
- broadly neutralizing antibodies
- therapeutic vaccine
- latency-reversing agents
- ...



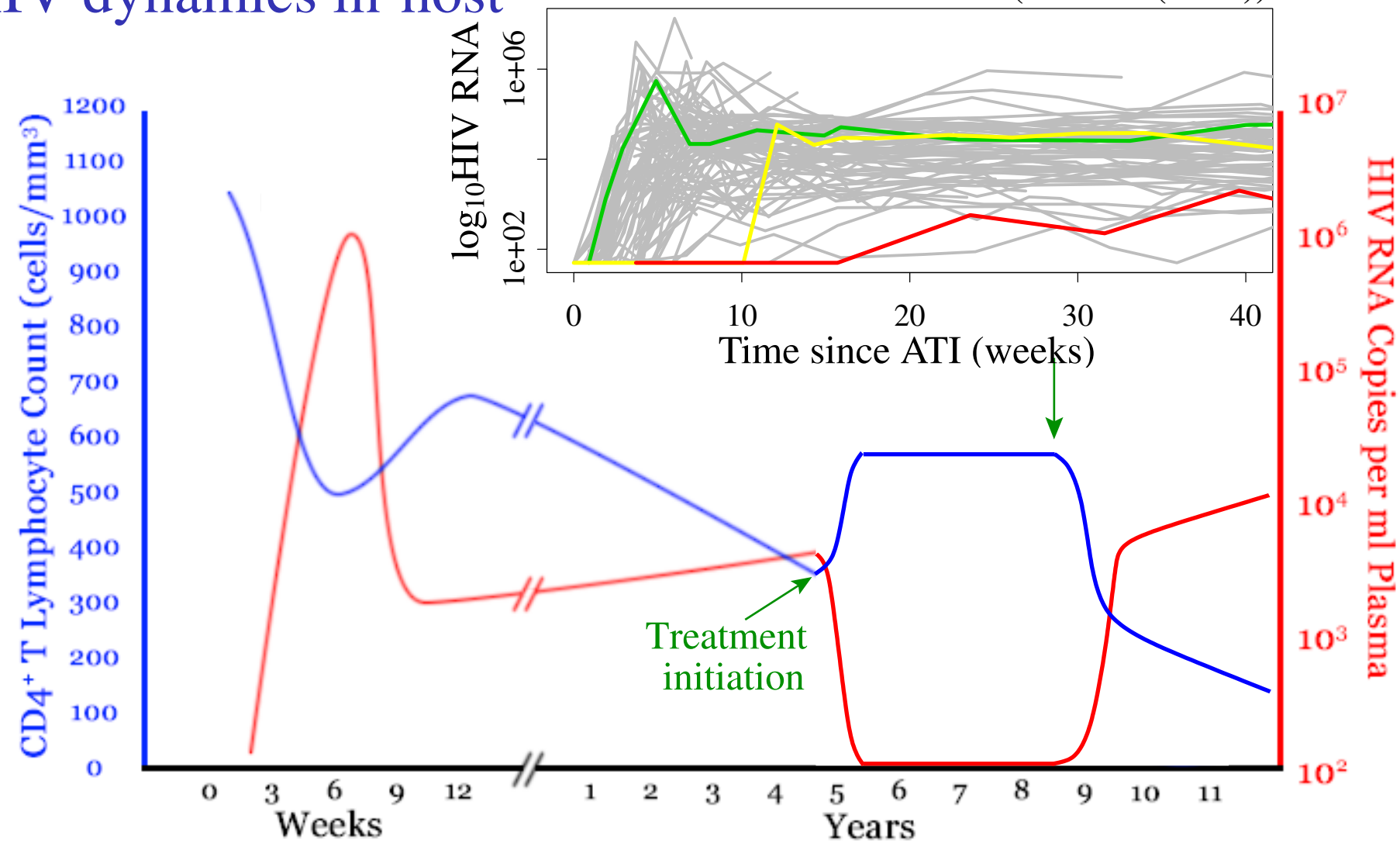
The only man cured of HIV. Timothy Ray Brown

HIV dynamics in-host



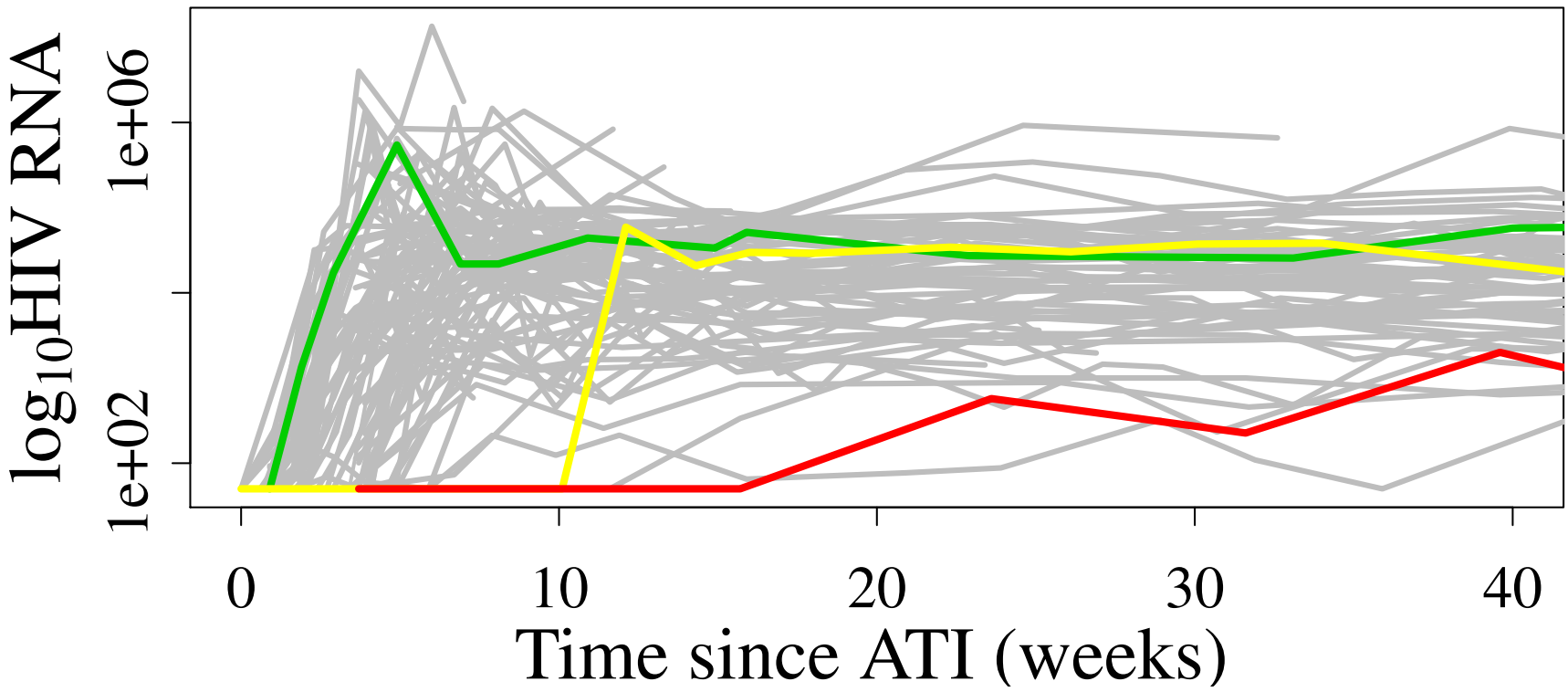
HIV dynamics in-host

(Li et al. (2016))



What are the dynamics of viral rebound and control post-analytic treatment interruption (ATI)?

Observations in 235 patients post-ATI



Aim: modeling to predict viral rebound times.

Clinical relevance: Design & evaluation of novel strategies for HIV cure.

(Data from ACTG studies A5197, A5170, A5068, A371, and A5024; Li et al. (2016)).

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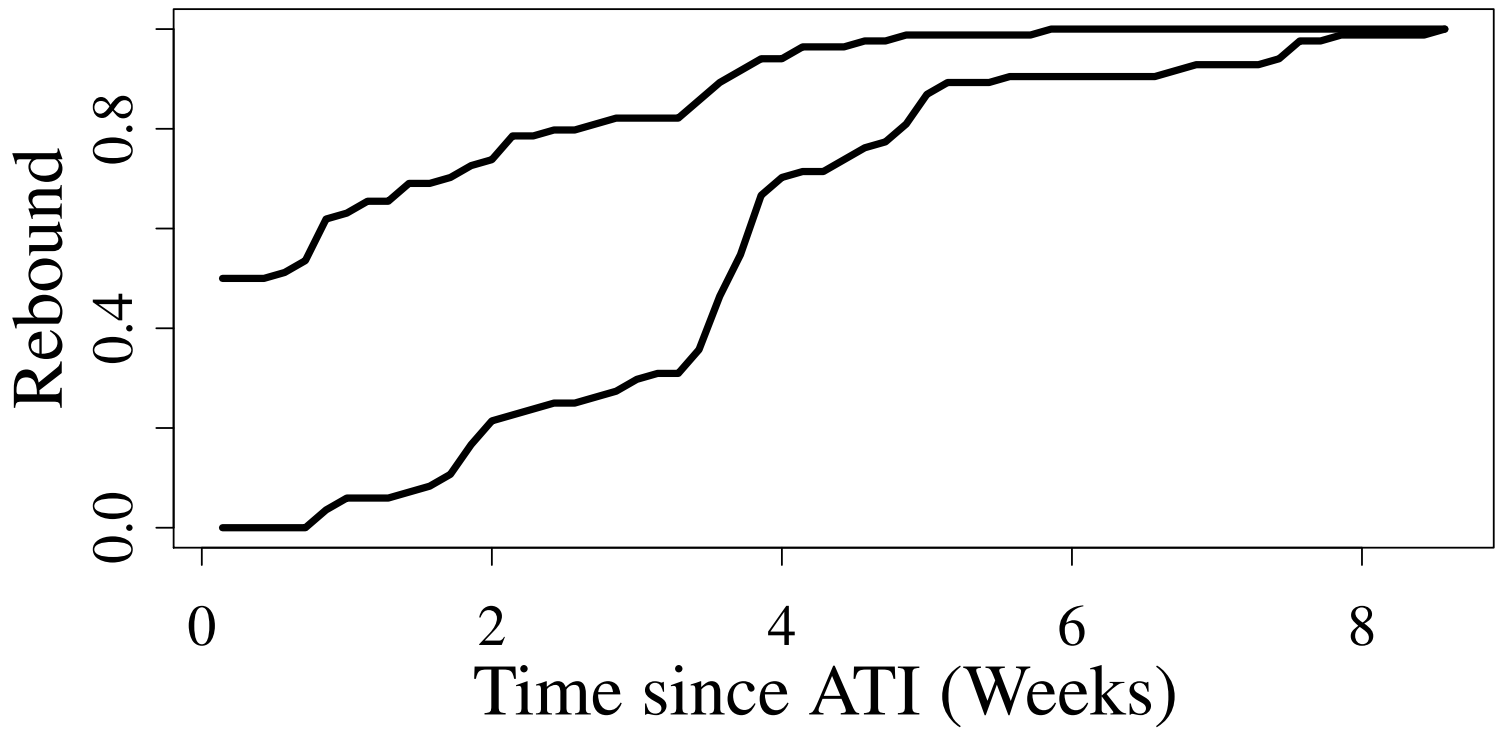

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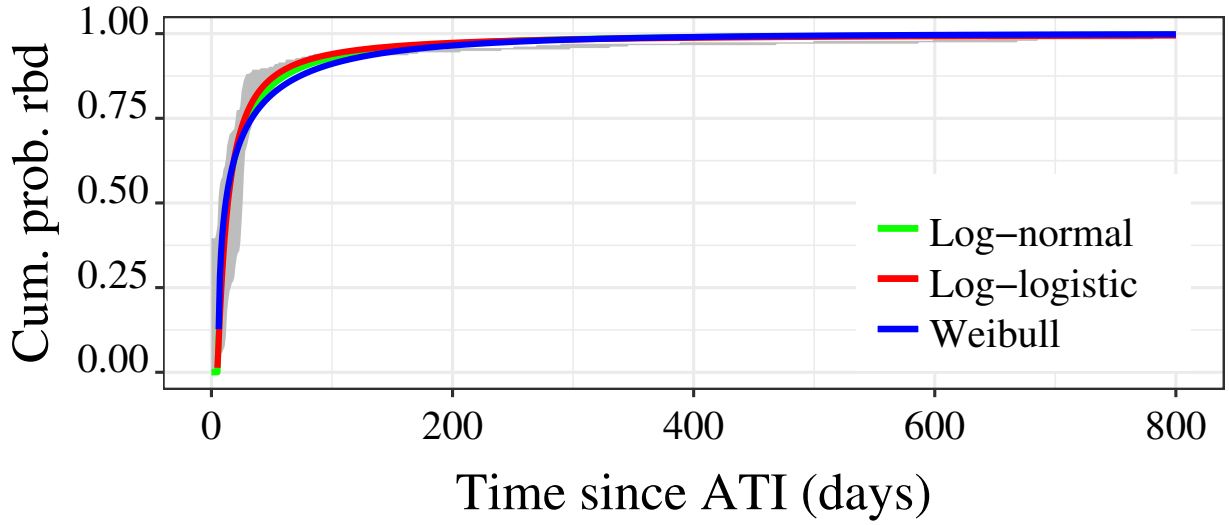
Survival analysis approach

