HIV-1 over time: fitness loss or robustness gain?

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In a recent issue of *Nature Reviews Microbiology*[1] Arien and colleagues discussed the possibility that HIV-1 is measurably attenuated over time, based on reduced replication fitness *in vitro*. Historical isolates out-competed recent isolates in 176 out of 238 comparisons[2], although only twice in 4 matched competitions between isolates of subtype B-CCR5. Whether decreased fitness *in vitro* equates with diminished HIV-1 virulence is debatable, especially without any evidence of reduced disease severity or transmission, as stable[3–5] or worsening[6,7] prognostic markers have been reported over time.

As an alternative to the possible adaptation to the host, we propose that HIV-1 is shifting towards the possession of increasingly robust population characteristics (providing greater resilience against niche perturbations), which sustain survival and proliferation during environmental fluctuations at the expense of replication fitness, so exemplifying the 'survival of the flattest' effect[8].

HIV-1 evolution over time may correspond to the relocalization of circulating viruses from regions of high fitness and low mutational support to lower fitness and high mutational support, so reflecting the trade-offs between intra-host replication and inter-host transmission (FIG. 1). Genotypes on high, narrow fitness peaks are hypersensitive to mutations compared with genotypes on flatter, lower peaks, where more mutants can retain near-optimum fitness. High mutational support refers to the greater numbers of offspring surviving a mutation, which offsets the disadvantages of lower fitness. This interpretation stems from the observation that despite similar mean intra-group fitness values between historical and recent isolates, inter-group fitness differences favoured the historical isolates[2] (FIG. 1).

As HIV-1 encounters fluctuating pressures within and between hosts (for example, different immune pressures or compartments, local extinctions and population outgrowths), genetic robustness (defined as phenotypic constancy despite mutational change[9]) could arise, as it allows biological systems to maintain their function despite perturbations. *In silico* studies have demonstrated that organisms on low, flat peaks can displace fast-replicating organisms on higher, narrower peaks — an effect termed 'survival of the flattest'[8–11]. This effect can also be viewed as a pressure to occupy highly connected, rather than sparse, areas of a network[9]. Although phenotypic constancy could appear to be at odds with the ever-increasing HIV-1 diversity, robustness and diversity are not mutually exclusive. Robustness combined with flexibility renders the exploratory behaviour of the virus less uncertain, by buffering it from lethal mutational effects[12,13].

Although robust properties and escape mutations accruing in HIV-1 are plausible explanations for its lower fitness as the epidemic proceeds, we stress that diminished fitness does not necessarily imply attenuation. For individuals infected with ever-newer HIV-1 generations, adverse outcomes could be expected. A partially debilitated virus could be better controlled by the host immune response, which would result in reduced or delayed disease progression and potentially attenuation. By contrast, a gain in robustness could ensure more transmissions and thus greater dissemination. Moreover, adaptation to common human leukocyte antigen alleles could gradually result in multi-escape variants, with impaired fitness balanced by a reduced susceptibility to cytotoxic T-lymphocyte recognition. This scenario of increased transmissions fostered by mutational robustness, coupled with less effective immune responses, contrasts starkly with attenuation.

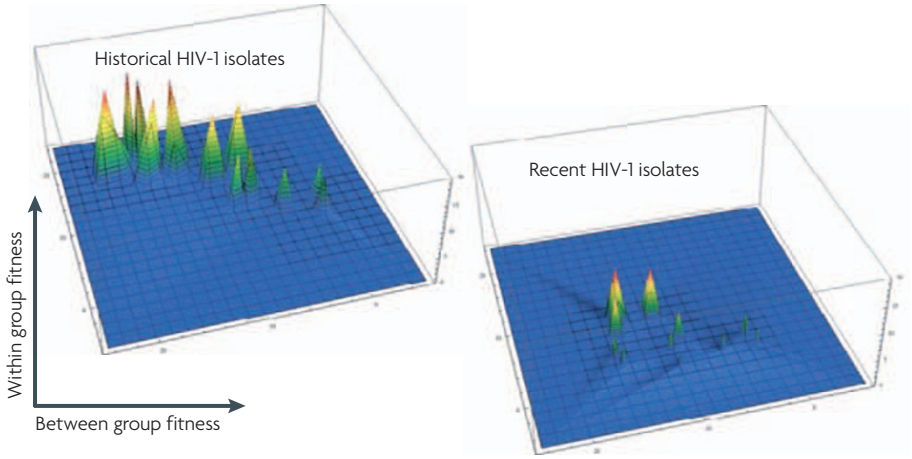

Figure 1 | **Fitness landscapes of historical and recent isolates of HIV-1.** The fitness landscapes shown represent data published by Arien and colleagues[1]. The height of the peaks corresponds to the mean replication fitness values for inter-group virus competitions, whereas the area under the peaks corresponds to the mean replication fitness values for intra-group competitions. Compared with historical isolates, recent isolates appear to constitute a network of lower fitness, with flatter peaks and fewer amplitude changes between peaks and valleys. 3D plots were obtained using Mathematica 6 (Wolfram Research, Champaign, Illinois, USA).

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