Modelling virological breakthrough due to VRC01 resistance during analytical treatment interruption suggests avenues for prolonging HIV-1 remission

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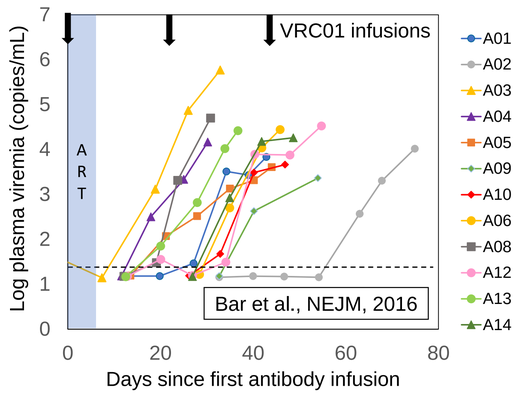
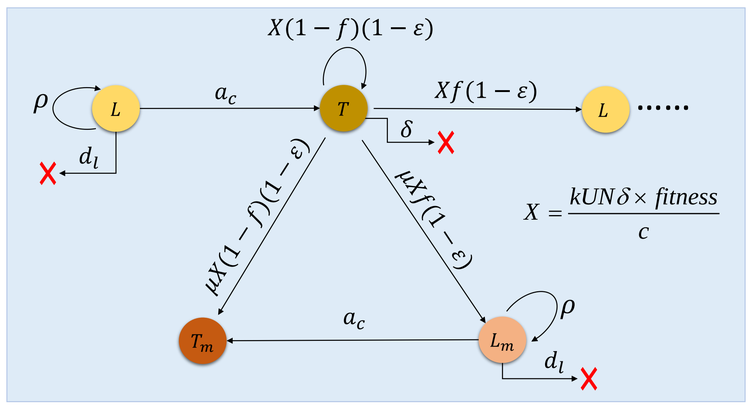
Introduction

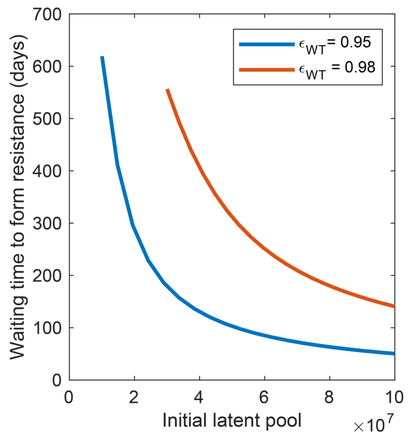
- Passive immunization with broadly neutralizing antibodies (bNAbs) after antiretroviral therapy (ART) can prolong viral remission.
- Recent clinical trials (Bar et al., 2016) using the bNAb VRC01 during treatment interruptions show fast viral rebounds in most of the patients in the presence of VRC01.
- The absence of active viral replication during ART indicates the crucial role of latency reactivation to the observed rebounds during ATI.



We hypothesize that latently infected cells harbouring VRC01 resistant proviruses cause rebound. We developed a stochastic model of viral dynamics with VRC01 to test this hypothesis.

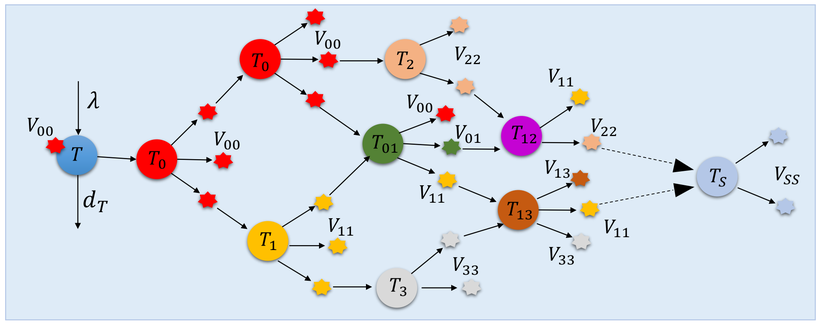
VRC01 sensitive strains can not explain rebound