Fit frequently-used distributions to empirical CDFs:



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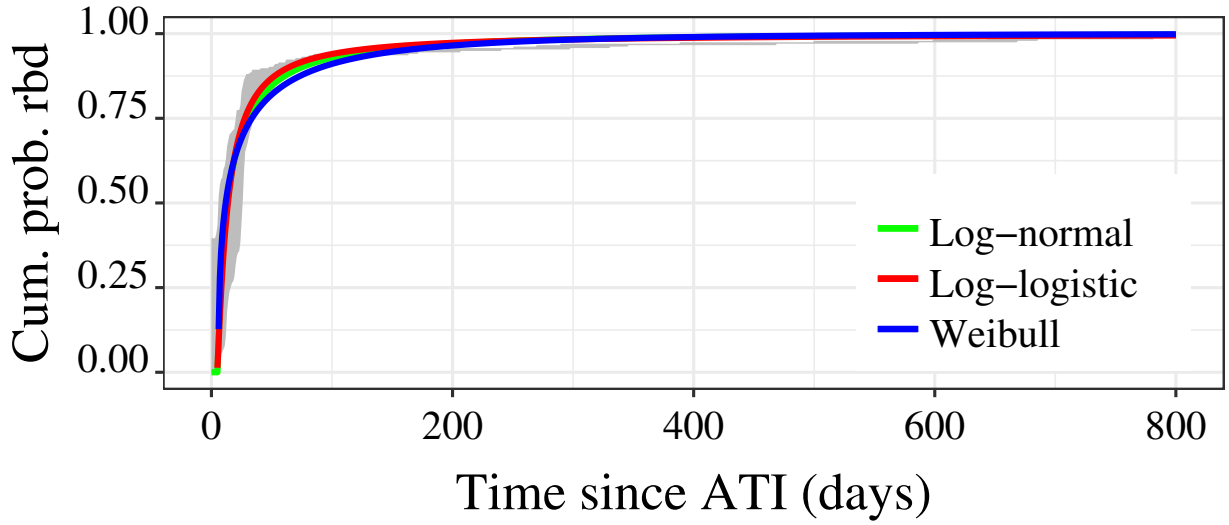
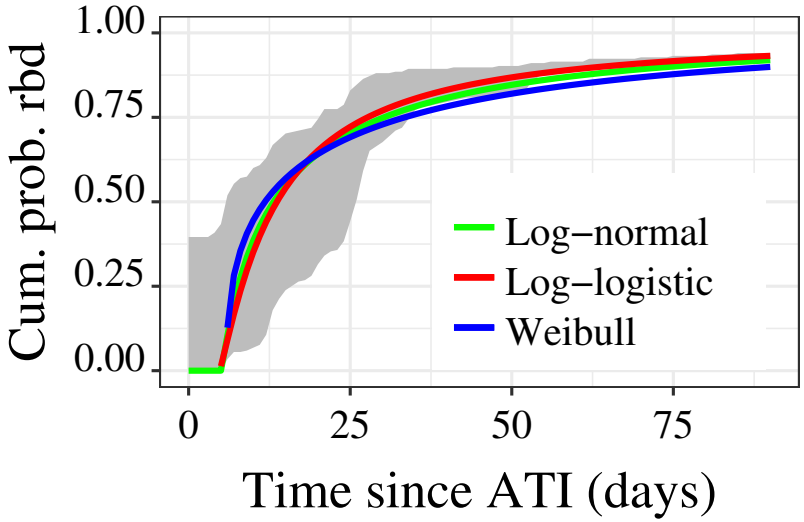


Fine for rapid rebound:



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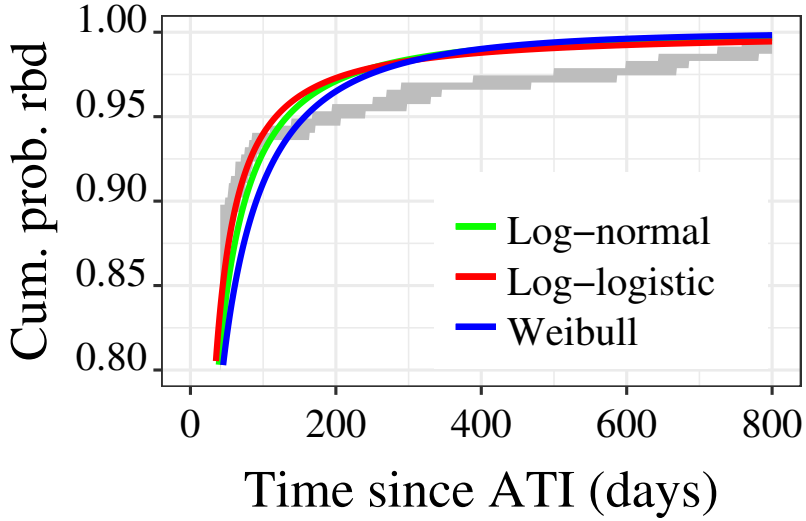
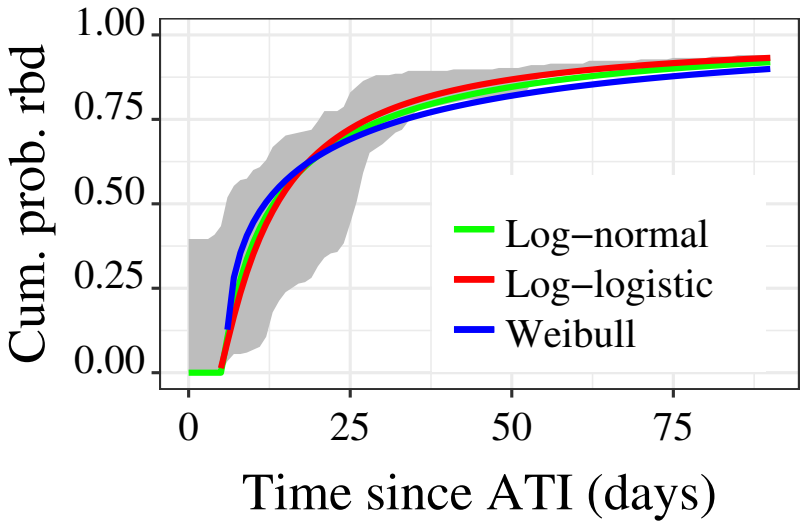


Survival analysis approach

Can we better predict **short & long-term** viral rebound by **modeling the underlying viral dynamics?**

Fine for rapid rebound:



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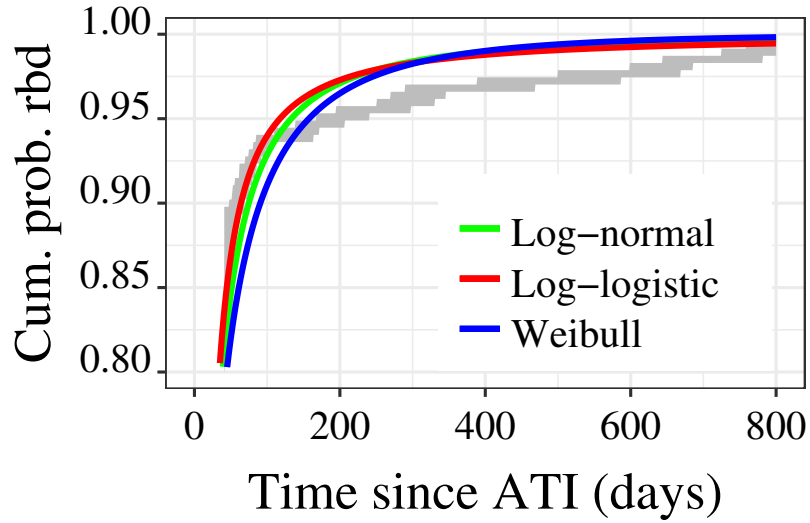
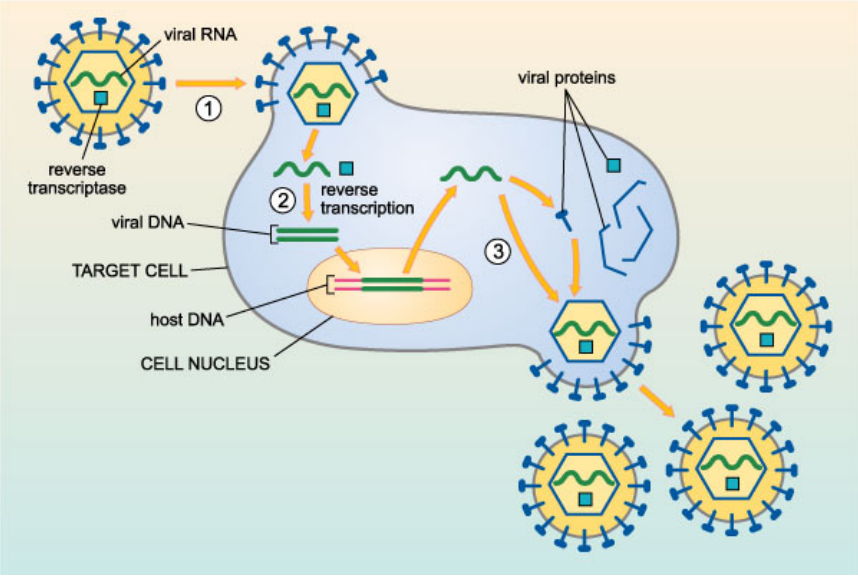


Source of viral rebound: the latent reservoir



Latently infected cells:
"quiet" after viral DNA integration.

~Major hurdle in HIV eradication~

- reservoir half-life $t_{1/2} \approx 44$ months (on ART)
- reservoir size varies, average 1 per 10^6 CD4+ T-cells
  enough so that decay under ART > a lifetime

Can activate produce HIV $\Rightarrow$ viral rebound post-ATI

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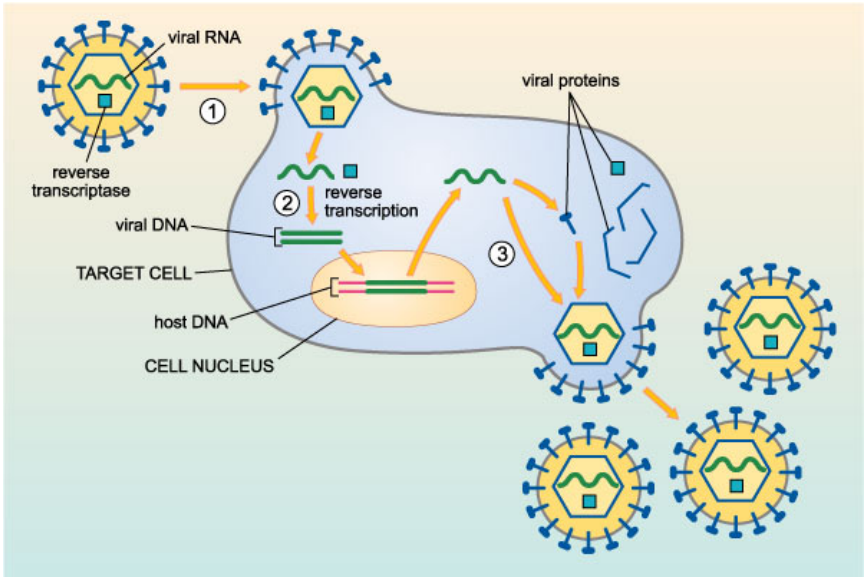

