

# The relationships between variability, architecture and mutation co-occurrence in the HIV-1 integrase: implications of Raltegravir treatment.

Lucas de Almeida Machado, Ana Carolina Ramos Guimarães

*Fiocruz*

## Abstract

The integrase of HIV-1 is one of the primary targets in antiretroviral therapy. This enzyme is responsible for integrating the viral DNA into the host genome, a crucial step in the HIV-1 replication cycle. The integrase inhibitor Raltegravir (RAL) has been widely used in antiretroviral therapy; however, the emergence of RAL-resistant HIV-1 strains has become a worldwide problem. Here, we compared the variability of each position of the HIV-1 integrase sequence in clinical isolates of RAL-treated and drug-naïve patients by calculating their Shannon entropies. We also built tridimensional models of the HIV-1 integrase and a mutation co-occurrence network. The relationship between variability, architecture, and co-occurrence was investigated. It was observed that positions bearing major resistance-related mutations are highly conserved among non-treated patients and variable among the treated ones. The integrase structure showed that the highest-entropy residues are in the vicinity of the host DNA, and their variations may impact the protein-DNA interface. The co-occurrence network and structural analysis support the hypothesis that the resistance-related E138K mutation compensates for mutated DNA-anchoring lysine residues. Our results reveal patterns by which the integrase adapts during the RAL therapy. This information can be useful to rethink the drugs currently used or to guide the development of new ones.

Funding: CAPES