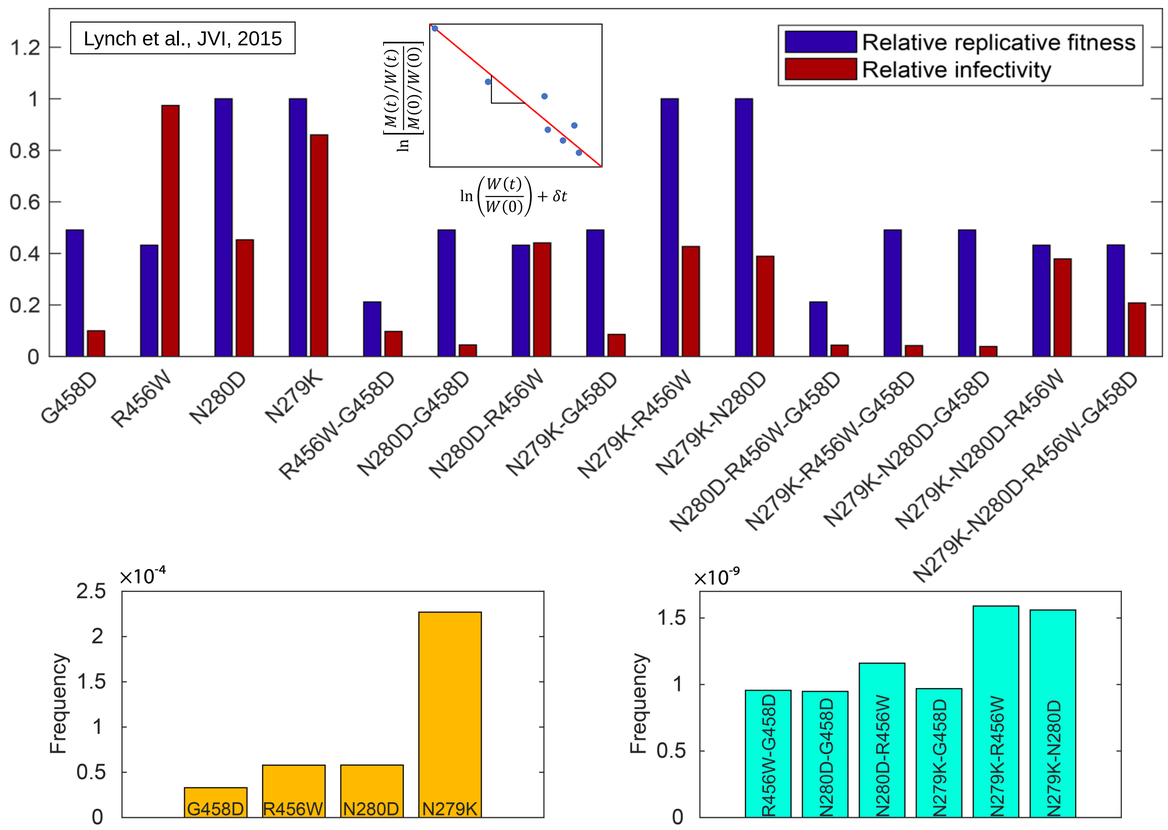




- In the presence of VRC01, $R_0^{WT} < 1$; replication of wild type virus is suppressed.
- The likelihood of *de novo* mutations is small; the average time to form resistant virus is more than the observed rebound times.

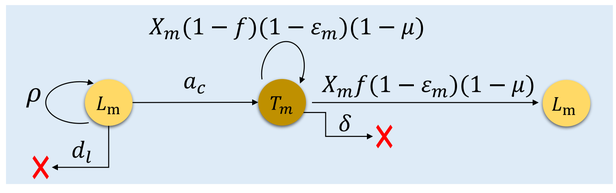
Single but not higher mutants resistant to VRC01 pre-exist

