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HAIR ANTIRETROVIRAL LEVELS STRONGLY PREDICT VIROLOGIC OUTCOMES IN ACTG'S A5257 TRIAL
Clinical: (H) Antiretroviral Therapy: Efficacy and Effectiveness Studies

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Background: AIDS Clinical Trials Group (ACTG) A5257 was a three-arm study comparing atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r) and raltegravir (RAL)-based regimens in naïve patients. The study showed similar rates of virologic success in all three arms, with RAL regimens better tolerated than protease inhibitor-regimens. Hair antiretroviral (ARV) levels reflect long-term exposure and have been associated with virologic outcomes in cohorts, but have never been evaluated in a treatment trial.
Methods: Hair samples were collected at weeks 4, 8, 16, and then quarterly; concentrations of ATV, DRV and RAL were measured by LC-MS/MS using methods approved by the NIH DAIDS Clinical Pharmacology and Quality Assurance (CPQA) Program. Self-reported adherence was assessed using visual-analog scales. The primary endpoint of A5257 was virologic failure (VF). Proportional hazards regression models estimated the association of ARVs in hair with VF. A time-varying predictor defined as the logarithm of the most recently measured hair level divided by the within-arm median enabled modeling a common hair level effect across arms.
Results: Hair and viral load data were available for 2192 person-visits among 599 participants followed for a median of 217 weeks. Rates of virologic failure by two years were 26%, 6%, and 3% for those with hair levels in the lowest, middle and highest tertiles, respectively. Lower hair ARV levels strongly predicted higher risk of VF [HR 1.69 (95% CI 1.43-2.04, $p<0.001$) for every 2-fold decrease in hair level], which remained consistent for each drug individually and when adjusting for self-reported adherence and other factors. The hazard of VF with hair ARV levels in the lowest tertile was 6.8 times that with levels in the highest tertile (Figure). Self-reported adherence (median 100% in each arm) and hair ARV levels were weakly correlated (Pearson's ρ 0.15, 0.15, 0.01 for ATV, DRV, RAL, respectively).
Conclusion: We show for the first time that higher long-term ARV exposure as assessed by hair levels predicted a significantly decreased risk of virologic failure in a randomized treatment trial. The risk of virologic failure was high following a low hair ARV level. Correlations between self-reported adherence and hair levels were poor, likely revealing limitations to self-report. Further study is warranted on whether early monitoring of hair ARV levels followed by targeted adherence interventions based on this metric will be able to reduce subsequent VF rates on HIV treatment.