DYNAMICS OF REACTIVATION FROM LATENCY IN SIVMAC239M INFECTED MACAQUES.

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Introduction: The major obstacle in eradication of HIV is the latently infected $CD4^+$ cells that cause the reactivation of virus after anti-retroviral treatment interruption.
However there is a lack of knowledge about the dynamics of reactivation from latency, such as the frequency of latent cell reactivation, whether reactivated cells live for a prolonged period, how much virus they produce, and whether they die following reactivation. In order to answer these questions we combined a novel method of 'sequence barcoded' viruses to track the reactivation of individual latent cells with mathematical modeling.

Methods: Rhesus macaques were infected with 2.2 x 10^5 IU of SIVmac239M - a sequence tagged virus with ≈10,000 different strains differing only at a 34bp barcode inserted between the Vpx and Vpr genes. Animals were treated with TFV/FTC/RAL at day 6 for 82 days (n = 3, group 1), or with TFV/FTC/IND/RTV on day 4 for >300 days (n = 6, group 2) prior to treatment interruption. Illumina sequencing was used to identify the frequency of individual clonotypes following treatment interruption.

Results: We analysed and modelled viral load and frequency of 'reactivation founders' in after treatment interruption. The frequency of reactivation from latency ranged from 30 reactivations per day to 0.36 per day. The frequency of reactivation was strongly correlated with pre-treatment viral load, and appeared only minimally affected by duration of therapy.

Conclusions: Analysis of SIVmac239M reactivation from latency after treatment interruption shows a high frequency of reactivation, consistent with previous studies. Modelling suggests that the production of virus from reactivated cells may be 'burst-like' consistent with these cells being short lived following reactivation.

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