Introduction.
- Current therapies aim to eradicate the latent reservoir, or decrease it enough to produce prolonged ART-free remission.
- We need to first understand the ‘normal’ rate of recrudescence of HIV from latency, in order to predict how much we need to decrease this to produce prolonged remission.

Goals.
Measure the ‘normal’ rate of HIV reactivation from latency after ART-interruption.

Method 1.
Time-to-detection of virus after ART-interruption.

Analyse time-to-detection from four published cohorts including 100 patients.

Results 1: Average frequency of reactivation is once every 5-8 days.

Cohort 1:
- 9 patients.
- Distribution in time-to-detection (TTD) consistent with random reactivation (exponential process).
- Growth rate not correlated with TTD.
- Average frequency of reactivation events = once every 7.6 days (95% confidence intervals (CI) = 6.5 - 9.1 days)

Cohort 2:
- 59 patients.
- TTD not simply due to growth rate.
- Reactivation every 6.3 days (95% confidence intervals (CI) = 5.7 - 7.1 days)

Cohort 3:
- 19 patients.
- TTD not correlated with growth rate.
- Reactivation every 5.1 days (95% confidence intervals (CI) = 4.2 - 6.5 days)

Cohort 4:
- 14 patients (average of 5 ART-I).
- Reactivation every 7.2 days (95% confidence intervals (CI) = 6.0 - 8.7 days)

Method 2.
Relative sizes of “reactivation founder” clones after ART-I

If reactivation occurs at some given frequency, then multiple reactivation events may occur sequentially. If we can identify ‘founder virus’ for each reactivation, then the relative sizes of each founder will depend on the frequency of reactivation.

The expected ratio of sizes of subsequent founders ($R$) will scale as:

$$ R = \frac{V_2}{V_0} = e^{\Delta V_0} $$

Where $V_0$ is the initial level of virus, $g$ is the growth rate of virus, $t_0$ is the time of reactivation of the first founder, and $\Delta V_o$ the time difference between reactivation events.

Results 2. Average delay between reactivation events is > 3.6 days.

- Apply to data from Joos et al, PNAS (2008).
- Ratios of 10 founders in six patients identified.
- Fit model of ratios ($* some ratios are minimum ratio$).
- Reactivation every 3.6 days (95% CI = 2.0 - 6.6). Likely longer due to min. ratios.

Conclusions.
- Both time-to-detection and ratio of ‘reactivation founders’ is consistent with random reactivation events.
- Average time between reactivation events is once every 5-8 days.
- 50-70 fold reduction in reservoir required to produce an average one year ART-free remission.