

17th International HIV Drug Resistance Workshop



10-14 June 2008, Sitges, Spain

FITNESS PROGRESSION AND PHENOTYPIC SUSCEPTIBILITY TO RALTEGRAVIR OF HIV-1 INTEGRASE ARE NOT RESTRICTED IN LONG-TERM HAART-TREATED PATIENTS

Antivir Ther 2008; 13 Suppl 3:A83 (abstract no. 76)

MJ Buzón¹, S Marfil¹, MC Puertas¹, E Garcia¹, B Clotet¹, J Blanco¹, C Cabrera¹ and J Martinez-Picado^{1,2}

¹irsicaixa Foundation, Badalona, Spain; ²Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

BACKGROUND: Protease (PR), reverse transcriptase (RT) and integrase (IN) share the same precursor polyprotein (Pr160^{Gag-Pol}), and several studies suggest functional interactions between IN and RT. Moreover, natural polymorphisms within IN have been associated with both RT resistance mutations in highly active antiretroviral therapy (HAART)-treated patients and resistance to IN inhibitors. In this study, we aim to elucidate whether long-term HAART targeting PR and RT may preclude IN fitness progression and raltegravir susceptibility.

METHODS: HIV-1 IN population-based sequences, from 45 heavily antiretroviral-treated patients with longitudinal samples separated for a median of 10 years, were obtained to estimate the rate of nucleotide substitutions. IN-recombinant viruses were generated from five patients whose HIV-1 IN accumulated between three and 14 amino acid substitutions over the study period. Changes in viral replication capacity were assayed by competition of intrapatient IN-recombinant virus in the absence of drugs. Phenotypic susceptibility to raltegravir was performed in TZM-bl cells. Additionally, the study included IN-recombinant virus generated from a patient failing a raltegravir-containing regimen and harbouring resistance mutations G140S/Q148H and from the site-directed mutant T66I, resistant to IN inhibitors other than raltegravir.

RESULTS: The rate of nucleotide substitutions within IN was 0.06% per year. Competition experiments showed that IN-recombinant viruses corresponding to IN samples after 10 years of HAART had similar or improved replication capacity than those corresponding to IN-recombinant viruses from baseline samples. Moreover, neither early nor late IN-recombinant viruses showed increase in phenotypic susceptibility to raltegravir. By contrast, recombinant IN from the raltegravir-experienced patient with mutations G140S/Q148H showed a 23-fold increase in drug susceptibility entailing a

replication capacity cost. Finally, the site-directed mutant T66I was susceptible to raltegravir, but less replicative in absence of drug than the wild-type virus.

CONCLUSIONS: Long-term drug pressure with PR and RT inhibitors is not enough to restrict fitness progression of IN. Additionally, HIV-1 IN from longitudinal samples obtained from patients treated with IN inhibitor-sparing regimens showed no evidence of genotypic and phenotypic resistance to raltegravir. These data suggest that current antiretroviral regimens do not preclude either IN fitness or efficacy of raltegravir.

2008-06-10

76

Copyright © 2008 - [International Medical Press Ltd.](#) Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.