Retention and Decay of HIV-1 Drug Resistance Mutations in Proviral DNA

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Background: The persistence of HIV-1 drug resistant mutations (DRM) in the reservoir of integrated, latent provirus and their fixation and decay rate over time may impact future treatment options. The retention of K103N and other DRM in subjects who failed an Efavirenz (EFV)-based regimen were assessed after suppression to <50 copies/ml for 2-11 years on a protease inhibitor (PI)-based regimen. PBMC proviral DNA was genotyped to determine the kinetics of retention and decay of K103N and other DRM.

Methodology: Proviral DNA was isolated from peripheral blood mononuclear cells (PBMC) of 28 subjects from ACTG 364 and ACTG 5095 with documented K103N in plasma viral RNA at time of EFV failure. HIV-1 pol was amplified and subjected to population sequencing. For most samples, genotypes were obtained at three time points (first suppression (t1), most recent suppression (t3), and between first and most recent suppression (t2)). Repeated measures logistic regression (generalized estimating equations) was used to identify factors associated with detectable K103N in proviral DNA.

Results: At t1, t2, and t3, 50% (14/28), 62% (13/21) and 48% (11/23) of subjects had detectable proviral K103N with median 0.6 (Q1-Q3: 0.6-0.7), 2.6 (1.8-4.0) and 4.2 (2.5-7.1) years of suppression. Years since suppression was not associated with the likelihood of detectable proviral K103N (P=0.53). In adjusted model with years since suppression, log10 plasma HIV RNA level at EFV failure was associated with increased likelihood of observing proviral K103N (P=0.04); odds of detectable proviral K103N was 2.6 (95% CI: 1.0-6.4) times higher per log 10 higher HIV RNA at EFV failure. Other covariates (protocol study, age, CD4 count and HIV RNA at baseline) were not associated with detectable proviral K103N. Frequency of NRTI mutations was 75% (21/28) in RNA at EFV failure, 54% (15/28) in DNA at t1, 48% (10/21) at t2, and 39% (9/23) at t3. Detection of nucleoside reverse transcriptase inhibitor (NRTI) mutations in DNA decreased with time on suppression (P<0.01).

Conclusions: K103N in plasma was subsequently identified in the proviral DNA of ~50% of subjects for up to 11 years during PI-based suppression. These results imply seeding of the HIV reservoir during viral failure and confirm the stability of drug resistance in HIV reservoirs during long-term suppressive ART among at least 50%. In those with undetected proviral resistance by population sequencing, persistent drug resistance can exist at lower levels and be clinically relevant.