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## **FITNESS OF HISTORICAL AND RECENT HIV-1 ISOLATES IN THE EPIDEMIC: EVIDENCE FOR ATTENUATION**

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**INTRODUCTION:** Co-evolution of viruses and hosts may result in altered virulence as an epidemic progresses. None of the natural primate hosts manifest severe clinical symptoms upon SIV-infection, suggesting that these viruses have reached balance with their natural host in terms of replicative fitness, intraspecies transmission efficiency, and host survival. It is still unknown whether the introduction of HIV into the human population will lead to similar adaptation(s) and if so, how long this process will take. We studied the replicative fitness of a dozen historical patient HIV-1 isolates (1986-1989) that were matched with recent HIV-1 viruses (2002-2003) for CD4 cell count, co-receptor tropism and genetic subtype.

**METHODS:** Viral fitness was evaluated using full pairwise dual infection competition assays in diverse primary human cell types (PBMC, dendritic cells (DC) and CD4+ T-cells). Sensitivity to TAK-779 and 3-TC of NSI/R5 primary isolates was measured in U87.CD4.CCR5 cells. Env and Pro-RT regions were sequenced and subject to phylogenetic analyses.

**RESULTS:** We showed that recent HIV-1 patient isolates (i.e. isolated in 2002 and 2003) have significantly lower fitness than viruses from the 80s when head-to-head competitions were performed in PBMC and DC/T cell. Recent viruses also showed increased sensitivity to inhibition by 3-TC and TAK-779. Pro-RT sequence analyses revealed that these differences are not caused by drug-resistance mutations. Finally, predicted amino acid sequences and genetic analyses suggest that these early and more recent viruses did not form distinct clusters in phylogenetic trees and did not differ in

average genetic distances. These results suggests that multiple evolutionary pathways may be responsible for this attenuation.

**CONCLUSIONS:** These results provide the first experimental evidence of diminished replicative fitness and increased sensitivity to TAK-779 and 3-TC of present-day HIV-1 patient isolates compared with historical samples. This observation also predicts a trend for attenuation of HIV-1 replicative capacity as the epidemic progresses.

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Mechanisms of drug resistance and fitness

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