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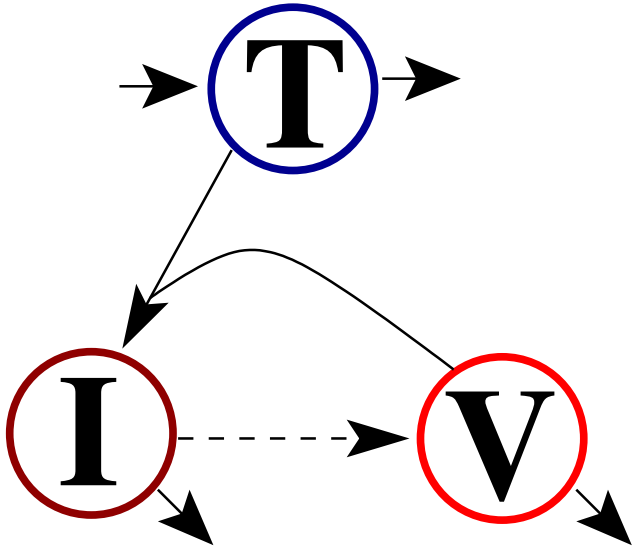

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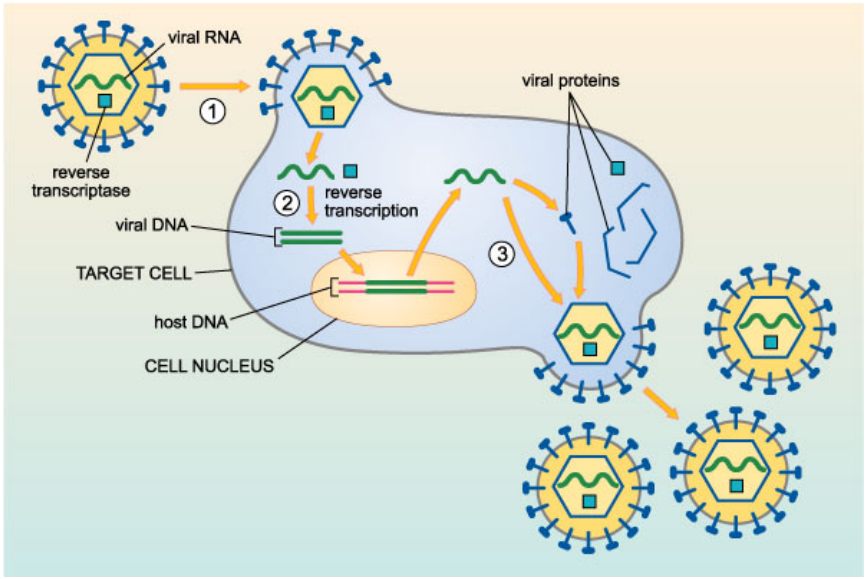

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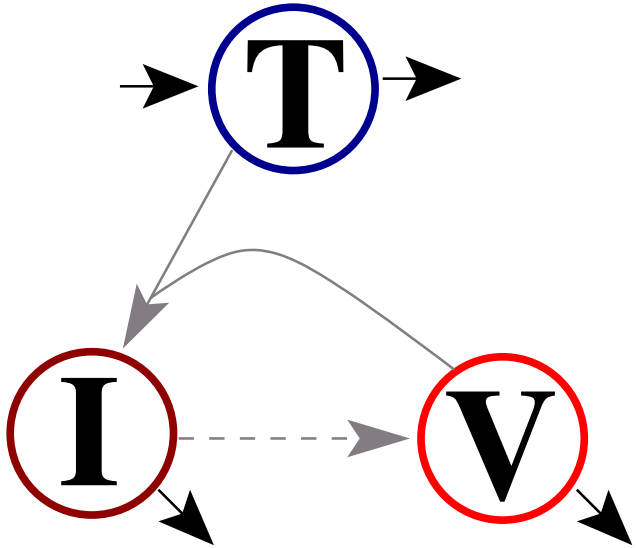

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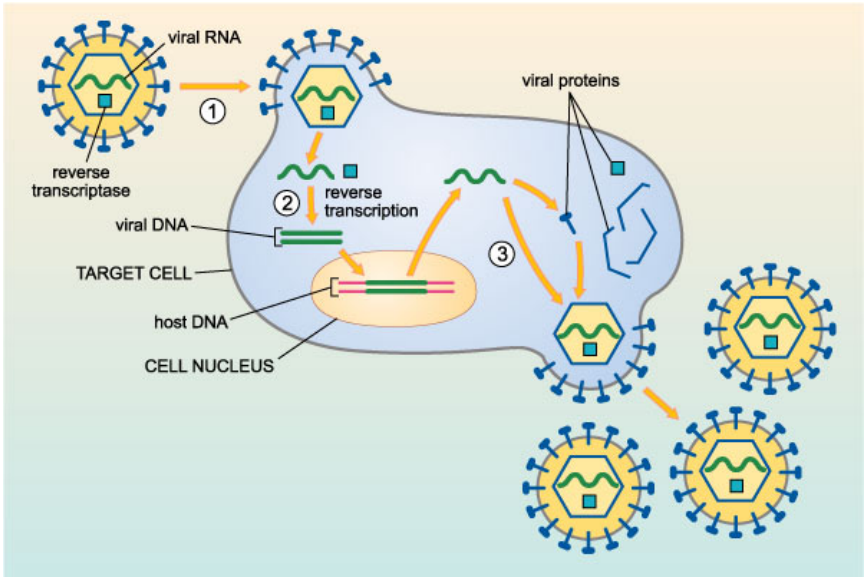

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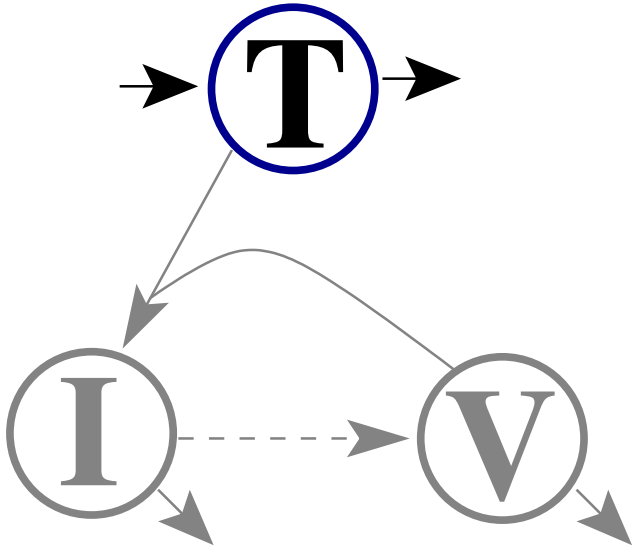

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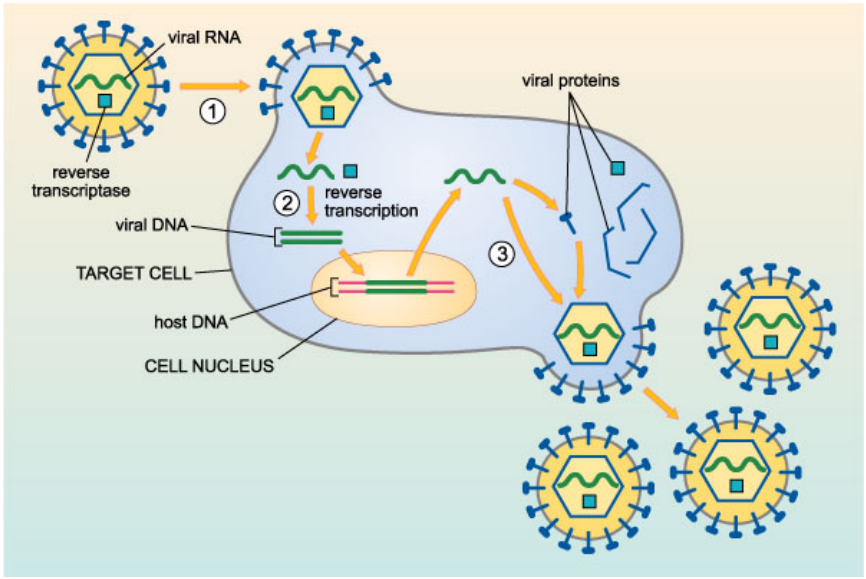

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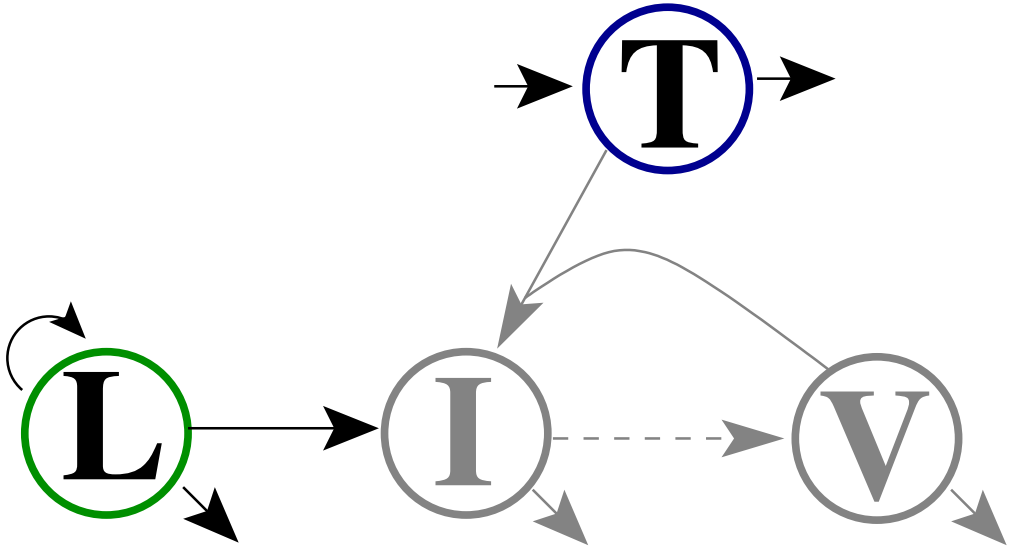

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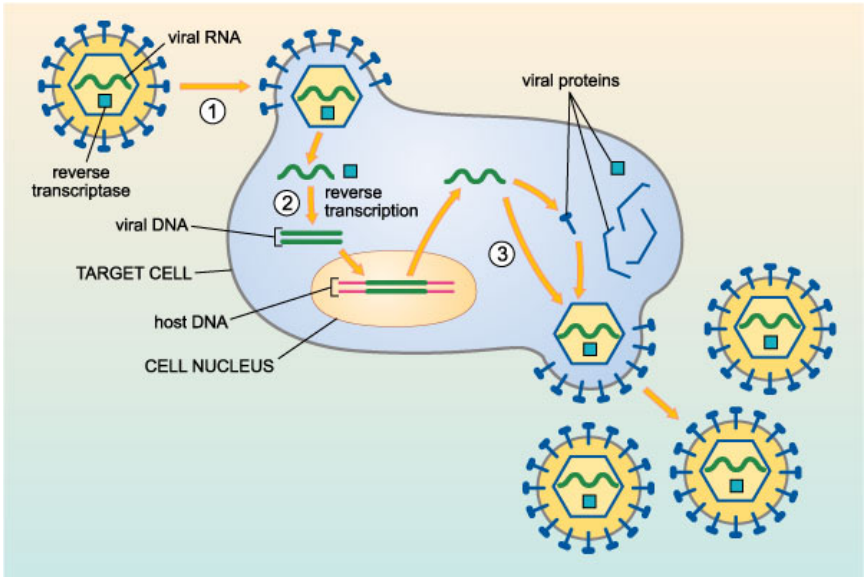

