Genetics of Plasma Rifapentine Clearance During Pulmonary Tuberculosis Treatment in Study 31/A5349

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Ava Y. Xu[1,2], Yuki Bradford[3], Gustavo E. Velásquez[4,5], Vincent K. Chang[1], Marjorie Imperial[1], Ekaterina V. Kurbatova[6], Kia Bryant[6], Phumla Sinxadi[7,8], Marylyn Ritchie[3], John A. Capra[2,9], David W. Haas[10,11], Radojka M. Savic[1,4]

[1]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA, USA, [2]Bakar Computational Health Sciences Institute, University of California, San Francisco, CA, USA, [3]Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [4]UCSF Center for Tuberculosis, University of California, San Francisco, CA, USA, [5]Division of HIV, Infectious Diseases, and Global Medicine, University of California, San Francisco, CA, USA , [6]Centers for Disease Control and Prevention, Atlanta, GA, USA , [7]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa, [8]SAMRC/UCT Platform of Pharmacogenomics Research and Translation, South African Medical Research Council, Cape Town, South Africa, [9]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA, [10]Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA,[11]Department of Internal Medicine, Meharry Medical College, Nashville, TN, USA.

BACKGROUND

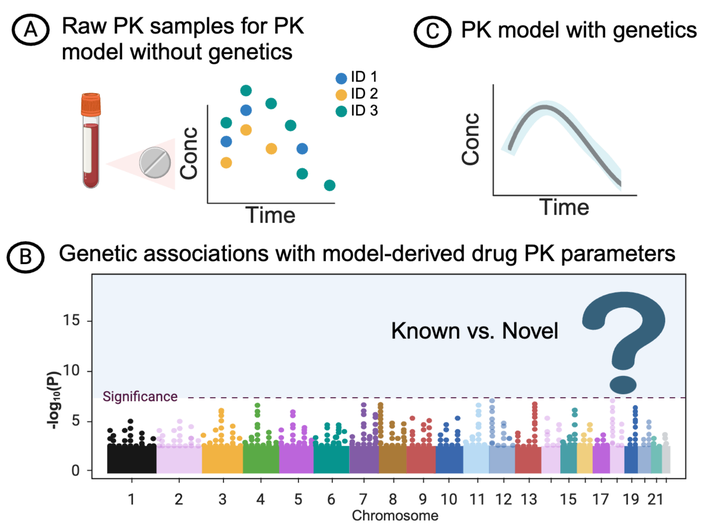
Optimizing rifapentine (RPT) dosing is critical for improving tuberculosis (TB) treatment response. Study 31/A5349 (NCT02410772) compared two 4-month RPT-containing regimens – one with and one without moxifloxacin (MXF) – to the standard 6-month regimen.

A key determinant of unfavorable TB outcomes in this trial was RPT exposure, with large interindividual variability. We hypothesized that host genetics contributed to variability in clearance (CL) of RPT and its metabolite, 25-O-desacetyl-RPT (des-RPT) and evaluated an arylacetamide deacetylase (AADAC) variant rs1803155 reported to affect RPT exposure.

METHODS

- Participants received RPT 1200 mg once daily. Plasma was collected for RPT and des-RPT assays between weeks 2 and 8 **(Figure 1, A)**.
- Genetic variants were imputed from low-coverage whole-genome sequence data using GLIMPSE2. Associations with RPT and des-RPT CL were studied genome-wide, adjusting for 8 genetic principal components (PC) and *NAT2* acetylator status **(Figure 1, B).**
- Impact of selected variants on RPT CL was assessed by population pharmacokinetic (PK) modeling using NONMEM **(Figure 1, C)**.

Fig. 1 Study schematic.



In participants receiving rifapentine 1200 mg daily, AADAC rs1803155 G allele was associated with more rapid rifapentine clearance at genome-wide significance. This association was most pronounced in the rifapentine-moxifloxacin arm.

