Detection of NNRTI Resistance Mutations After Interrupting NNRTI-Based Regimens

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Background: There is evidence that NNRTI mutants emerge after ART interruption (ATI) of suppressive NNRTI-based ART, due to the long half-life of NNRTIs. This has implications for both loss of treatment options for people undergoing ATI (e.g. due to poor adherence or stock-outs) and potential transmission of drug resistance. The aim of this study is to quantify the extent to which NNRTI mutations can be detected in the rebound viremia following ATI of suppressive NNRTI-based ART.

Methodology: The study population comprised patients in the UK HIV Drug Resistance Database who interrupted a suppressive NNRTI-based regimen, defined as viral load (VL) consistently <200 copies/ml after at least 6 months on ART and who had no evidence of NNRTI-mutations on previous resistance tests. NNRTI mutations in IAS December 2008 list were considered. Crude and adjusted relative risks (RR) of having NNRTI resistance detected in the rebound viremia after interruption were calculated using a modified Poisson regression approach. Covariates considered included demographic variables, antiretroviral drugs experienced, length of virologic suppression, time from ATI to resistance test, CD4 count nadir, CD4 count at ATI and at resistance test, VL at ATI, maximum VL ever measured and subtype.

Results: Of 1,636 eligible patients, 208 (13%; 95% CI: 11-14) had a resistance test performed after stopping suppressive NNRTI-based ART. They were either on EFV (39%) or NVP (61%) most commonly in combination with 3TC (85%) and/or AZT (63%). ART interruptions occurred after a median of 12 months since starting ART (IQR: 5-32 months). Among these, 25 (12%, 95% CI: 8-17) had ≥1 NNRTI resistance mutation detected at the first resistance test following ATI, a median of 12 months after ATI (IQR: 3-20 months). Similar rates of resistance were observed in patients with simultaneous (n=188) and staggered interruptions (n=20). The most common mutation found was K103N (64%), followed by G190A (12%), while K101E, V108I, Y181C, L100I, V106A, Y188L and P225H were found in 8% (n=2) or less. In multivariate analysis (including as covariates CD4 at ATI, CD4 nadir and being on NVP at ATI), the only independent predictor of NNRTI resistant mutations was a lower CD4 count nadir (RR per 100 cells higher = 0.67; 95% CI: 0.53-0.85).

Conclusions: To our knowledge this is the largest study to evaluate the detection of NNRTI resistance in the rebound viremia that follows interruption of a suppressive NNRTI-based regimen. It confirms that resistance is a relatively common phenomenon, occurring in 12% of patients tested. These estimates support the concept that interruption of EFV or NVP based ART carries a significant risk to the patient and inform models that incorporate HIV drug resistance emergence.