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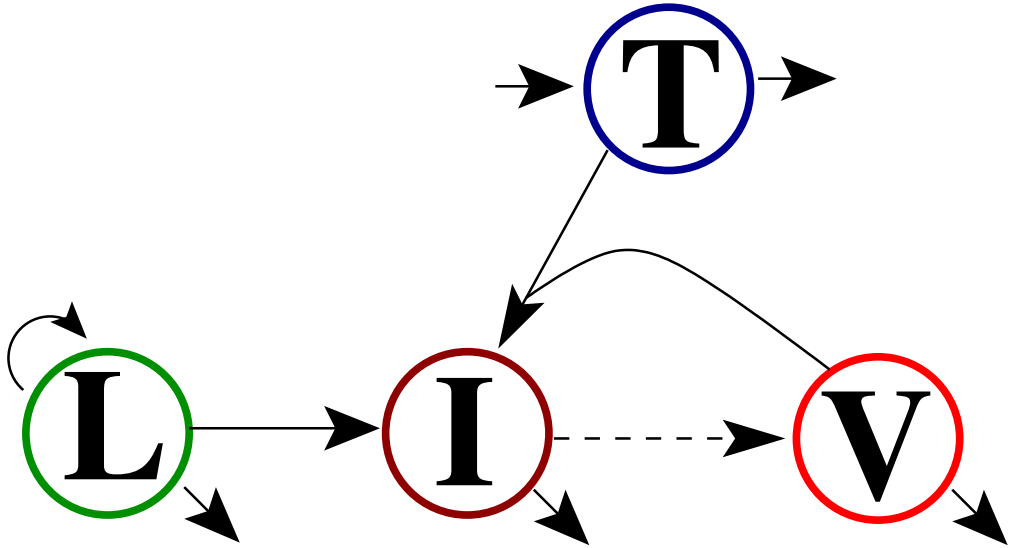
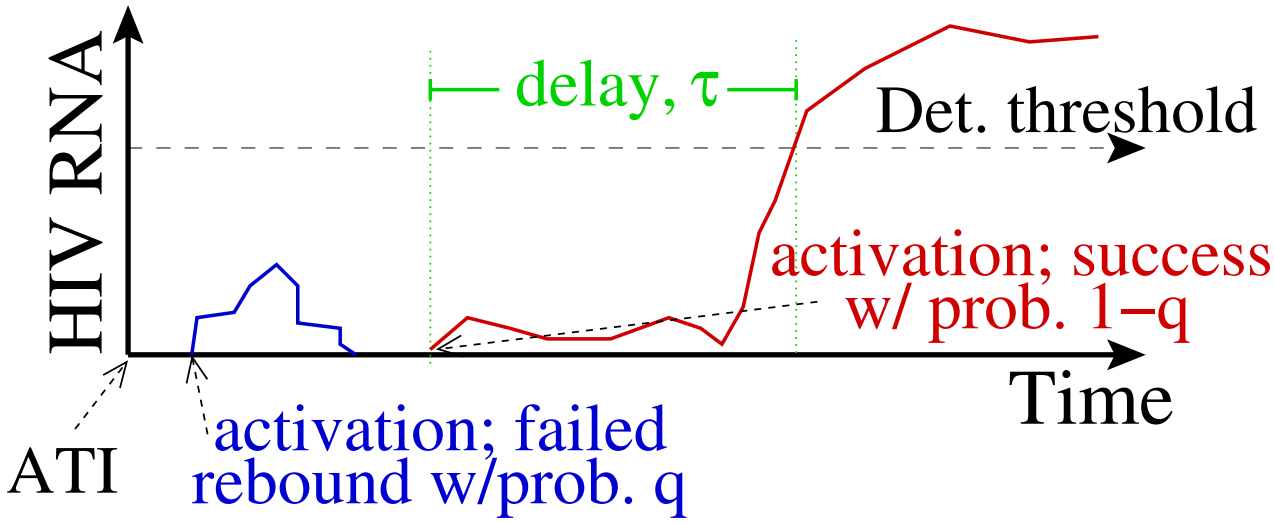


Approach

Hypothesis: rebound induced by **latent cell activation.**



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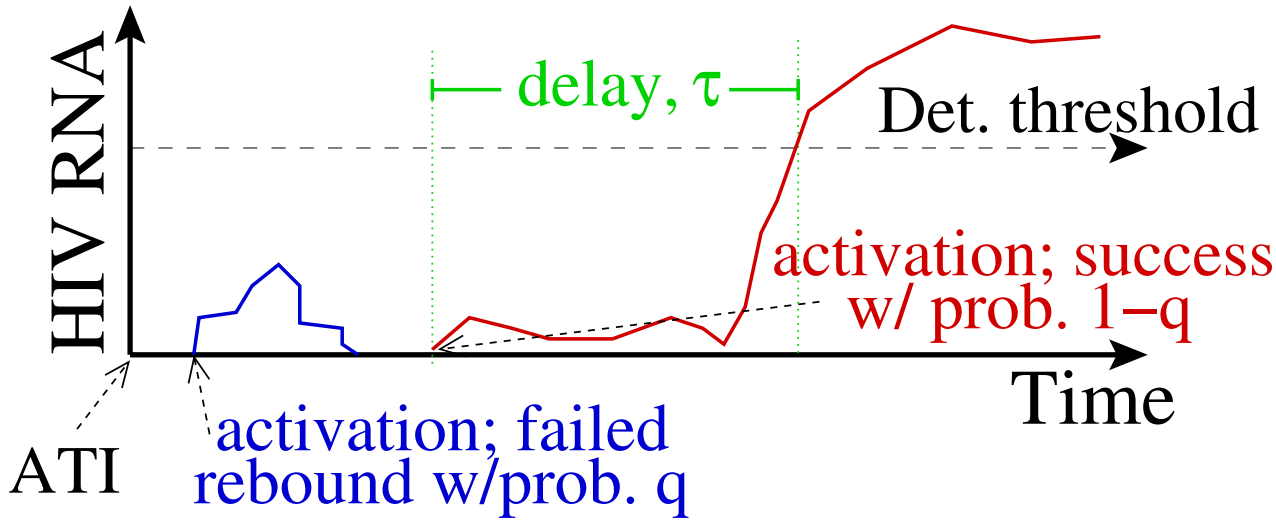
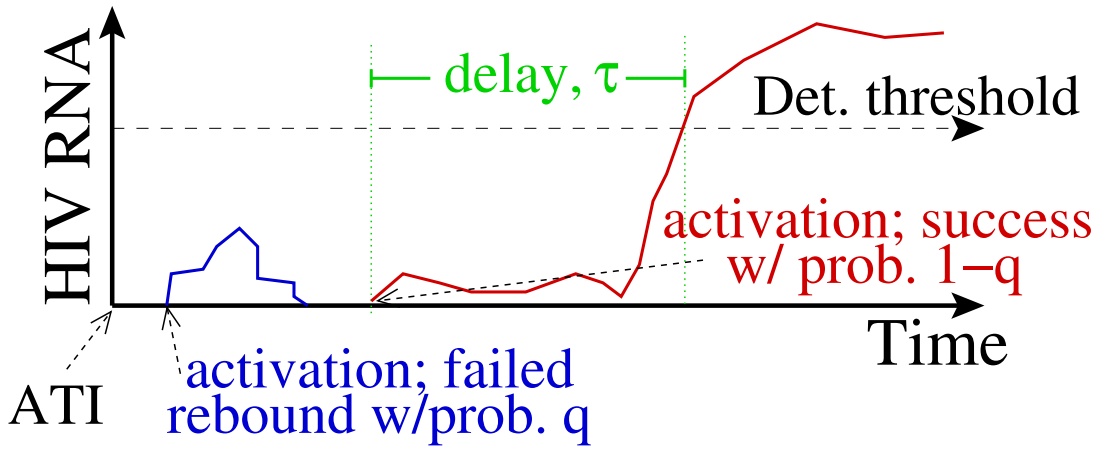


Cumulative probability of viral rebound by time t =

$$\sum_{n=0}^{\infty}\left[\int_0^t \left(\begin{array}{l}\text{Prob of n}^{th}\text{ activation at time } t-\tau \\ \times\ \text{Prob that n}^{th}\text{ activation leads to a successful rebound} \\ \times\ \text{Prob of virus detection by time } \tau\end{array}\right) d\tau\right]$$

Viral rebound calculation overview



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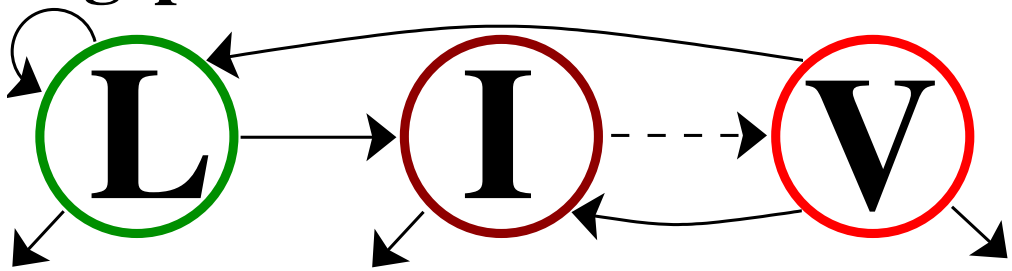
From **branching process** formulation of simplest model:



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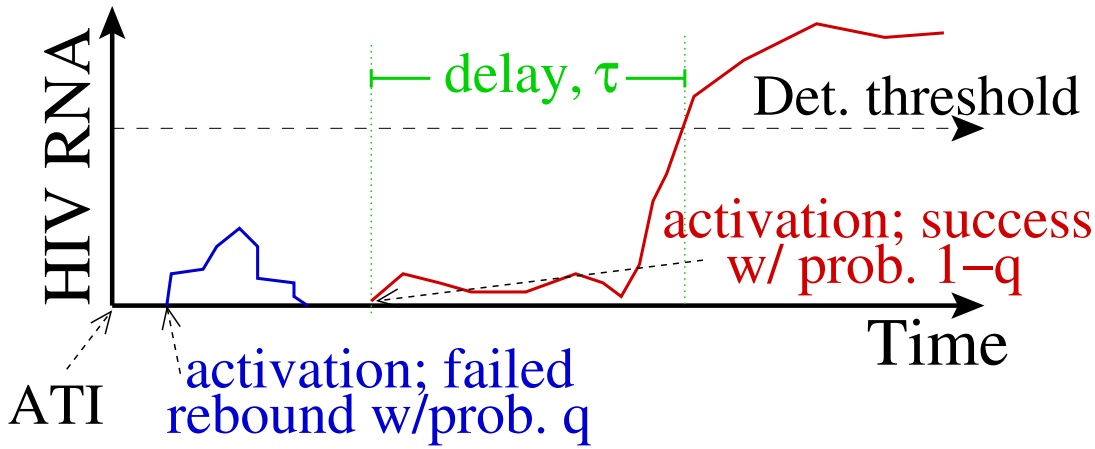

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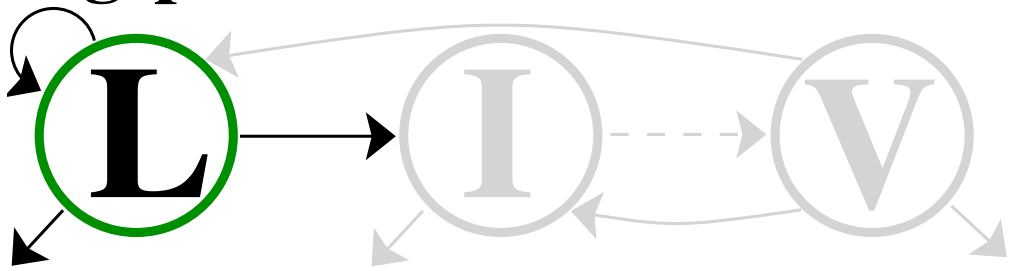

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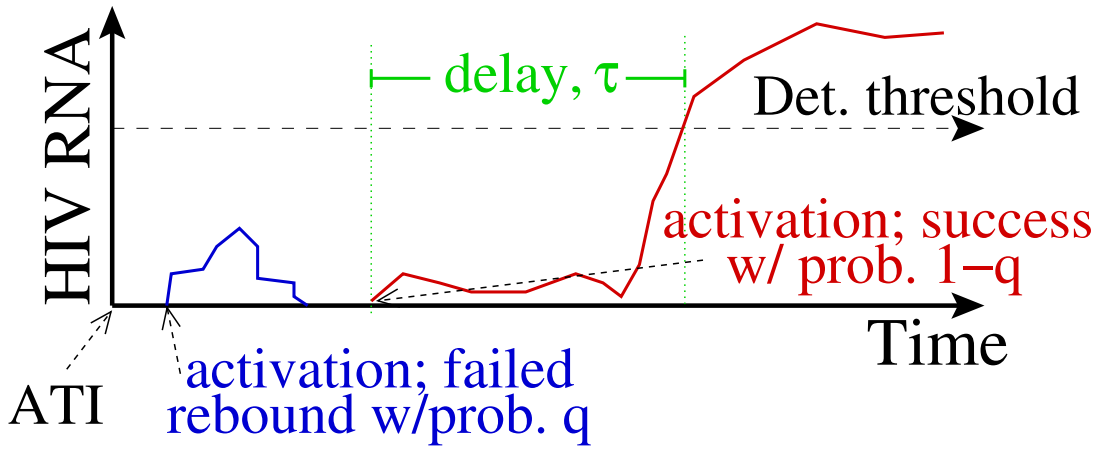

