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SELECTION OF NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI) RESISTANT HIV-1 AFTER DISCONTINUATION OF A VIROLOGICALLY SUPPRESSIVE REGIMEN

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BACKGROUND: The frequency of emergence of drug-resistant virus after discontinuation of suppressive antiretroviral therapy (ART) is undefined.

METHODS: Study subjects were on NNRTI-containing regimens with HIV RNA <400 c/ml enrolled in ACTG A5170, a prospective 2-year treatment discontinuation study of individuals with CD4>350 cells/mm³. Other components of ART were stopped within 2 days of NNRTI. At first RNA >5000 c/ml after ART discontinuation, resistance in plasma was measured by standard genotype (SG) and allele-specific PCR (ASP). Predictors of NNRTI resistance at rebound examined include prior regimens, HIV RNA, CD4, baseline PBMC resistance by oligonucleotide ligation assay, NNRTI drug concentrations and CYP2B6 polymorphisms.

RESULTS: NNRTI resistance mutations were detected at virological rebound in 11 of 54 (20%) subjects (33 on efavirenz, 21 on nevirapine): 5 (9%) by SG; and 6 (11%) by ASP. Resistance mutations by SG were all K103N; by ASP – K103N (4), Y181C (1), and K103N/Y181C (1). After ART discontinuation, RNA >5000 c/ml was reached at week-4 in 23 subjects, Week-8 in 25, and ≥week-16 in 6. Subjects with baseline RNA 51–400 c/ml had a 3.3 fold (95% CI=1.3, 8.5) increased risk for resistance at rebound compared to subjects with RNA ≤50 c/ml. NNRTI resistance emerged in 45% of subjects with baseline RNA 51–400 c/ml versus 14% with RNA ≤50 c/ml (*P*=0.03). PBMC resistance was more frequent among subjects with RNA 51–400 c/ml at baseline and was associated with a 2.9 fold (95% CI=1.1, 7.4) increased risk for resistance at rebound. Resistance

persisted for the duration of treatment interruption (36–48 weeks) in 3 of 5 subjects with mutations by SG. Five virological failures occurred among 23 subjects who restarted ART during observation; all 5 restarted the same prior regimen and 2 of 5 had NNRTI resistance.

CONCLUSIONS: Individuals who discontinue NNRTI-containing ART while virologically suppressed are at substantial risk (20%) of demonstrating NNRTI resistance at virological rebound that may persist in plasma for months. The highest risk of resistance is associated with low-level viral replication (HIV RNA 51–400 c/ml) at treatment discontinuation (45% resistance). The effect of this resistance on response to subsequent NNRTI-containing ART warrants further study.

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