

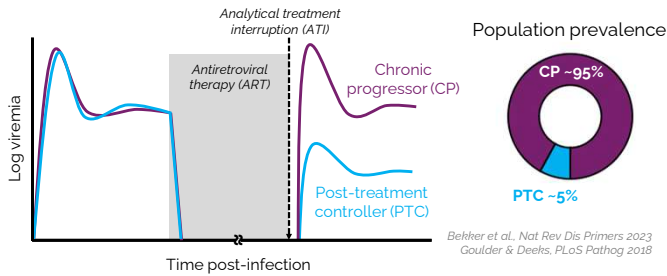
Modeling the influence of antiretroviral treatment initiation time on post-treatment control of HIV infection

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Background

Post-treatment control observed in human and animal studies



Comparison of features between CPs and PTCs

	PTCs	CPs
Intact proviral DNA levels	↑	↑↑
T cell activation	↑	↑↑
Exhaustion	↑	↑↑
ART initiation time	↑	↑↑
NK cell antiviral activity	↑↑	↑

Etemad et al., Proc Natl Acad Sci USA 2023

Sharaf et al., J Clin Invest 2018

Laanani et al., Clin Invest Dis 2015

Assoumou et al., AIDS 2015

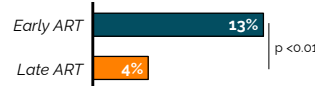
Saez-Cirion et al., PLoS Pathog 2013

Mechanisms underlying post-treatment control are unclear

Early ART initiation confers higher possibility of post-treatment control

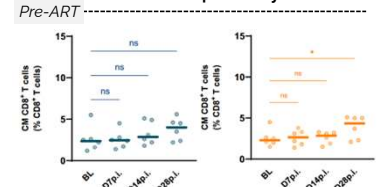
CHAMP study cohort

Percentage of participants mounting post-treatment control



Namazi et al., J Infect Dis 2018

SIV-macaques study

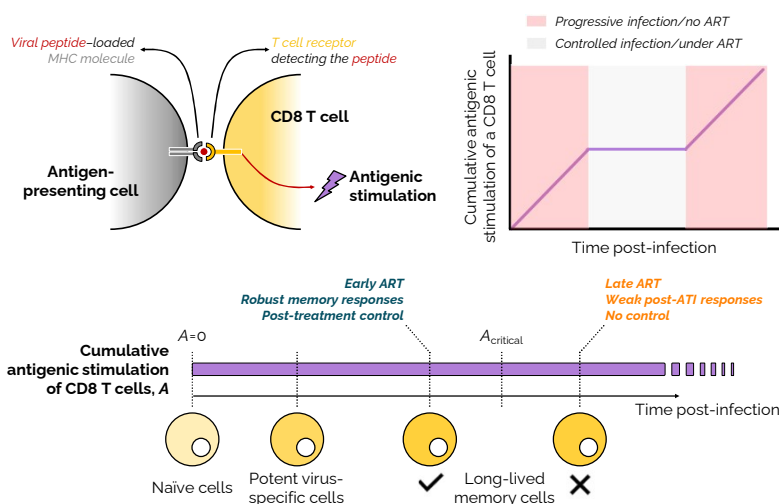


Passaes et al., Nat Commun 2024

- ART initiation time is strongly associated with the probability for mounting post-treatment control
- Robust CD8 T cell responses, driven by expansion of memory cells, may underlie viral control post-ATI

Hypothesis and the mathematical model

Cumulative antigenic stimulation governs survival of memory CD8 T cells



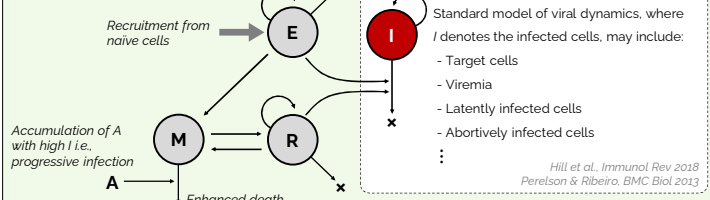
- Chronic stimulation of CD8 T cell pool hampers survival of memory CD8 T cells
- Early ART initiation mimics acute infection, limiting antigenic stimulation

ODEs-based mathematical model

- Tested the only existing model for post-treatment control; failed to explain the influence of ART initiation time
- Encoded different mechanisms of CD8 T cells (exhaustion, changing killing efficiency, etc.); model recapitulating the phenomenon is presented below

Conway & Perelson, Proc Natl Acad Sci USA 2015

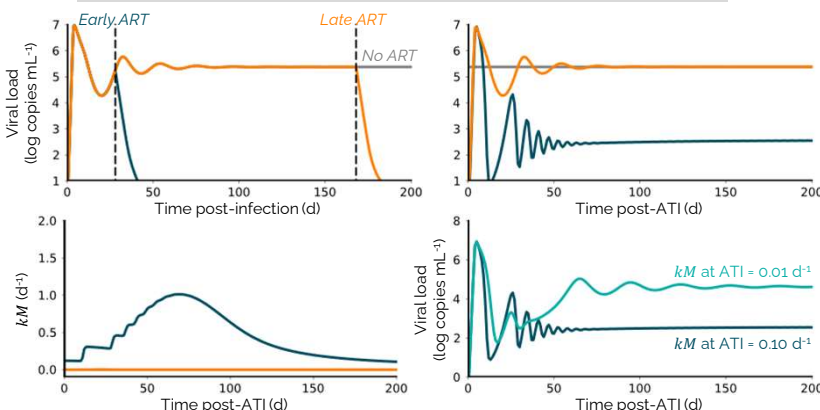
Model schematic



$$\begin{aligned} \text{Primary response effector cells} \quad \frac{dE}{dt} &= (\rho_E + \alpha_E E) \frac{I}{\theta_E + I} \left(1 - \frac{E+R}{\phi}\right) - d_E E - r_{EM} \left(1 - \frac{I}{\theta_M + I}\right) E \\ \text{Memory cells} \quad \frac{dM}{dt} &= (r_{EM} E + r_{RM} R) \left(1 - \frac{I}{\theta_M + I}\right) - r_{MR} \frac{I}{\theta_R + I} M - \left(d_M + d_x \frac{A^n}{\theta_A^n + A^n}\right) M \\ \text{Recall response effector cells} \quad \frac{dR}{dt} &= (r_{MR} M + \alpha_R R) \frac{I}{\theta_R + I} \left(1 - \frac{E+R}{\phi}\right) - d_R R - r_{RM} \left(1 - \frac{I}{\theta_M + I}\right) R \\ \text{Cumulative antigenic stimulation} \quad \frac{dA}{dt} &= \alpha_A \frac{I}{\theta_A + I} \end{aligned}$$

Results

Model recapitulates preservation of memory CD8 T cells with early ART



Conclusions

- Hypothesized that early ART mimics acute infection, generating long-lived memory CD8 T cells, while delayed ART initiation irreversibly modulates the CD8 T cell pool
- Constructed a mathematical model that recapitulates the virological and immunological features of post-treatment control influenced by ART initiation time
- Model predicted that a large memory CD8 T cell pool at ATI is necessary for viral control
- The framework could be employed to estimate quantitative targets for therapies designed for long-term remission

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