Pharmacogenetics of Bedaquiline and Clofazimine Plasma Clearance among South Africans

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BACKGROUND

- Drug-resistant tuberculosis (TB) is a public health threat worldwide.
- Bedaquiline (BDQ) and clofazimine (CFZ) are widely used to treat drug-resistant TB.
- BDQ is metabolized primarily by hepatic cytochrome P450 (CYP) 3A4.
- CFZ undergoes hydrolytic reactions and is excreted largely unchanged.
- Plasma BDQ clearance is reportedly more rapid with African ancestry [1].

OBJECTIVE

To determine whether genetic polymorphisms (SNPs) explained between-individual variability in plasma clearance of BDQ, its M2 metabolite, and CFZ in a cohort of patients treated for drug-resistant TB in South Africa.

METHODS

- PROBeX was a prospective observational cohort study conducted between 2016 and 2020 at three TB referral hospitals in South Africa.
- The regimen typically included BDQ, CFZ, linezolid, levofloxacin, ethionamide, terizidone and pyrazinamide.
- Sparse pharmacokinetic (PK) sampling was done at ~1, 2 and 6 months. A subgroup underwent intensive PK sampling at 2 months.
- Population PK was described with nonlinear mixed-effects models [2,3].
- Between-individual variability in estimates of BDQ and CFZ clearance were of primary interest. We also studied the BDQ M2 metabolite.
- Genome-wide genotyping with MEGA^{EX} was followed by imputation.
- Multivariable linear regression models included genetic ancestry principal components.
- We focused on SNPs previously associated with any drug or trait in PharmGKB and the NHGRI-EBI GWAS Catalog.

RESULTS

- A total of 140 and 136 PROBeX participants were evaluable for BDQ and CFZ genetic associations, respectively.
- Baseline characteristics are shown in the **Table**.

	Total PROBeX cohort (n=195)	BDQ genetic analysis (n=140)	CFZ genetic analysis (n=136)
Age in years, median (IQR)	33 (28 - 42)	33 (27 - 41)	33 (27 - 42)
Females, n (%)	111 (57)	71 (51)	71 (52)
Race, n (%)			
black	160 (82)	112 (80)	106 (78)
mixed race	33 (17)	26 (19)	28 (21)
white	2 (1)	2 (1)	2 (1)
BMI, kg/m^2, median (IQR)	20 (18 - 23)	20 (18 - 23)	20 (18 - 23)
HIV positive, n (%)	123 (63)	82 (59)	80 (59)

Among patients treated for drug-resistant TB in South Africa, in which between-individual variability in BDQ and CFZ clearance were estimated with non-linear mixed-effects modelling, *CYP3A5*3* was significantly associated with slower BDQ clearance. *CYP3A5*3* C/T and C/C were associated with 15% and 30% slower BDQ clearance, respectively. Different *CYP3A5*3* frequencies among populations (30% in Africans, 70% in East Asians, 93% in Europeans) may help explain the more rapid BDQ clearance reported in Black Africans.

- Of 21 SNPs common to PharmGKB and the GWAS Catalog, the lowest P-value for BDQ_{CL} was *CYP3A5* rs776746 T→ C (*CYP3A5*3,* p = 0.0017), which withstood multiple testing cut-off.
- Of 1,214 *CYP3A* locus SNPs (±150kB of *CYP3A4* and *CYP3A5*), the lowest P-values for BDQ_{CL} were 4 SNPs in linkage disequilibrium (LD) with rs776746 (**Figure 1**).
- rs776746 improved population PK model fit. Based on log-likelihood profiling, C/T and C/C were associated with 15% (95% CI 3.5% to 25.5%) and 30% (7.0% to 51%) slower BDQ clearance.
- Model-predicted effects of rs776746 on BDQ and M2 exposure are shown in **Figure 2**.
- Genome-wide, the lowest P-value for BDQ_{CL} was *RFX4* rs763450 (p = 6.4x10^{-7}, **Figure 3**). *RFX4* is involved in brain development.
- Genome-wide, the lowest P-value for CFZ clearance was *CNTN5* rs75285763 (p = 2.9x10^{-8}, **Figure 4**). *CNTN5* encodes a member of the immunoglobulin superfamily.