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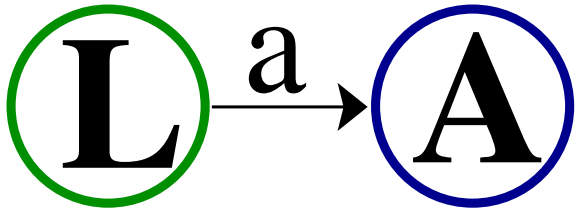

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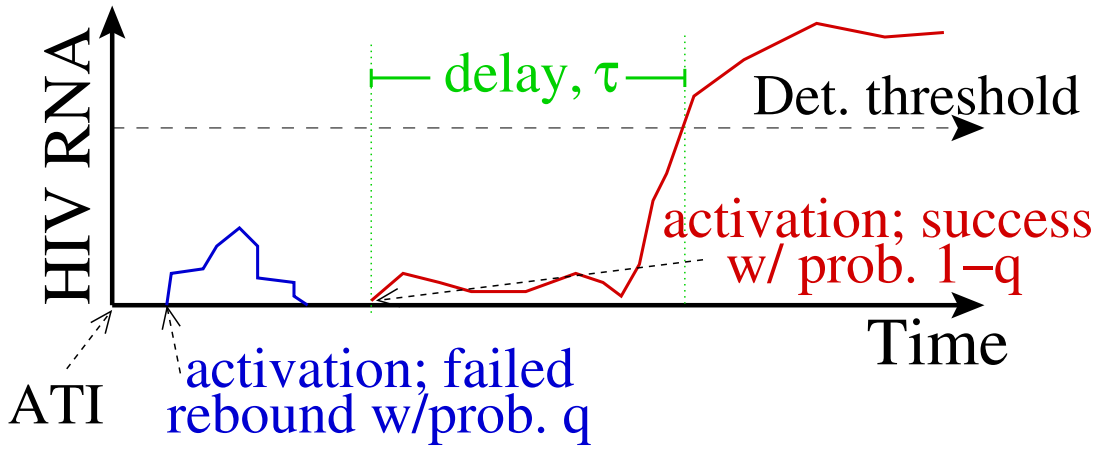

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Assume q = prob. activated cell does *not* induce rebound

$$\Rightarrow q^{n-1}(1-q)$$

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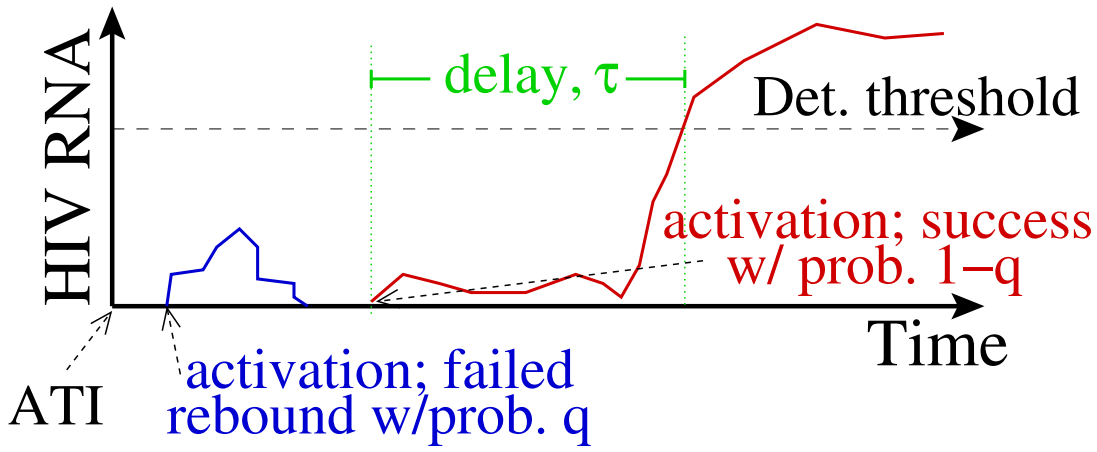

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- *For now:* fixed detection delay τ
- *Later:* stylized distribution of detection delays $D(\tau)$

Approach

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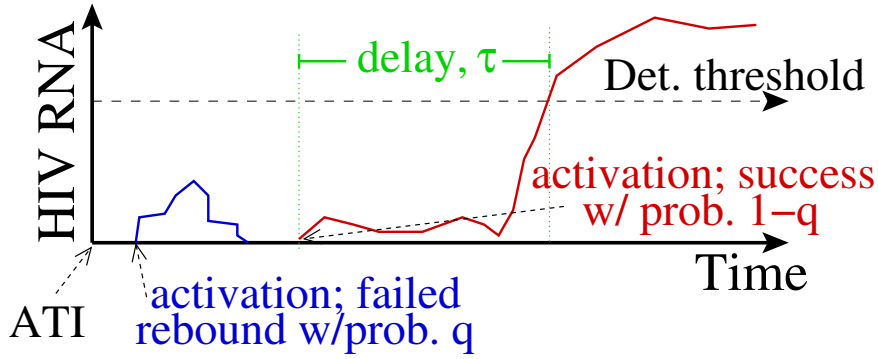

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Mathematical approach - keywords: Probability generating functions, *(time inhomogeneous)* branching processes...

Cumulative probability of viral rebound: simple model

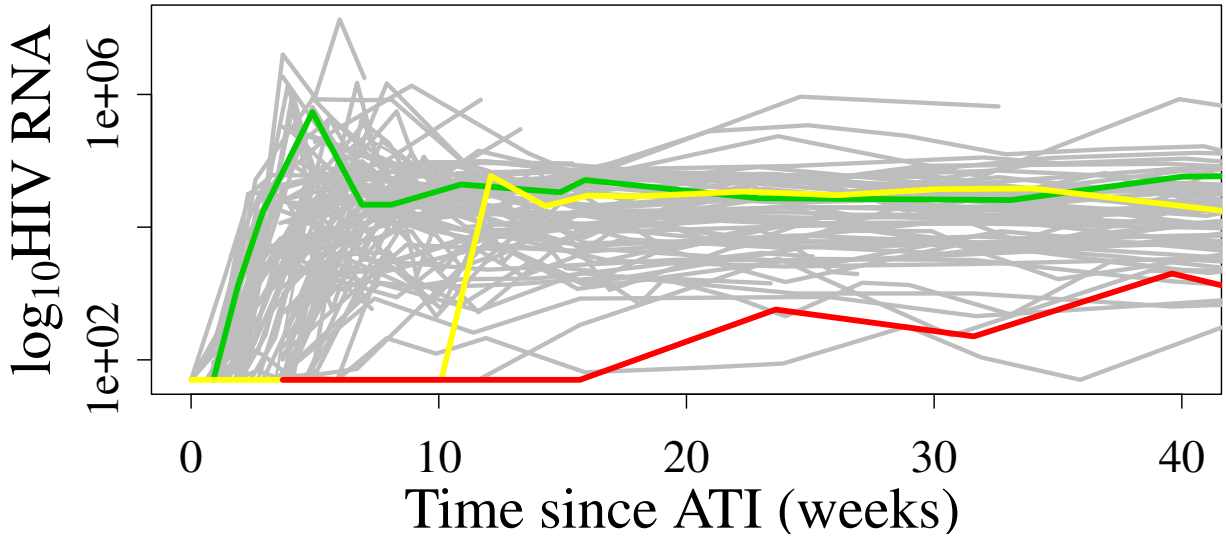
How long until viral load is detectable after treatment interruption?

ASSUME:
- Treatment cessation at $t = 0$.
- Latent reservoir size $L(0) = L_0$.
- Detection delay τ.
- Rate of latent cell activation is a.
- Probability activation "successful" is $1 - q$.

Cumulative probability of viral rebound at time t, $P_{\mathrm{VR}}(t)$

$$P_{\mathrm{VR}}(t) = \begin{cases} 0, & 0 \leq t < \tau \\ 1 - e^{-aL_0(1-q)(t-\tau)}, & t \geq \tau \end{cases}.$$

Parameter estimation



$$P_{VR}(t) = \begin{cases} 0, & 0 \le t < \tau \\ 1 - e^{-aL_0(1-q)(t-\tau)}, & t \ge \tau \end{cases}.$$

Method:

- Lik $= P_{VR}(\text{First det. date}) - P_{VR}(\text{Last Undet. date})$
- Fit detection delay τ, **"recrudescence rate"** $aL_0(1-q)$.
- To estimate: Maximize likelihood summed across all patients using the Davidon-Fletcher-Powell optimization algorithm.

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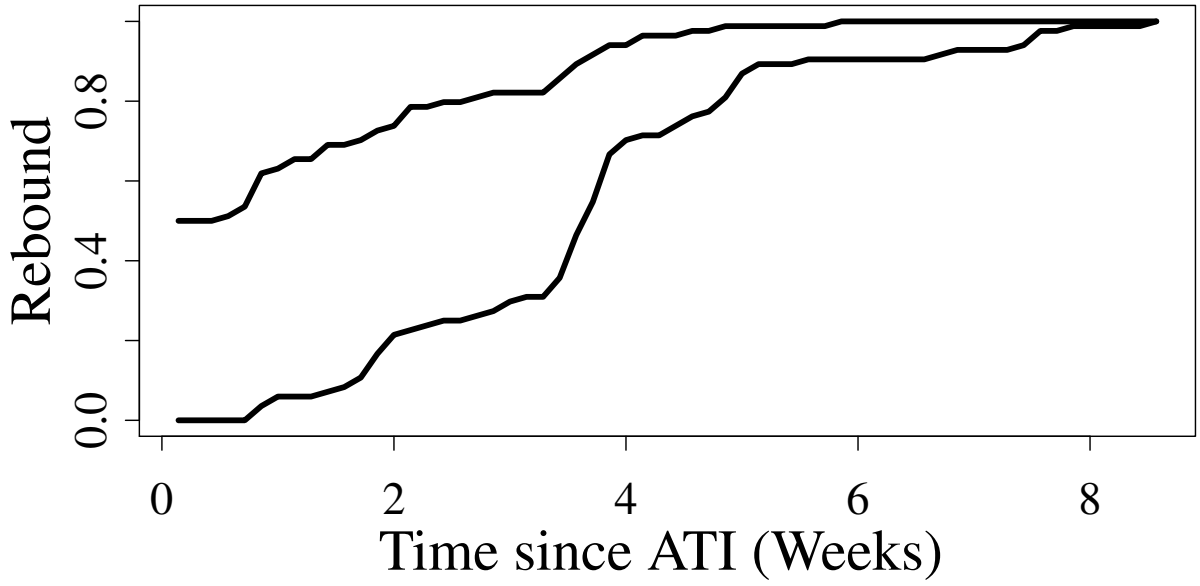

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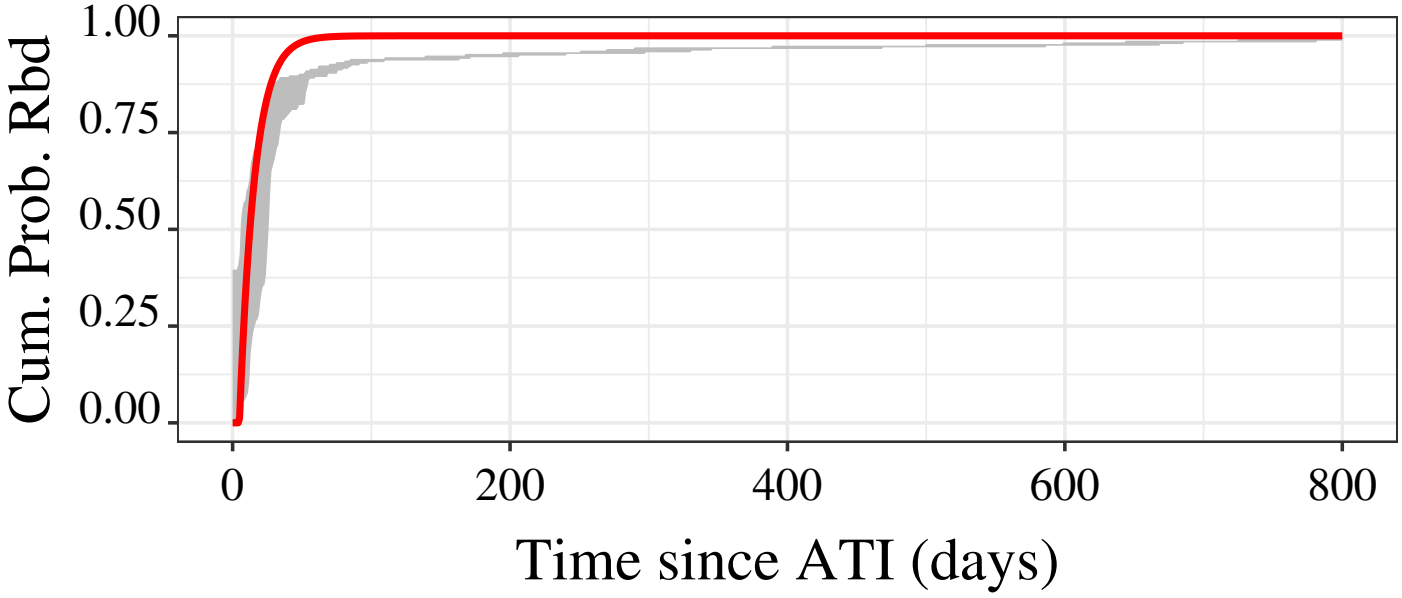
Model DOES NOT explain data for late rebound



Motivates investigation of recrudescence rates that are **heterogeneous in time.**

- Pre-rebound, expect the latent reservoir to decay in time. (Siliciano et al. 2003, Crooks et al. 2015).
- The latent reservoir is *heterogeneous*. (Strain et al. 2003, Chomont et al. 2009, Bui et al. 2017).

