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MULTIDRUG RESISTANT HIV-1 RESULTING FROM INTRAPATIENT VIRAL RECOMBINATION

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INTRODUCTION: Multidrug resistant HIV-1 is increasing worldwide. Although inpatient HIV-1 recombination has been postulated to result in highly resistant strains, such recombinatorial events have not yet been observed. We studied the evolution of HIV-1 resistance in the female genital tract and plasma, examining the role of inpatient recombination in the development of multidrug resistance.

METHODS: We compared HIV-1 variants in contemporaneous plasma and cervicovaginal lavage (CVL) obtained at five timepoints from a US woman who initiated AZT, 3TC, and NVP. After sequencing pol (protease and RT, ~1600bp) and gp120 (V1-V5) derived by endpoint dilution PCR or cloning, we determined genotypic resistance, phenotypic resistance, and replicative capacity (RC). Phylogenetic studies included Bayesian analyses.

RESULTS: Before treatment, HIV-1 variants in both compartments exhibited no resistance and high RC. Soon after HAART was initiated, however, variants evolved differently in each site. CVL and plasma strains both displayed NVP resistance, but mutations initially differed in each compartment; K103N predominated in plasma, with G190S in CVL. RC's of CVL strains were substantially lower than those from plasma, and computational analyses showed sequences compartmentalized between the two sites. Six months later, CVL and plasma strains were intermingled phylogenetically. Furthermore, strains from both sites generally showed a predominance of the K103N mutation and comparably high RC's. Computational analyses revealed multiple inpatient recombinants between strains from CVL and plasma, with breakpoints in

both *pol* and *env* genes. Bayesian analysis demonstrated a multidrug resistant recombinant that had acquired the K103N mutation from a plasma-derived strain and the M184V and G190S mutations from a strain in the CVL.

CONCLUSIONS: We have documented inpatient recombination resulting in multidrug resistance. Serial analyses of viral resistance, RC, and phylogenetic relationships in two anatomic compartments during HAART revealed the evolution of HIV-1 strains displaying multidrug resistance and high fitness in both sites.

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