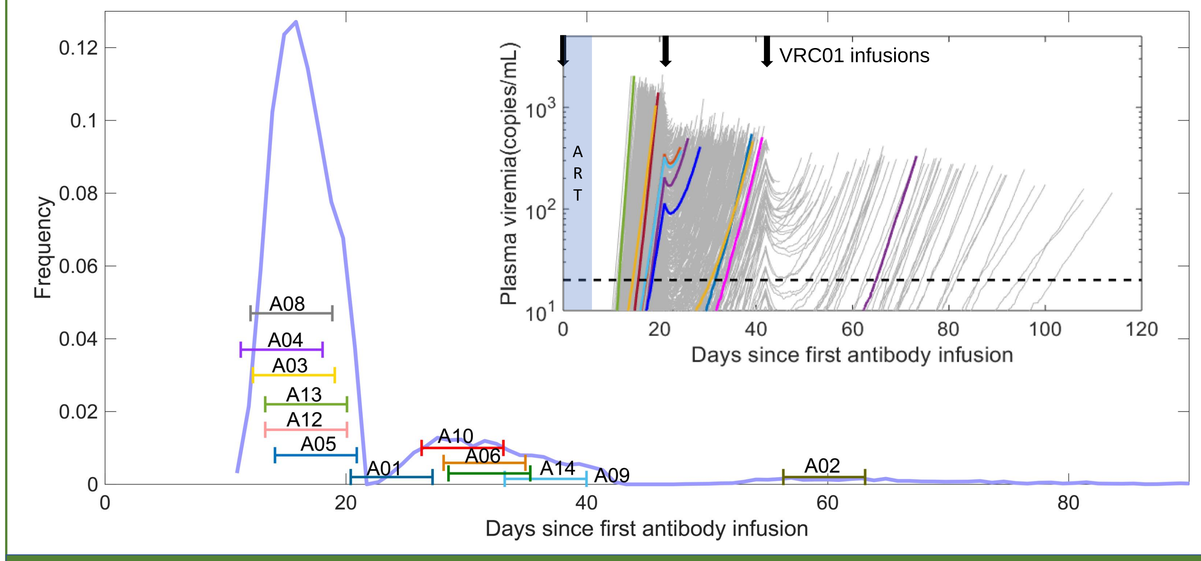




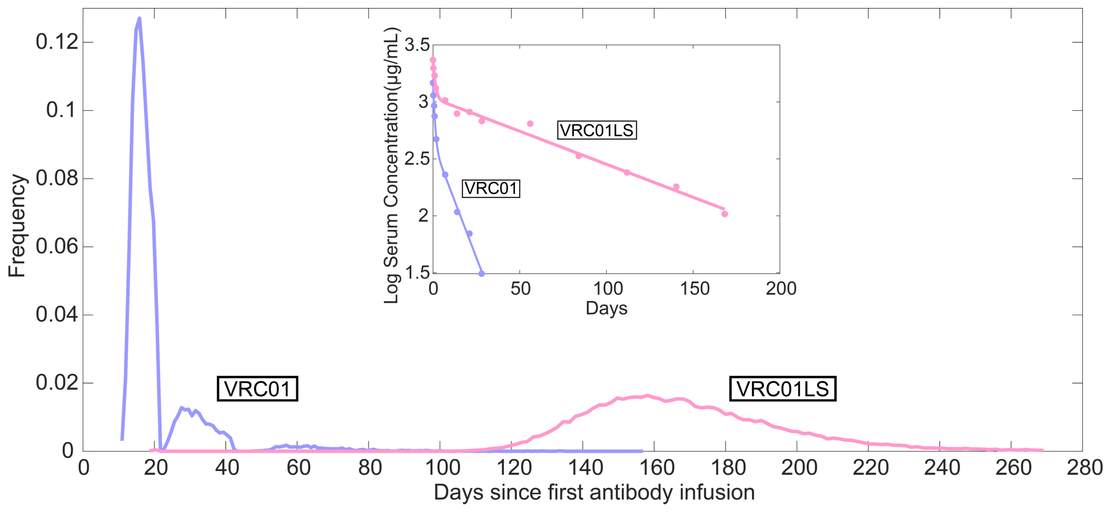
Total body burden of latent cells is $\sim 10^8$ cells (Estes et al., Nature, 2017). So single but not higher mutants are likely to cause the observed breakthroughs.

Model captures experimental rebound times





VRC01LS can extend remission



With the same dosing protocol, VRC01LS, with a >4-fold longer half-life than VRC01, can extend remission, on average, to ~5 months.

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