Time-varying recrudescence rate

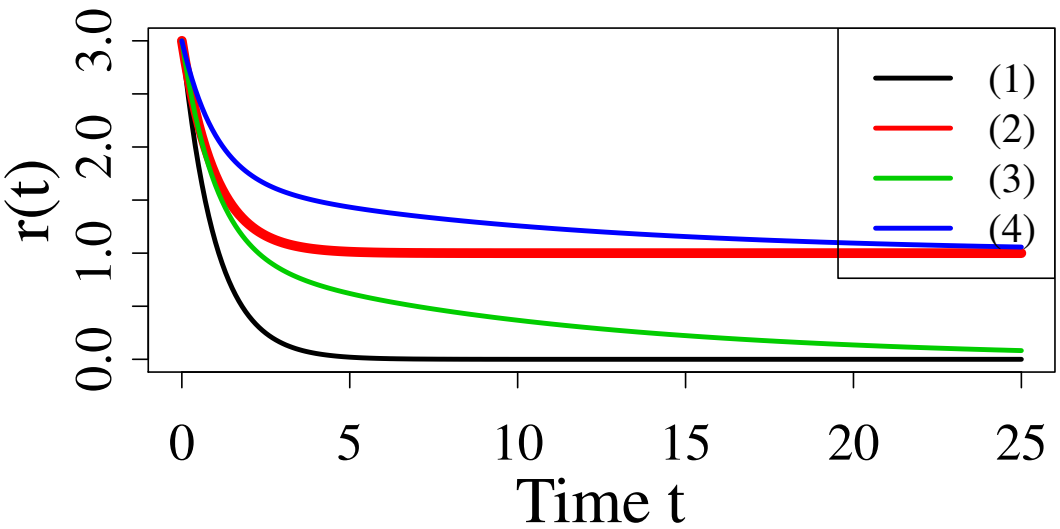
Take **time-heterogeneous recrudescence rate**, $r(t) = (1-q)a(t)L(t)$,

$$P_{VR}(t) = \begin{cases} 0, & 0 \le t < \tau \\ 1 - e^{-\int_0^{t-\tau} r(s)\,ds}, & t \ge \tau \end{cases}$$

Motivation: exponential decay dynamics following ART in

- Latent reservoir (Strain et al., Siliciano et al. 2003; Crooks et al. 2015).
- Viral load (Perelson & Ribeiro 2013; many others).

Test **exponential decay models** for $r(t)$:



$r(t)$ *model*	Δ *AIC*
(1)	47.3
(2)	**-11.5**
(3)	-9.6
(4)	-10.8

Single-phase decay (2), $r(t) \to r_\infty$ as $t \to \infty$

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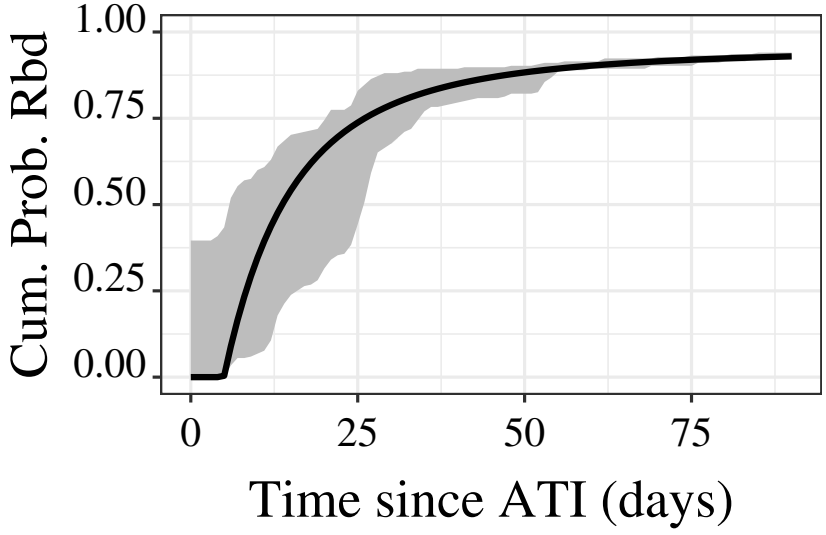

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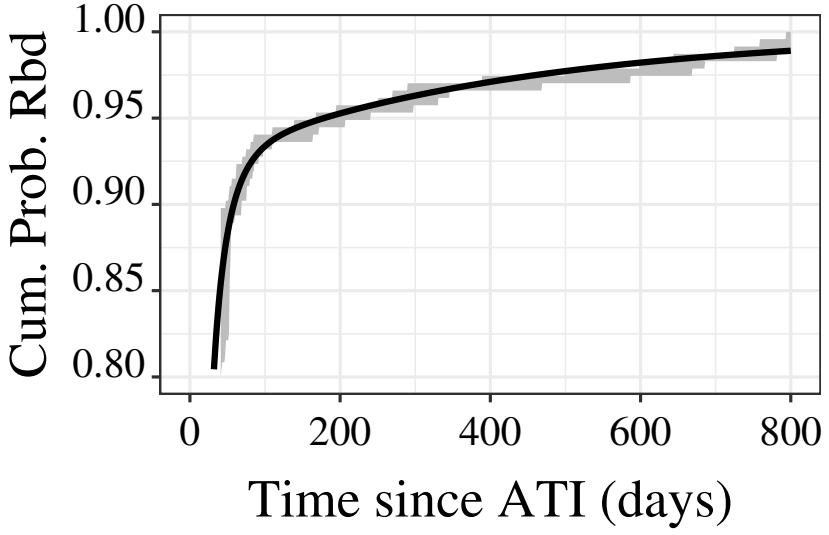


Recrudescence rate $r(t) = r_\infty + (r_0 - r_\infty)e^{-kt}$ with

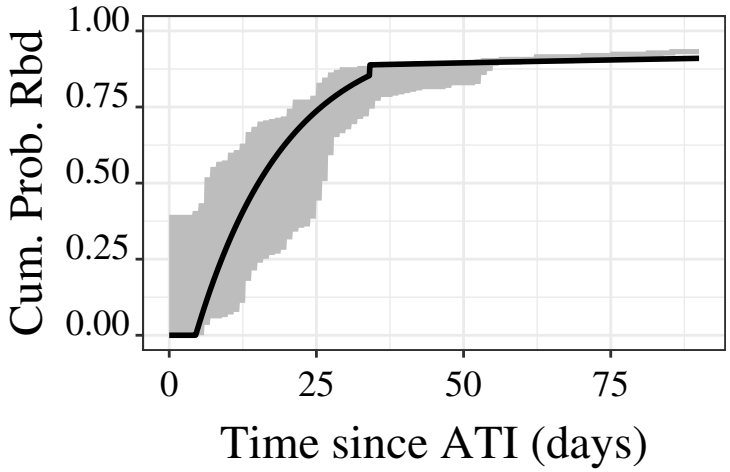
$$P_{VR}(t) = \begin{cases} 0, & 0 \le t < \tau \\ 1 - e^{-\int_0^{t-\tau} r(s)\, ds}, & t \ge \tau \end{cases},$$

in good agreement with data. **But why?**

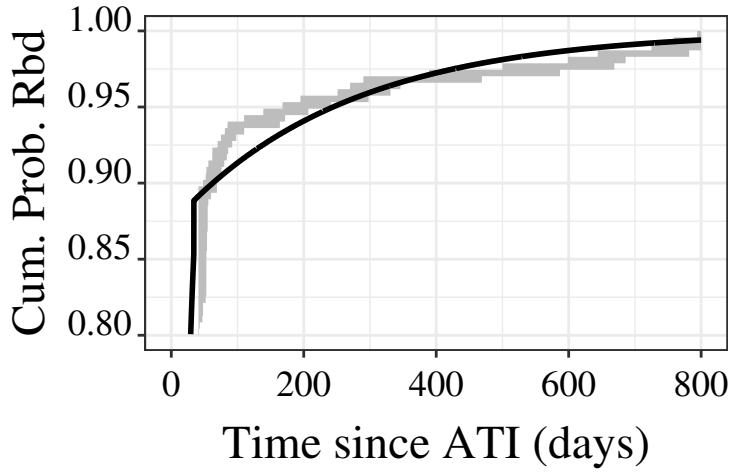
To build intuition: simpler model

Step-wise **recrudescence rate** (ΔAIC<2): $r(t) = \begin{cases} 0, & 0 \le t < \tau \\ r_0, & \tau \le t < T \\ r_\infty, & t \ge T \end{cases}$

Sill fine for rapid rebound:



OK for long rebound delays:



Suggests latent reservoir composed of two major sub-populations:

(1) cells that activate frequently & deplete rapidly ($T \approx$ a month).

(2) cells that activate infrequently.

To build intuition: simpler model

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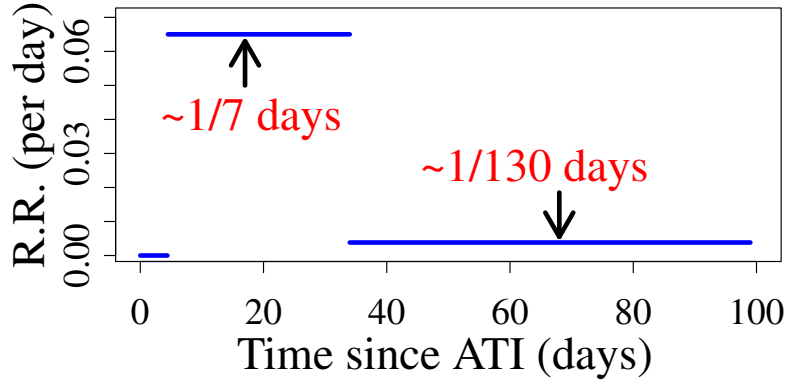

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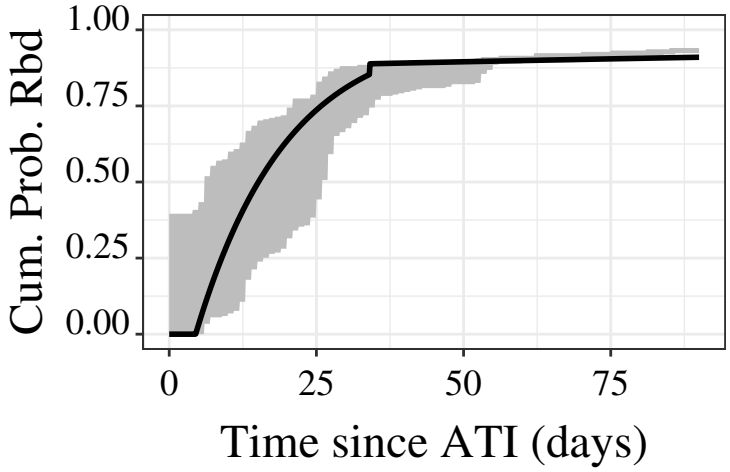

