Influence of *UGT1A1*28* on Raltegravir PK/PD in the NEAT001/ANRS143 study

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Background

Raltegravir is metabolised by UGT1A1 and polymorphisms in the *UGT1A1* gene have been associated with plasma concentrations in some but not all previous studies.[1,2,3,4,5] For example, the *UGT1A1**28 gene has been associated with reduced clearance and increased plasma concentrations of raltegravir. The current analysis represents the largest study to date for the effect of *UGT1A1* polymorphisms on raltegravir pharmacokinetics/pharmacodynamics.

Methods

Randomised, open-labelled, non-inferiority trial
(NEAT001/ANRS143)
(n = 805)

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Darunavir/ritonavir (800/100 mg o.d) +
Raltegravir (400 mg b.d)
Vs
Darunavir/ritonavir (800/100 mg o.d) +
Tenofovir/Emtricitabine (245/200 mg o.d)

↓

Random single samples collected at week 4 and week 24 for drug concentrations

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DNA extracted. *UGT1A1* polymorphisms genotyped using Sequenom MassARRAY iPLEX (n = 349)

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Statistical Analysis

1. Nonlinear mixed effects modelling (NONMEM v 7.3) was applied to raltegravir concentrations data. Weight, age, sex, ethnicity and *UGT1A1* genotypes were investigated for association with raltegravir apparent oral clearance (Cl/F)
2. Model was used to predict $AUC_{0\text{-}12}$ and C_{12} and a post-hoc analysis was performed to evaluate associations with *UGT1A1* genotype.
3. Kaplan-Meier estimates and Cox regression used to assess relationship between virological failure at week 96 and *UGT1A1* genotype.

Results

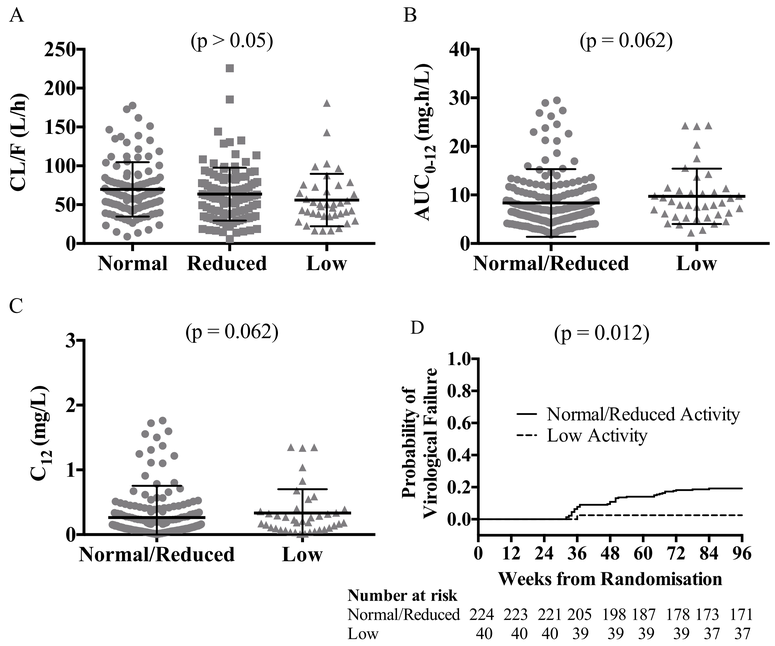


Figure A. Apparent oral clearance (CL/F) of raltegravir (Mean and SD) in patients with normal (*1/*1, *1/*36), reduced (*1/*6, *1/*28, 1/*37, *28/*36, *36/*37) and low (*28/*28, *28/*37, *37/*37) UGT1A1 activity. CL/F reduced by 21% in patients with *28/*28 *UGT1A1* genotype. However, this was not statistically significant (p > 0.05).

Figure B. Raltegravir $AUC_{0\text{-}12}$ in patients (Mean and SD) with low vs normal/reduced UGT1A activity. Geometric Mean Ratio (95% CI) = 1.34 (0.99 – 1.84). p = 0.062.

Figure C. Raltegravir C_{12} in patients (Mean and SD) with low vs normal/reduced UGT1A activity. Geometric Mean Ratio (95% CI) = 1.32 (0.99 – 1.77). p = 0.062.

Figure D. Virological failure in patients with low vs normal/reduced activity activity at week 96. p = 0.012. This remained significant when adjusted for baseline CD4 count (p = 0.048) but not when adjusted for baseline viral load (p = 0.082) or both CD4 and viral load (p = 0.089)

Discussion

This analysis within the NEAT001/ANRS143[6] study analysed UGT1A1 genotypes with the largest sample size to date and suggested little impact on a single raltegravir PK profile. The high intra-patient variability in raltegravir PK may mask the effect of polymorphisms on a single drug concentration profile, but the impact on pharmacodynamics seen here suggest that global differences in exposure over multiple doses may be important.

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