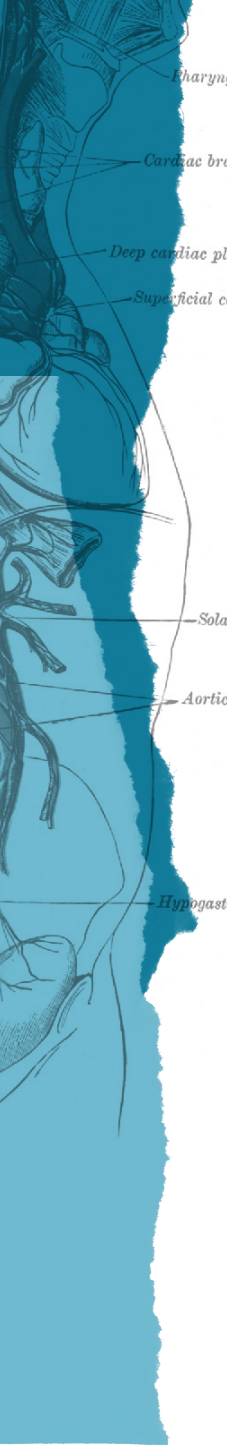

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Mechanisms of HIV Drug Resistance: Survival of the Fittest?

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ABSTRACT

Introduction: Despite the success of antiretroviral therapy (ART) in transforming HIV from a fatal disease into a manageable chronic condition, the emergence of drug resistance remains a major obstacle to sustained virological suppression.

Methods: This presentation explores the complex interplay of molecular mechanisms driving resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), with a focus on excision and discrimination pathways mediated by mutations in the HIV-1 reverse transcriptase (RT).

Results: In addition, we also present evidence that RNase H activity and its modulation by the nucleocapsid (NC) protein—particularly the immature forms NCp9 and NCp15—significantly influence drug resistance by destabilizing the primer-template complex and suppressing excision-based rescue of chain-terminated primers. Using biochemical assays, structural modeling, and a large-scale bioinformatics analysis of over 6,000 viral genomes, we identify specific RT and Gag mutations—including insertions—that may act as compensatory mechanisms for maintaining replication fitness in resistant strains.

Conclusions: Our findings support a systems-level view of HIV replication, highlighting the interconnected roles of RT, NC, and Gag in shaping drug resistance phenotypes. These insights may inform future therapeutic strategies aimed at limiting viral escape and improving ART durability.

Keywords: HIV-1, reverse transcriptase, drug resistance, nucleocapsid, RNase H, excision, NRTIs, viral fitness.