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LOW REPLICATION CAPACITY OF SUBTYPE C HIV IN THE PHENOSENSE ASSAY IS NOT A RESULT OF HETEROLOGOUS SUBTYPE B GAG OR POL SEQUENCES

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BACKGROUND: Currently available recombinant virus susceptibility assays for HIV-1 are performed using subtype B based resistance test vectors (RTVs) into which patient-derived protease (PR) and reverse transcriptase (RT) sequences are transferred. The potential effects of mixed-subtype RTVs on drug susceptibility and replication capacity (RC) are not well understood. Here we examine the influence of mismatched regions from subtypes B and C on RC results.

METHODS: Infectious subtype C cDNA clones were used to construct two versions of a subtype C RTV and subtype B/C chimeric RTVs. HIV genomes were divided into five different cloning regions: i). 5'LTR to the start of *pol*; ii). the start of *pol* to the C-terminal region of RT; iii). the C-terminal region of RT to the middle of VPR; iv). the middle of VPR to the middle of envelope; and v). the middle of envelope to the end of the 3'LTR. RC was measured using the PhenoSense HIV assay. Immunoblot analysis using antibodies to p24 was performed to evaluate virus particle production in transfected cells and supernatants.

RESULTS: The standard subtype B RTVs containing PR/RT regions derived from subtype C HIV patient samples lacking recognized resistance mutations had a median RC of 49.6% ($n=309$), compared to 97.1% for subtype B PR/RT regions ($n=12,223$). The two complete subtype C RTV exhibited RC equal to, or greater than the standard subtype B RTV. Chimeric B/C RTVs containing subtype C *pol* (region II) on a subtype B backbone had reduced RC (15–40%). Matching the subtype C *gag* and *pol* sequences (regions I and II, respectively), such that *gag* and *pol* were derived from the same subtype, did not restore RC. RC was not strictly related to virus production or *gag* processing as assessed by p24 levels in transfected cells and supernatants.

CONCLUSIONS: The lower RC values observed for subtype C-derived patient sequences does not appear to be a result of mismatched *gag* and *pol* sequences. Therefore, additional sequences outside of the *gag* and *pol* regions significantly influence RC. The location of these sequences, effects on drug susceptibility and the clinical relevance of these findings are under investigation.

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