

## Changes in Viral Fitness following acute HIV-1 infection and interrupted antiretroviral therapy

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**Introduction:** The aim of this study was to investigate the relationship between viral fitness and control of viral load (VL) in acute and early HIV-1 infection. Relative to disease progression, it has been observed in several clinical studies that isolates which are less fit are also less pathogenic. Samples were obtained from subjects participating in two clinical studies. In the PULSE study, HAART was initiated prior to, or no later than six months following, seroconversion. Subjects then underwent a maximum of three structured treatment interruptions (STIs). Participants in the PHAEDRA study were identified after seroconversion, forming an observational cohort that did not receive HAART.

**Methods:** A combined total of 51 isolates were obtained from cohort members. Isolates from more than one time point were obtained from 20 subjects (eight PULSE and 12 PHAEDRA subjects). Viral fitness was examined *ex vivo* using a standardised input of 600 pg of p24 in parallel with a reference isolate, HIV-1<sub>MBC925</sub>. Cells were cultured for 96 to 158 hours, prior to quantification and analysis of total viral DNA using a real time PCR assay developed in our laboratory, to determine viral fitness.

**Results:** The relative fitness of isolates obtained from six and nine participants of the PULSE and PHAEDRA studies, respectively, was investigated in this study. The fitness of isolates obtained from 5 of 6 PULSE subjects decreased over time, following intermittent HAART. Although decreasing VL correlated with decreasing viral fitness for 4 of 6 PULSE subjects, overall, viral fitness did not correlate with plasma VL. The fitness of paired isolates obtained from 7 of 9 PHAEDRA subjects increased significantly over time ( $p=0.03$ ). Viral fitness did not correlate with VL for the PHAEDRA subjects investigated. The relative fitness of isolates obtained at Baseline from PULSE subjects was equal to, or greater than that of isolates obtained 36 or 52 weeks subsequent to Baseline from PHAEDRA subjects. At baseline, the majority of PULSE subjects were at an earlier stage of infection than PHAEDRA subjects, confirmed by Western blot. Furthermore, the relative fitness of several isolates obtained from plasma collected at Baseline from PULSE subjects, prior to initiation of HAART, was greater than that of a highly pathogenic primary reference strain obtained from an individual with AIDS.

**Discussion:** Changes in relative viral fitness over time were observed for six and nine subjects participating respectively in the PULSE and PHAEDRA studies. However, viral fitness did not correlate with plasma VL. Most unexpected was the high relative fitness of isolates obtained at Baseline from PULSE subjects, prior to initiation of HAART. It is widely thought that the fitness of strains present during the acute phase is low relative to strains present during chronic HIV-1 infection, due to the bottleneck imposed upon transmission. The findings of this study provide evidence that the relative fitness of strains present during acute HIV-1 infection may be higher than previously thought. Furthermore, these viral fitness data may add considerable weight to the debate over when, during the course of HIV-1 infection, HAART should be initiated. If initiation of HAART during acute HIV-1 infection can reduce relative viral fitness, then the viral set-point and the rate of disease progression may also decrease.