

Viral mechanisms of HIV/SIV persistence and latency

PE7

Low frequency of HIV rebound after antiretroviral treatment interruption

Pinkevych M.¹, Cromer D.¹, Tolstrup M.², Cooper D.³, Lewin S.^{4,5}, Søggaard O.², Rasmussen T.², Kent S.⁴, Kelleher A.³, Davenport M.¹

¹UNSW Australia, Sydney, Australia, ²Aarhus University Hospital, Denmark, Norway, ³Kirby Institute, Sydney, Australia, ⁴Doherty Institute for Infection and Immunity, The University of Melbourne, Melbourne, Australia, ⁵Alfred Hospital and Monash University, Melbourne, Australia

Background: HIV persists in latent reservoirs and produces viral rebound upon interruption of antiretroviral therapy (ART). Understanding the temporal kinetics of viral recrudescence upon interruption of ART is important for current curative strategies aimed at achieving ART-free viral remission.

Methods: We have analysed clinical data on time to viral rebound after ART-interruption from four independent patient cohorts totaling 100 patients. This includes patients treated with a variety of ART regimes, treated at different stages of HIV infection (including primary infection, n = 59), treated with latency reversing agents (n=9) and monitored regularly for viral recrudescence early after ART-interruption. We fitted a model of exponential distribution of time to recrudescence to each cohort to estimate the average frequency of viral recrudescence that would be required to produce the observed distribution of time-to-infection. The same approach was also applied to data on viral rebound in macaques treated early in infection.

Results: The time between ART-interruption and viral detection varied widely amongst different patients. However, within all patient cohorts, time to detection followed an exponential distribution. Fitting the distribution of time-to-detection, we derived an average frequency of viral recrudescence of once every 6 days (range 5.1 - 7.6 days between the four cohorts). This rate is over 30 times lower than previous estimated and suggests that a reduction in the reservoir size of around 61-fold would be required to extend the average time-to-recrudescence to about one year. Analysis of the time-to-recrudescence in a cohort of SIV infected macaques treated early in infection reveals an average frequency of reactivation events of once every 1.7 days - over three times more frequent than in HIV infection in humans.

Conclusions: Previous studies have suggested that HIV reactivates from latency around five times per day, based on indirect estimates of rates of acquisition of drug resistance under ART. We estimate a frequency of reactivation that is 30 times lower (once every 6 days), based on analysis of time to recrudescence. This has important implications for how much the latent reservoir will need to be reduced to produce significant remissions after ART-interruption.