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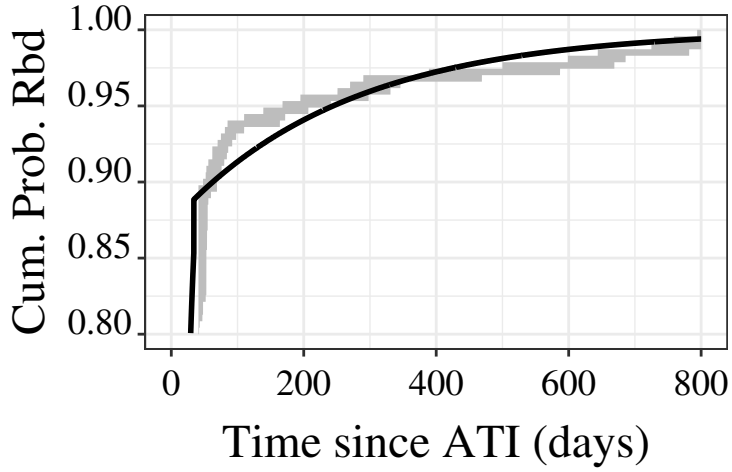

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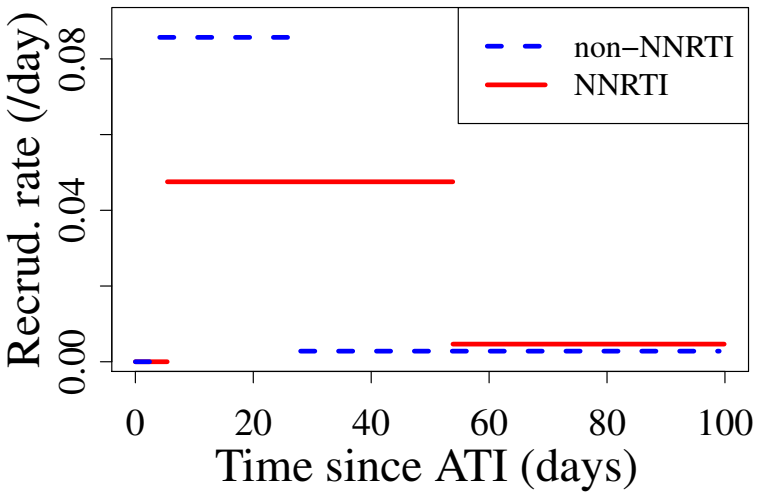
Population split: pre-ATI ART regimen

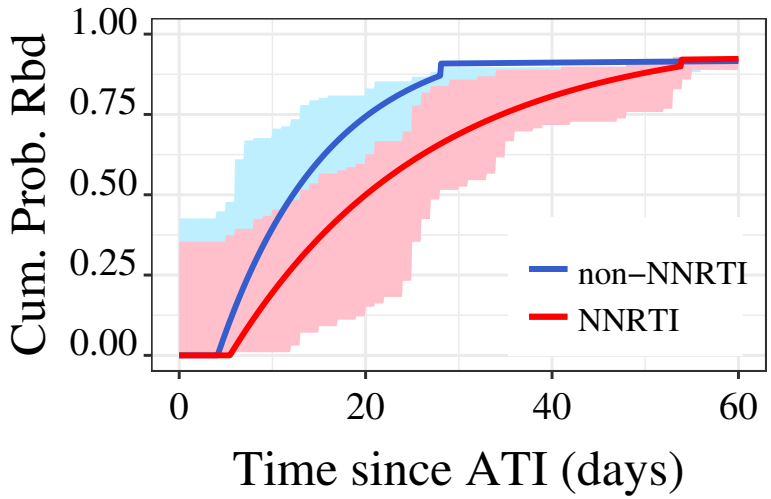
Li et al. (2016): NNRTIs yield statistically significant rebound delays.

Explanation: NNRTIs can have longer half-lives (Ribaudo et al. (2006), Maggiolo (2009)).

Predicted $r(t)$ (ΔAIC=-23.7):



Predicted & empirical CDFs:



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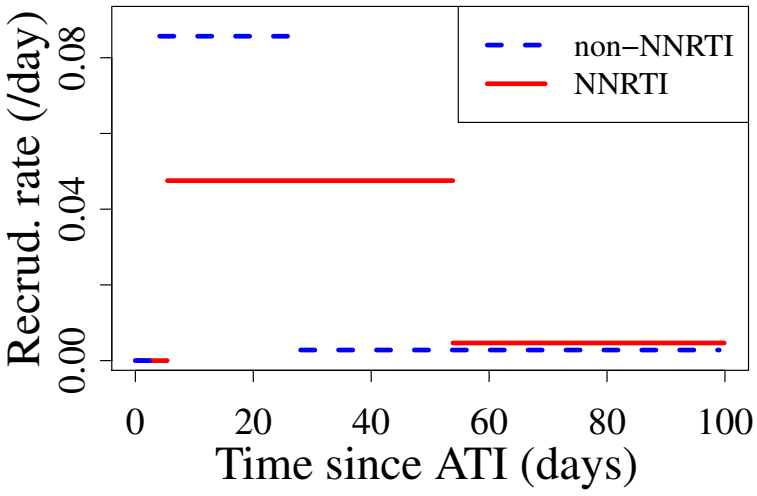

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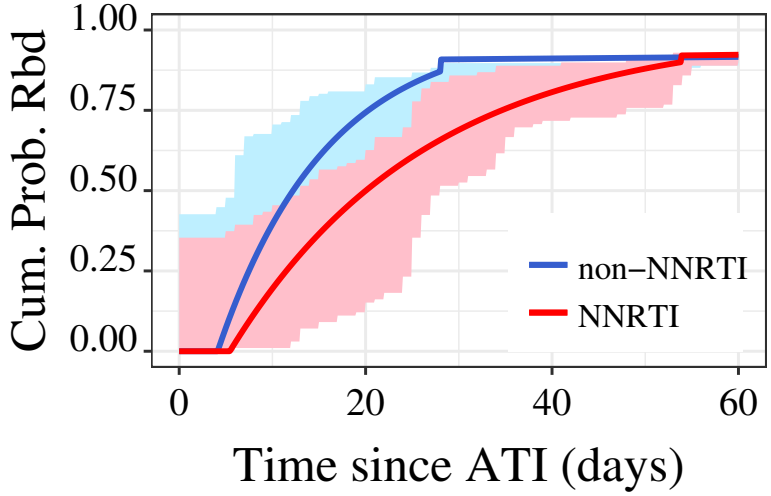


Unexpected outcome:

Transition to r_∞ later when pre-ATI ART regimen excluded NNRTIs.

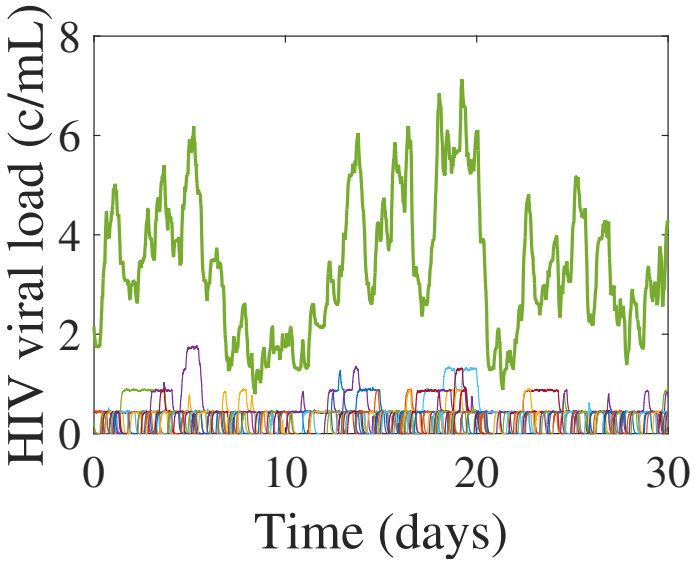
$\Rightarrow$ "frequently-activating" population depletes more slowly.

Hypothesis on why NNRTIs yield slower depletion

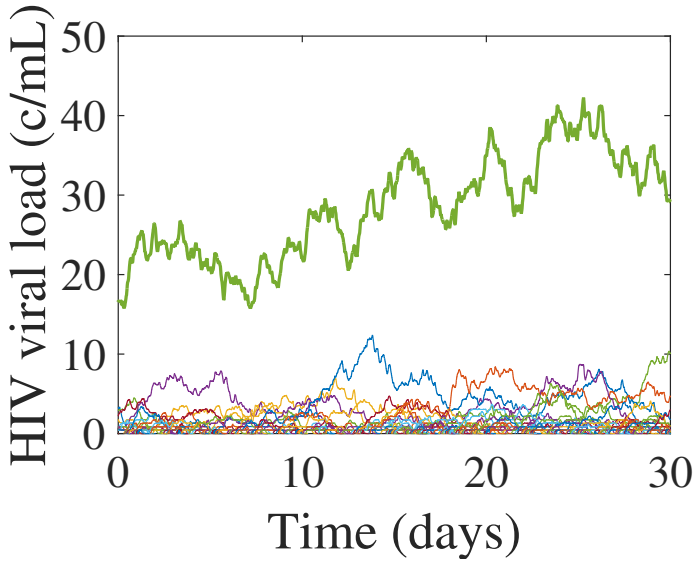
NNRTIs can have longer half-lives: Better infection control, for longer.

Previous modeling, viral dynamics given suppressive ART:

High drug efficacy ($R = 0.23$):



Low drug efficacy ($R = 0.92$):



(Conway & Perelson (2017))

One tentative hypothesis:

Latent reservoir is primarily composed of memory cells (Chomont et al. (2009)).

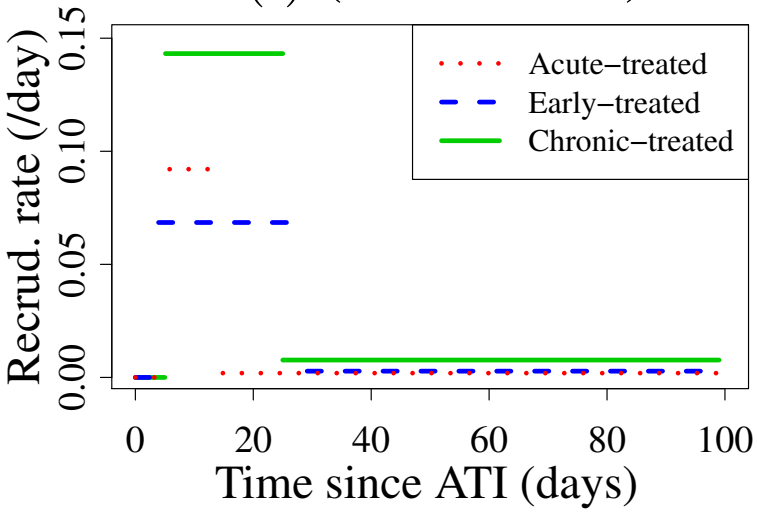
"Frequent-activators" may be getting stimulated with less intensity.

HIV specific memory responses?...

