Modeling viral kinetics predicts a rapid establishment of the cytotoxic immune response targeting distinct infected cell compartments in SIV controller macaques

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Introduction

- Cynomolgus macaques from Mauritius intrarectally infected with SIV_{mac251} and harboring H6 MHC allele or challenged with a low inoculum are a recently developed model to reproduce mechanisms associated with HIV control.
- Although specific CD8 T cell mediated cytotoxic response is likely critical to achieve this control (2), the quantitative aspects of this response are poorly understood.
- The aim of this work was to characterize with mathematical models (3) the complex host-pathogen interaction driving this control as well as to quantify the dynamics of the different compartments of infected cells over time.

Methods

Data:

Viral kinetics of both viral SIV RNA and DNA were followed for 18 months after infection in 16 SIV_{mac251} infected cynomolgus with various MHC allele and inoculum levels (Fig 1). Ten of 16 macaques were found to control at 6 months post infection.

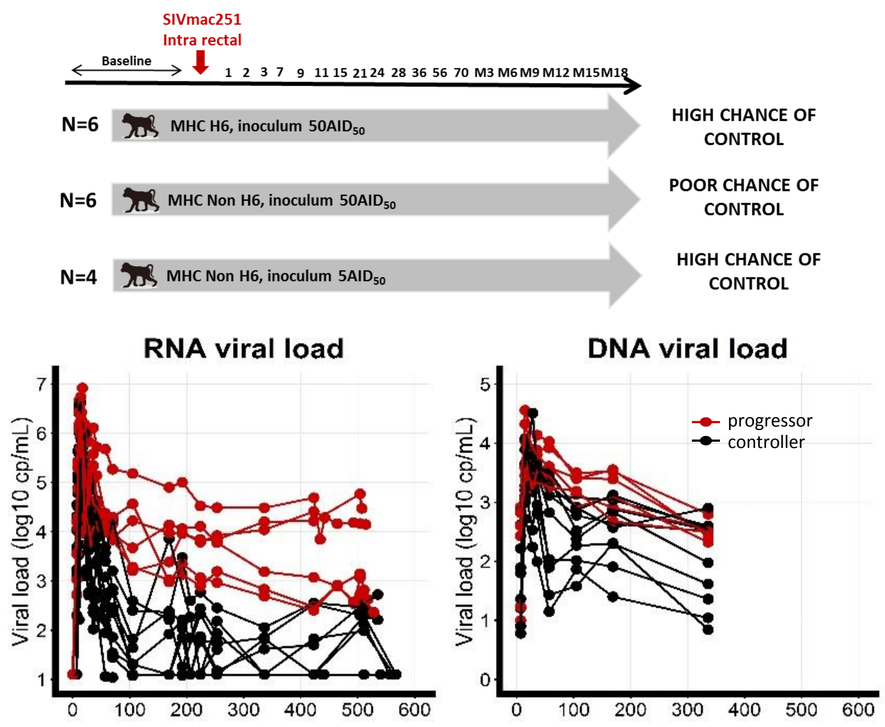

Figure 1: Top: design of the NHP experiment; bottom: RNA (left), and DNA (right) viral load in blood, in controller macaques (black) and progressor macaques (red)

Viral kinetics model selection:

A model assuming a cytotoxic adaptive immune response was selected to describe SIV RNA data from previously published models, based on Bayesian Information Criterion. Parameter estimation was performed using non-linear mixed effect models with SAEM algorithm implemented in Monolix software (4). Then, the selected model was extended to incorporate SIV DNA data as a measure of infected cell amount in peripheral blood (5).

Results

Viral kinetics model and evolution of the half-life of actively infected cells:

The best model to describe SIV RNA kinetics (Fig 2) incorporated immune response compartment E with a saturation term: $\frac{dE}{dt} = \lambda_E + \frac{\alpha_E EI}{(I+\theta)} - d_E E$

This model predicts that the half-life of actively infected cells changes from 5.5 day to 0.3 day over infection. The number of infected cells inducing half of the maximal proliferation rate θ is the key parameter driving the viral setpoint. More than the maximal strength of the immune response, its development rate is critical to observe the virological control.