RESULTS

- A total of 1105 participants had both PK and genetic data (564 in the RPT/MFX arm, 541 in the RPT arm).
- Analyses included 71% male sex, 73% Black, and 12% Asian participants. Participant characteristics at baseline are presented in **Table 1**.
- *AADAC* rs1803155 was associated with RPT CL in all participants ($p=1.1x10^{-11}$), the RPT/MFX arm ($p=1.1x10^{-9}$), and the RPT arm ($p=4.3x10^{-4}$) in **Figure 2**.
- *UGT1A1* rs887829 was associated with both RPT and des-RPT CL in all participants ($p=6.3x10^{-19}$ and $p=3.7x10^{-26}$), the RPT/MFX arm ($p=4.5x10^{-16}$ and $p=6.2x10^{-14}$), and the RPT arm ($p=6.8x10^{-6}$ and $p=1.5x10^{-14}$, respectively) in **Figures 2-3**.

Table 1. Participant Characteristics. Continuous variables are reported as median and interquartile range. Categorical variables are reported as n (%).

	Rifapentine	Rifapentine-moxifloxacin
Participant with quality host genomic and evaluable PK samples	n = 564	n = 541
Age, yr	30 (24-40)	30 (24-41)
Male sex	390 (69.1%)	390 (72.1%)
Weight, kg	53 (48-59)	53 (48-59)
BMI, kg/m²	18.8 (17.4-20.7)	18.9 (17.4-20.8)
Self-reported race		
Black	411 (72.9%)	397 (73.4%)
Asian	68 (12.1%)	66 (12.2%)
Mixed/Multiracial	82 (14.5%)	74 (13.7%)
White	3 (0.5%)	4 (0.7%)
Living with HIV	35 (6.2%)	37 (6.8%)

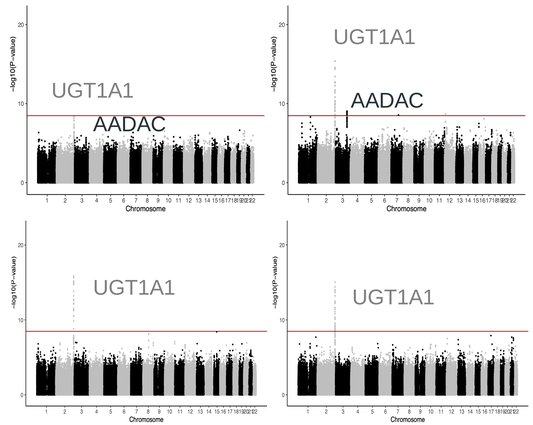


Fig 2. Genome-wide associations for RPT stratified by regimen (left) without and (right) with MXF, accounting for 8 PCs and *NAT2* acetylator status.

Fig 3. Genome-wide associations for des-RPT stratified by regimen (left) without and (right) with MXF, accounting for 8 PCs and *NAT2* acetylator status.

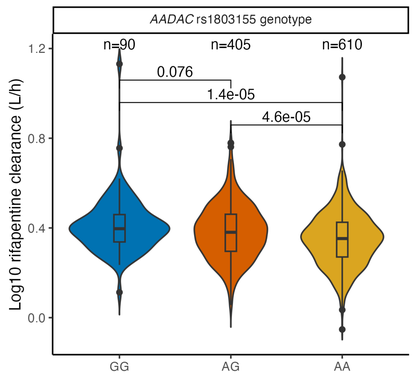


Fig 4. Log_{10} transformed RPT CL stratified by *AADAC* rs1803155 genotype. Violin plots depict the distribution of clearance values, with width indicating proportion of individuals. Boxplots represent medians and interquartile ranges.

- *AADAC* rs1803155 GG was associated with more rapid RPT CL and lower plasma exposure.
- In PK modeling, RPT CL increased by 0.266 L/h with *AADAC* GG and 0.059 L/h with AG compared to AA. *AADAC* rs1803155 was not associated with des-RPT CL.
- Despite genome-wide association of *UGT1A1* poor metabolizer T allele with more rapid CL of both RPT and des-RPT, in PK modeling *UGT1A1* only impacted des-RPT CL.

CONCLUSIONS

- Incorporation of AADAC rs1803155 into PK modeling helps to explain interindividual variability of RPT CL.
- Host genetics will be important to consider when evaluating efficacy and safety of RPT-containing regimens.

ACKNOWLEDGEMENTS

We especially thank the study participants for their time in this trial and the local Tuberculosis program staff who assisted in clinical management. We thank our IND sponsor, the U.S. Centers for Disease Control. We also thank the Tuberculosis Trial Consortium and AIDS Clinical Trial group for their dedication to improving HIV care and innovating TB treatments.