CROI-0271: Vulnerable targets in HIV-1 Pol for attenuation-based vaccine design

**Introduction**

CD4+ T cell mediated escape mutations in Gag can reduce viral replication and alter HIV-1 disease progression, but less is known about immune-mediated attenuation in other HIV-1 proteins. Identification of viral mutants that compromise HIV’s ability to replicate may aid rational vaccine design.

Here, we aimed to investigate whether specific amino acid mutations are associated with altered RT-integrase fitness and its impact on the clinical course of HIV infection, using a large population of individuals infected with HIV-1 subtypes C, the most prevalent subtype worldwide.

**Methods**

We generated 487 recombinant viruses encoding RT-integrase sequences from individuals with chronic infection (n = 408) and recent (n = 81) HIV-1 subtype C infection and measured their in vitro RC using a GFP-reporter T-Cell assay.

**Pol-driven RC is clinically relevant**

Pol (HXB2)-driven RC is clinically relevant.

**Phylogenetic analysis**

Phylogenetic analysis identified several key mutations associated with altered RC.

**Amino acid variants associated with altered RC**

Amino acid variants associated with altered RC were identified through sequence analysis.

**Conclusion**

Together, our data suggest that RT-integrase-driven RC is clinically relevant, and provide evidence that sequence- and residue selection of residues in RT-integrase can compromise RC:

- Identification of the specific RT-integrase amino acids that are significantly associated with altered RC, support prior studies on escape/mutation-driven mutation in the integrase RC.
- RT-integrase variants in vital domains of the RT pol (A595 and RT b'141 and 207F) represent potential vulnerable targets for an attenuation-based vaccine.
- The multiplex experiments confirm the impact of the identified RT mutations on the viral process of one reverse transcription.
- Extended integrase is associated with decreased replication capacity.

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