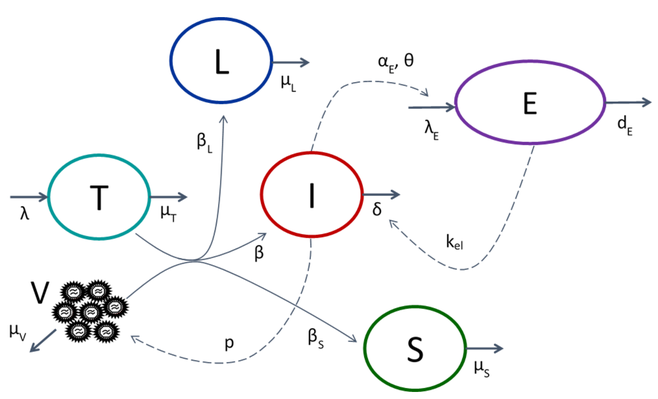

Figure 2: Final joint model of SIV RNA and SIV DNA viral loads

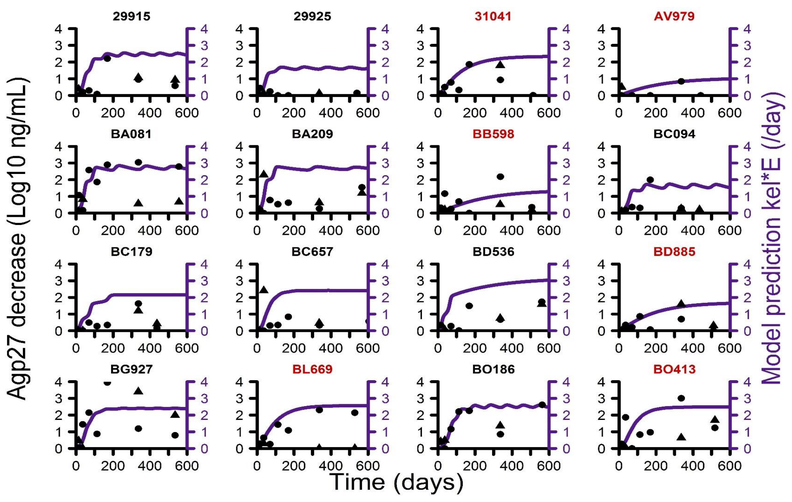

Figure 3: Model individual prediction of cytotoxic immune response strength (kel*E, purple line) and observed *ex vivo* CD8 T cell cytotoxic specific activity in blood (black dots) and in nodes (black triangle)

Immune response predictions:

Model prediction of the infected cell elimination rate mediated by the immune response compartment closely match the *ex vivo* cytotoxic activity of CD8 T cells (2) in a majority of individuals, when plotted over time with an arbitrary 1:1 ratio (Fig 3).

Results

SIV RNA and DNA kinetics:

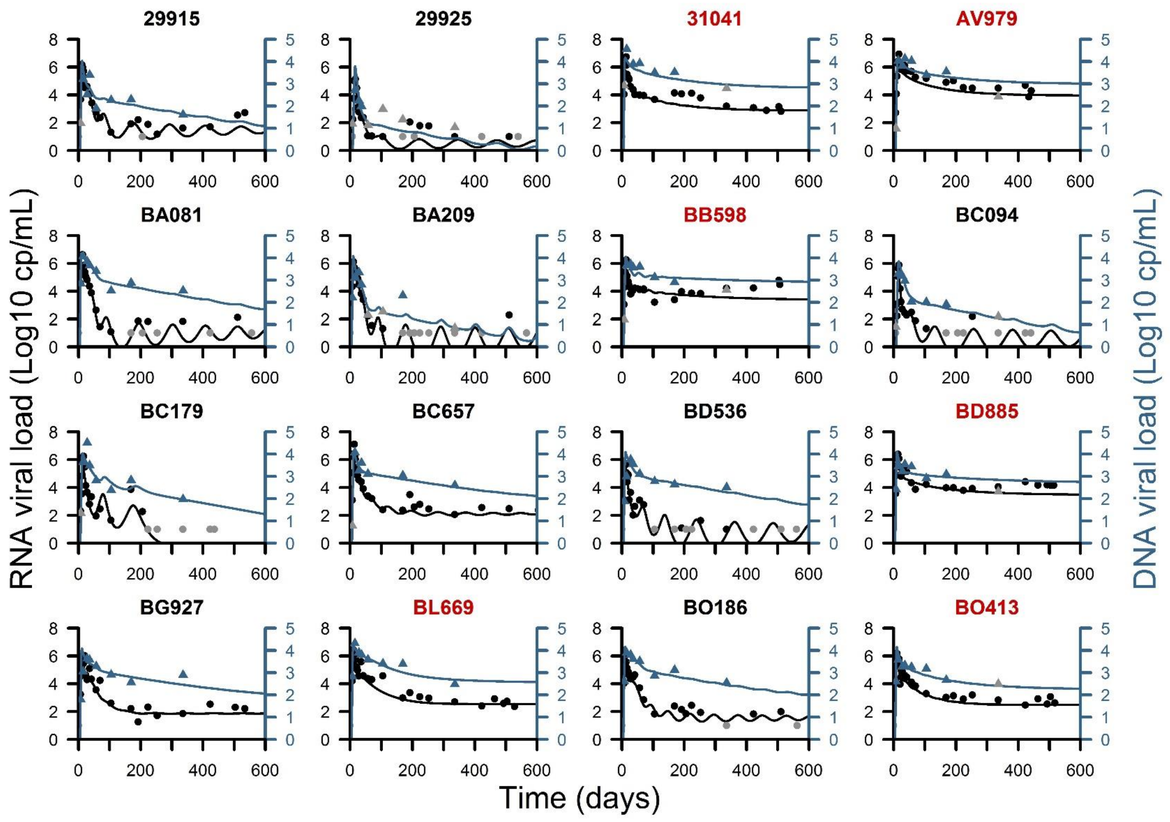

Figure 4: Observations (dots and triangles) and individual fits (solid lines) of RNA viral load (black, left axis) and DNA viral load (grey blue, right axis). Gray dots and triangles are data below the limit of quantification.