Population split: time of ART initiation (non-NNRTI only)

Initiated ART during: - acute infection (< 3 mos post-exposure)
- early infection (3-6 mos post-exposure)
- chronic infection (> 6 mos post-exposure)

Predicted $r(t)$ (ΔAIC=-4.9):



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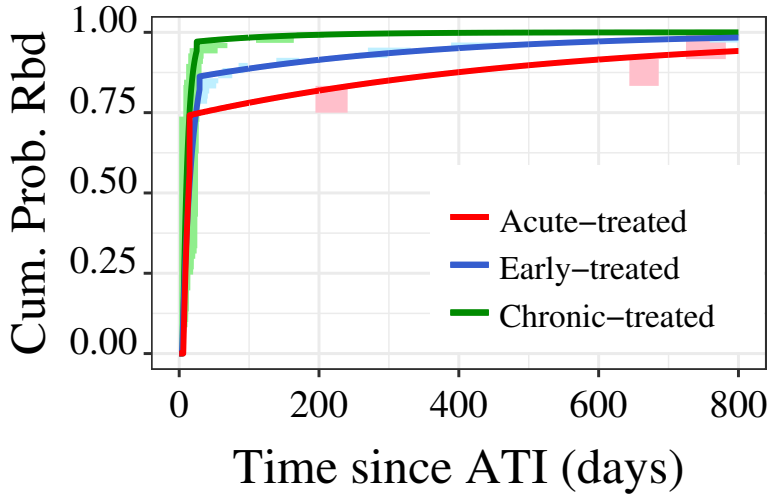

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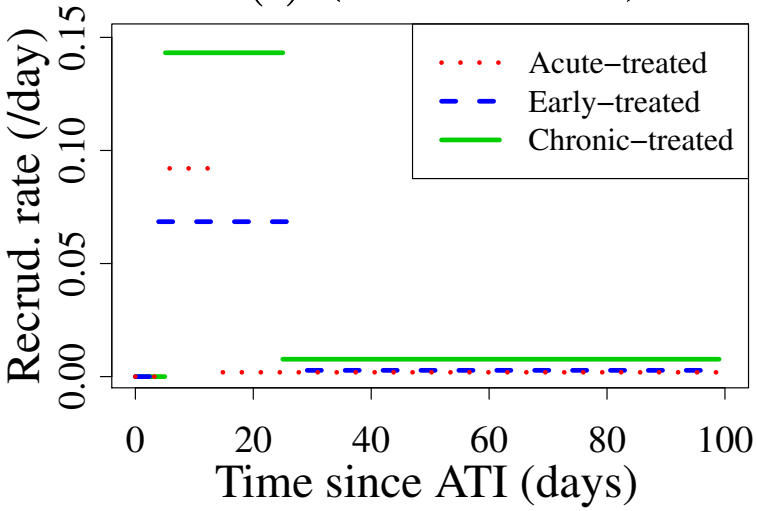
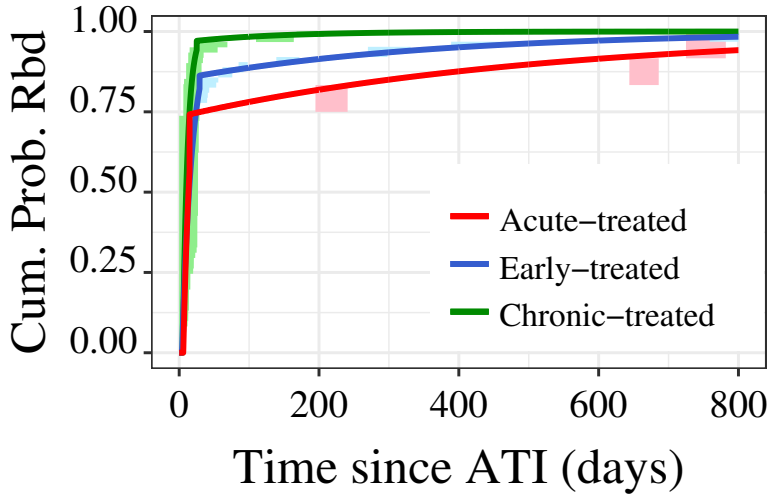


Predicted & empirical CDFs:



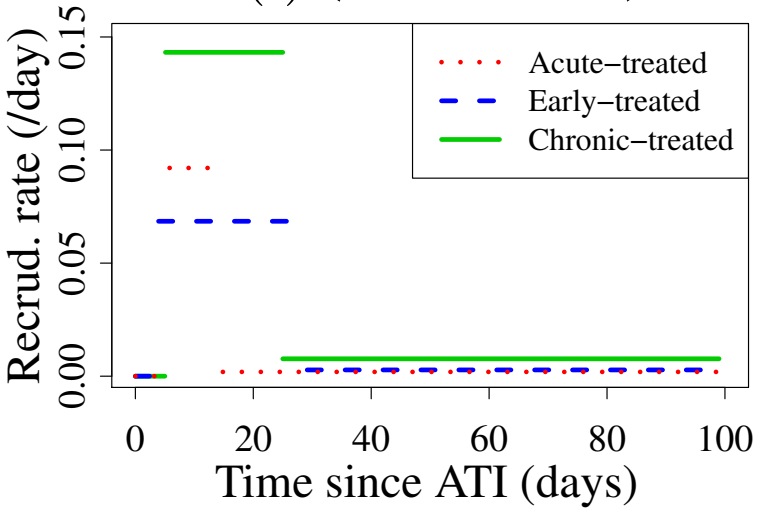
- Early-treated recrudescence rate r_0 **slowest**!

  Hypotheses: - adaptive immune responses better developed than in acute-treated (Li et al. (2016)).
  - fewer accumulated CTL escape mutations than in chronic-treated (Deng et al. (2015)).

Population split: time of ART initiation (non-NNRTI only)

Initiated ART during: - acute infection ($<$ 3 mos post-exposure)
- early infection (3-6 mos post-exposure)
- chronic infection ($>$ 6 mos post-exposure)

Predicted $r(t)$ (ΔAIC=-4.9):



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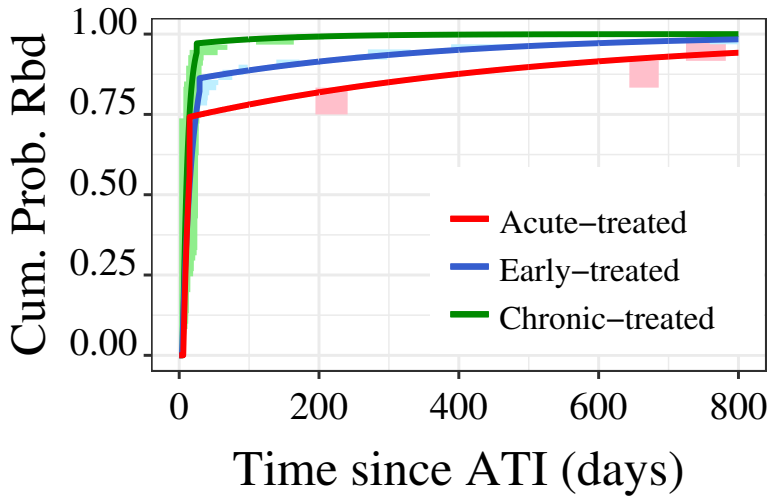


- Acute-treated recrudescence rate r_0 **shortest in duration**.
  Hypothesis: smallest HIV-specific reservoir, per tentative hypothesis?

Discussion

Viral rebound dynamics using a phenomenological, time-dependent recrudescence rate. *Preliminary results.*

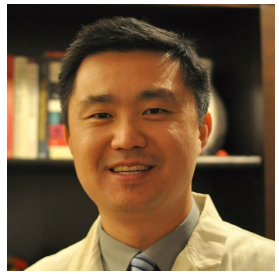
- Improved on survival models by considering underlying biology.
- Time-dependent models explain **short** *and* **long-term** viral rebound.

  Average recrudescence rate predictions:
  - Shortly after ATI: 1/7 days (Pinkevych et al. (2015)).
  - Roughly 1-2 months later: 1/130 days.
- Refinements: model selection, alternative detection delay models, sharpening biological picture...

Applications:

Given some intervention that will delay viral rebound and some testing frequency, can predict how many study participants are required to achieve the desired statistical power to detect delay.

Acknowledgements



- JMC: NSF grant no. DMS-1714654
- ASP: NIH grants R01-AI028433, R01-OD011095, and P01-AI131365; US Department of Energy Contract DE-AC52-06NA25396.
- JZL: NIH grants AI114448, UM1 AI068636 (AIDS Clinical Trials Group); subcontract from UM1 AI068636 to the Harvard Virology Support Laboratory.
- We thank the participants, staff, and principal investigators of the ACTG studies A371 (Paul Volberding, Elizabeth Connick), A5024 (J. Michael Kilby, Ronald Mitsuyasu), A5068 (Jeffrey Jacobson, Ian Frank, Michael Saag, Joseph Eron), A5170 (Daniel Skiest, David Margolis, Diane Havlir), and A5197 (Robert Schooley, Michael Lederman, Diane Havlir). We also thank the efforts of the ACTG NWCS 371 study team.

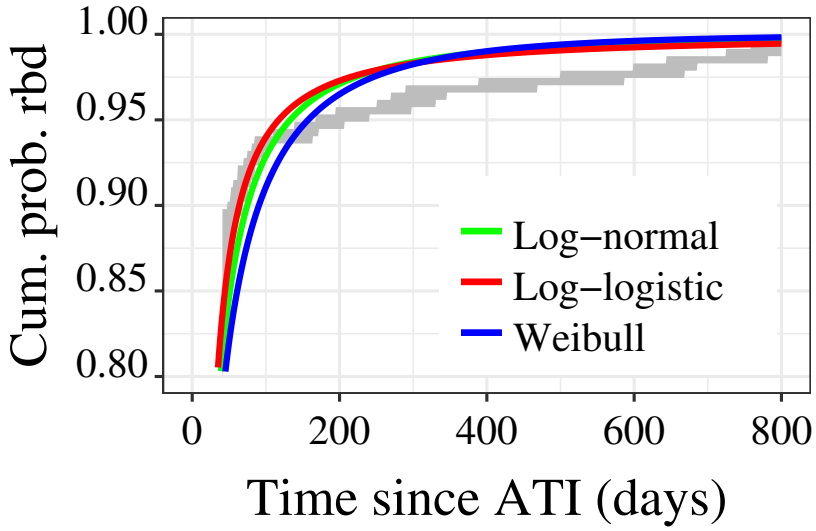
NIH

NSF

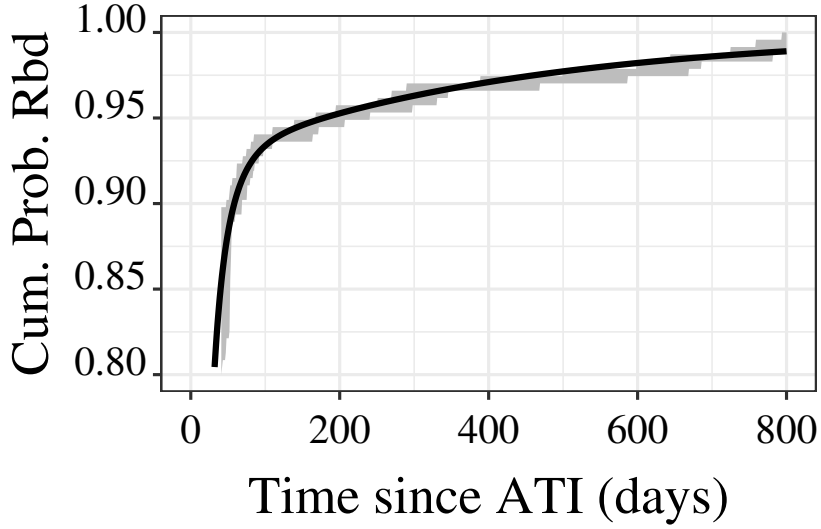
Utility: clinical trial planning & analysis

Even if you're skeptical of the underlying biology, new model predicts late viral rebounds very well.

Standard survival models:



Exp. decaying r.r. (Δ AIC=-11.5):

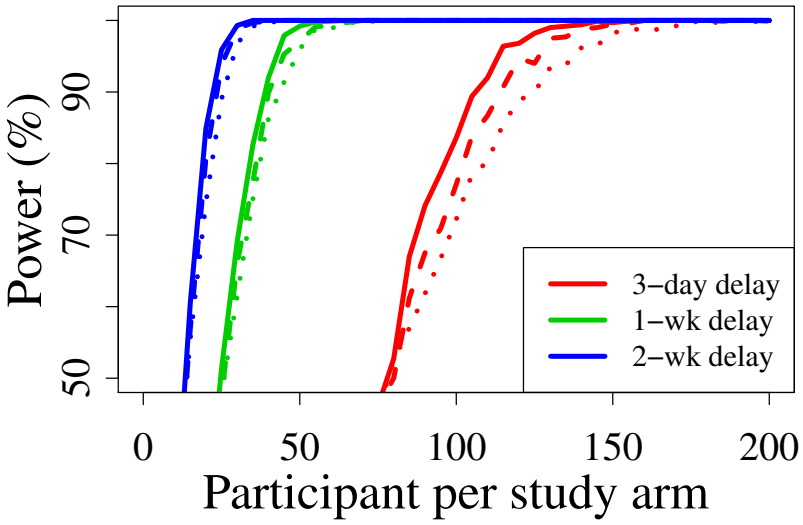


Treat recrudescence rate as the hazard rate for analysis.

- Baseline to evaluate efficacy of intervention in a clinical trial setting.
- Predict # of study participants required to achieve desired statistical power.

Example: predicting # of study participants

Over 1000 *in silico* trials, % that yield statistically significant difference in **mean rebound time** (Wilcoxon rank-sum test).



- Testing frequency: twice weekly (solid), weekly (dashed), bi-weekly (dotted).
- Delay associated with reduced hazard ratio.
  HR 0.7 = 3 days; HR 0.5 = 1 wk; HR 0.4 = 2 wks.

Note that these are preliminary results.

With good support for underlying biological hypotheses, can make similar predictions for interventions that target rebound mechanisms.