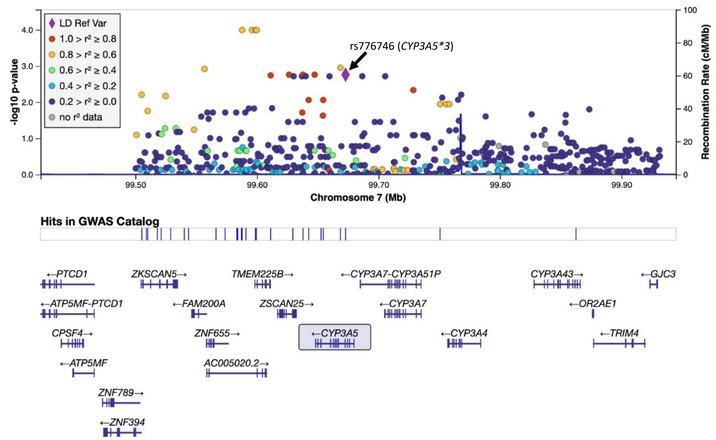

Figure 1. LocusZoom plot of the *CYP3A* locus for associations with between-individual variability in BDQ clearance. The purple diamond and arrow identify *CYP3A5* rs776746 (*CYP3A5*3*), which is the reference for LD values. Each other marker is color coded based on r^2 for LD with rs776746, using "ALL" LocusZoom setting for the reference population.

Acknowledgements: This work was made possible by grants from National Institutes of Health (NIAID, Fogarty International Center, and NCATS), Wellcome Trust, National Research Foundation of South Africa, and the European & Developing Countries Clinical Trials Partnership. The authors are grateful to the study participants.

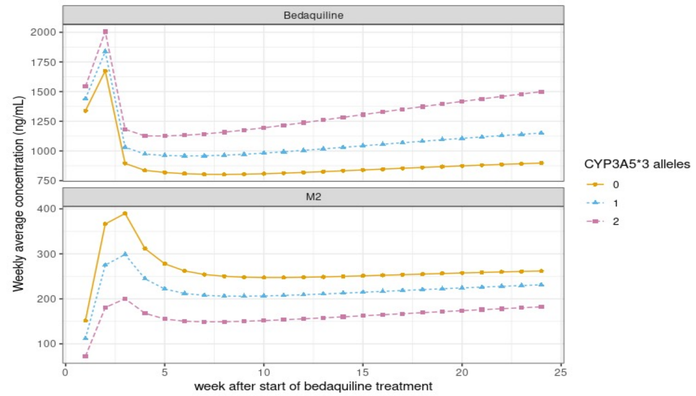

Figure 2. Typical predicted weekly average BDQ and M2 concentrations by number of *CYP3A5*3* alleles, using the PK model without random effects. The virtual patient was 32 years of age, 56.6 kg, albumin = 3.6 g/dL. BDQ was 400 mg daily for 2 wks, then 200 mg 3 times per wk.

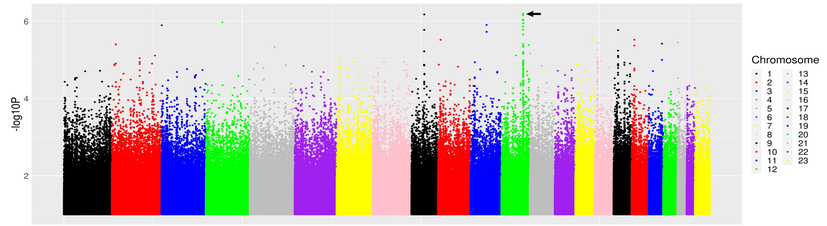

Figure 3. Manhattan plot of associations with between-individual variability in BDQ clearance. The lowest P-value (arrow) is for *RFX4* rs763450 on chromosome 12 (p = 6.4x10^{-7}, β = 0.20).

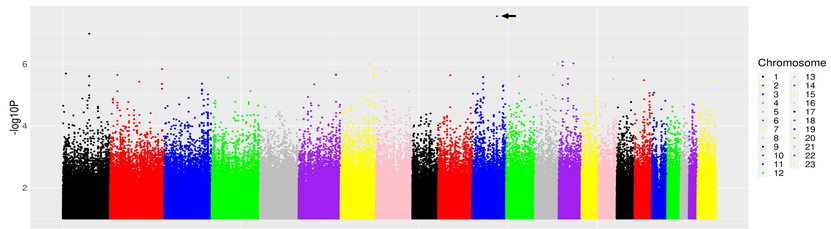

Figure 4. Manhattan plot of associations with between-individual variability in CFZ clearance. The lowest P-value (arrow) is for *CNTN5* rs75285763 (p = 2.9x10^{-8}, β = 0.46).

CONCLUSIONS

- Among patients treated for drug-resistant TB in South Africa, *CYP3A5*3* was associated with slower plasma BDQ clearance.
- Different *CYP3A5*3* minor allele frequencies among populations (30% in Africans, 70% in East Asians, 93% in Europeans) [4] may explain the more rapid BDQ clearance reported with African ancestry.
- The genome-wide-significant association of a *CNTN5* SNP with CFZ clearance is likely a chance finding.

References:

1) McLeay et al. *Antimicrob Ag Chemo* 2014, PMC4135833;
2) Svensson et al. *CPT Pharmacometrics Syst Pharmacol* 2016, PMC5192973;
3) Abdelwahab et al. *J Antimicrob Chemother* 2020; 75:3269-77, PMC7566350;
4) dbSNP at: https://www.ncbi.nlm.nih.gov/snp/rs776746

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