In order to fit both RNA and DNA kinetics, we found that it was necessary to incorporate three infected cell compartments: actively infected cells I, short lived non actively infected cells S and long lived non actively infected cells L (Fig 2). The model reveals a biphasic decline of the DNA viral load in controller macaques (Fig 4).

Model compartments predictions:

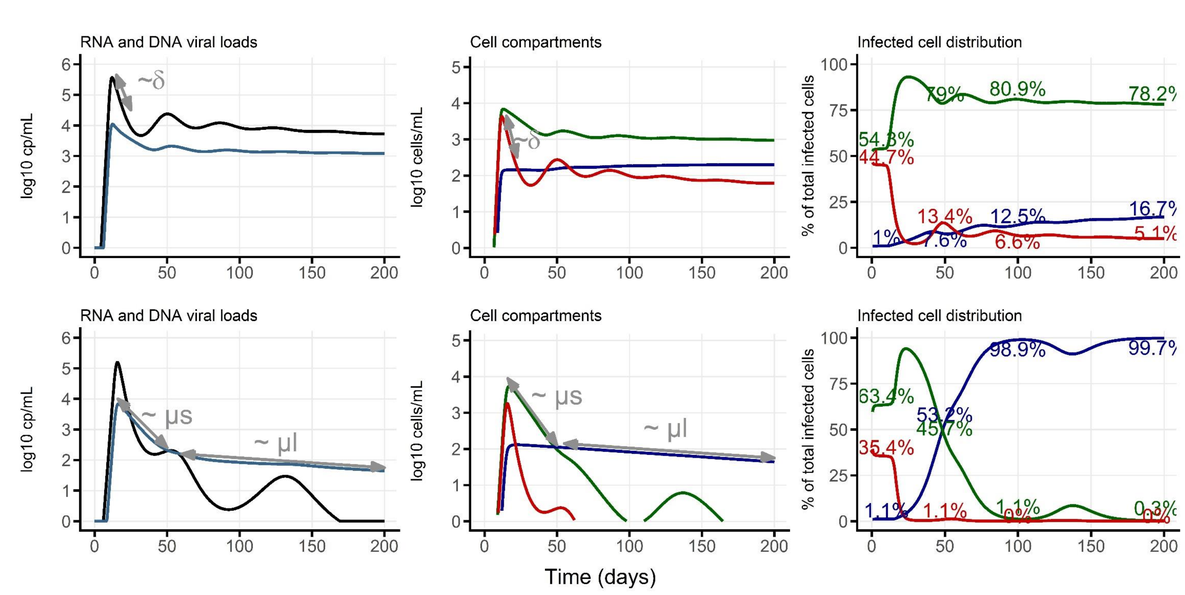

Figure 5: Model compartment prediction over time in a typical progressor macaque (top) and controller macaque (bottom). RNA (black), DNA (grey-blue), actively infected (red), short lived (green) and long lived (blue) non actively infected cells

The two slopes of DNA kinetics after the peak in controllers unravel the half-lives of the short lived and long lived non actively infected compartments (Fig 5) that we estimate to about **5.1** and **118.1 days**.

According to the model, the chance for a target cell to become actively, short lived or long lived non actively infected are equal to **47, 52 and 1%,** respectively.

In the months following acute infection, the model predicts that the **long lived** non actively infected cells become majority in controller, and **less than 0.1%** are **actively infected**. In contrast, in progressor macaques, the short lived non actively infected remain majority, due to the high level of new infections.

Conclusion

Our model predicts that an early establishment of an effective cytotoxic response is key to achieve viral control. Simultaneous analysis of SIV-RNA and SIV-DNA kinetics allows one to quantify distinct infected cell compartments and reveals that more than 90% of SIV-DNA containing cells do not significantly contribute to the viral production and are not highly targeted by the immune response.

References

1. **Bruel T, Hamimi C, Dereuddre-Bosquet N, Cosma A, Shin SY, Corneau A, et al.** Long-term control of simian immunodeficiency virus (SIV) in cynomolgus macaques not associated with efficient SIV-specific CD8+ T-cell responses. J. Virol. 2015;89:3542–56. 2. **Sáez-Cirión A, Lacabaratz C, Lambotte O, Versmisse P, Urrutia A, Boufassa F, et al**. HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T lymphocyte activation phenotype. Proc. Natl. Acad. Sci. U. S. A. 2007;104:6776–81. 3. **Perelson AS, Ribeiro RM.** Modeling the within-host dynamics of HIV infection. BMC Biol. 2013;11:96. 4. **Lavielle M.** 2014. Mixed effects models for the population approach: models, tasks, methods and tools. CRC Press. 5. **Avettand-Fènoël V, Hocqueloux L, Ghosn J, Cheret A, Frange P, Melard A, et al.** Total HIV-1 DNA, a Marker of Viral Reservoir Dynamics with Clinical Implications. Clin. Microbiol. Rev. 2016;29:859–80