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The role of pharmacogenetics in HIV/tuberculosis co-infected Ugandan patients

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Background: Management of tuberculosis in HIV-positive patients is complicated by drug-to-drug interactions, side effects and incomplete efficacy. Assessing antitubercular drugs serum concentrations and patients' genetic background might be helpful but they are seldom performed in limited-resource settings.

Material/methods: Between May 2013 and November 2015, a three-year prospective observational study was conducted in HIV-infected individuals with pulmonary tuberculosis at the Infectious Diseases Institute, Kampala, Uganda where all laboratory analysis were performed. Serum concentrations of anti-TB drugs (1, 2, 4 hours post-dosing) and efavirenz C_{12} (600 mg, collected 12 ±2 hours post-dosing) were measured through HPLC; AUCs were estimated using a non-compartmental analysis. Single nucleotide polymorphisms (Table 1) were analyzed through real-time PCR by allelic discrimination. Side-effects and tolerability were monitored clinically and through laboratory tests.

Results: 182 patients [59.4% male; median age 34 years (29-40)] were included in this analysis. Current and nadir CD4 count were 168 cells/uL (46-273) and 162 cells/uL (68-272). On 563 samples, AUC_{0-4} and C_2 were 10.850 ug*h/mL (7.200-5.990) and 4.640 ug/mL (2.850-6.739) for rifampicin,

3.835 ug*h/mL (2.230-5.467) and 1.670 ug/mL (0.940-2.440) for isoniazid, 4.810 ug*h/mL (3.040-7.350) and 1.845 ug/mL (1.075-3.077) for ethambutol, 76.495 ug*h/mL (58.215-100.070) and 32.278 ug/mL (2.500-39.375) for pyrazinamide. Efavirenz C_{12} was 3.320 ug/mL (1.876-5.790). The prevalence of genetic variants is shown in Table 1. A significant association was observed between the following variants: *NR1I2* and isoniazid AUC_{0-4} (p=0.015), *SLCO1B1* and *NAT2* with isoniazid C_2 (p=0.033 and p=0.007), *CYP2B6* with pyrazinamide AUC_{0-4} (p=0.025), *VDR* with pyrazinamide C_2 (p=0.039), *CYP2B6* and weight with efavirenz C_{12} (p<0.001 and p=0.001). Hepatic and neurological toxicities were reported in 85 (46.4%) and 31 (16.9%) patients. The incidence of hepatotoxicity was lower with *HNF4A* and *SLCO1B1* variants (p=0.018 and p=0.04) and higher with *VDR* and *ABCB1* variants (p<0.001). Lower nadir CD4 cell counts (130 vs. 160 cells/uL, p<0.001) and *CYP2B6* (trend, p=0.1, 95% IC 0.2-1.13) were associated with an increased risk of neurotoxicity.

Conclusions: This study identified associations between genetic variants and serum concentrations of anti-TB drugs and ARVs and the risk of drug-associated side effects. Studies are needed to determine the clinical relevance of these associations.

	ABCB1	***SLCO1B1***	***NAT2***	***CYP2B6***	***NR1I2***	***HNF4A***	***VDR***
	rs1045642	rs4149032	rs1799930	rs3745274	rs2472677	rs1884613	rs11568820
	P-gp	OATP1B1	NAT2	CYP2B6	PXR	HNFalpha4	VDR
WT	122	64	69	54	48	113	113
n (%)	86%	46%	49%	39%	34%	80%	81%
HET	17	52	66	67	75	28	25
n (%)	12%	38%	46%	48%	53%	19%	18%
MUT	3	22	7	19	19	1	2
n (%)	2%	16%	5%	13%	13%	1%	1%

Table 1 Prevalence of genetic variants (SNPs, single-nucleotide polymorphisms). Genes, SNPs and coded proteins are listed in every column. “WT” wild-type; “HET” heterozygous for mutation; “MUT” homozygous for mutation.