Large-Scale Gene-Centric Exploration of Risk for NRTI/NNRTI-Associated Toxicities in Bostwana

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BACKGROUND

- Access to antiretroviral therapy (ART) in sub-Saharan Africa (SSA) has expanded due to a large number of national and international initiatives.
- Previous studies have shown higher rates of NRTI and NNRTI-related toxicity when comparing patients on ART in SSA with those in resource-replete settings.

OBJECTIVE

To explore for the first time the impact of host genetic factors on ART-related toxicity heterogeneity in SSA.

SUBJECTS AND METHODS

The *Tshepo* study. 3-year randomized clinical study following 650 ART-naïve adults (69.4% female) from Botswana who initiated first-line NNRTI-based ART.

Genotyping. The Illumina Human CardioMetabolo chip is a gene-centric array enriched in markers for metabolic and cardiovascular genes (198K), including mitochondrial, ADME, renal, and immune response genes.

Quality control (QC). Individuals with ≥5% of missing data, and SNPs with ≥2% missing data, minor allelic frequency≤1%, or deviation from the Hardy-Weinberg equilibrium ($P<10^{-3}$ in controls) were excluded from analysis. Gender concordance and potential relatedness were also evaluated. Population stratification was assessed through a principal component analysis implemented in Eigensoft.

Statistical analysis. After QC, 133,822 SNPs were tested for association with 5 NRTI/NNTRI-associated toxicities in **568** individuals (87%). Of these, **62** had peripheral neuropathy (PN), **20** had NVP-associated hypersensitivity cutaneous reaction (NS), **19** had ZDV-related anemia (ZA), **19** had pancreatitis (PA), and **17** had moderate-severe hyperlactatemia/lactic acidosis (LA). Logistic regressions in an additive model were performed and adjusted for gender, age, CD4, HIV-RNA, and BMI at baseline, as well as for the first two eigenvectors from the population stratification analysis.

RESULTS

	Rate of treatment modifying toxicities
NRTI-Associated	
Neutropenia	4.9%
Anemia	3.8%
Lipodystrophy/atrophy	2.2%
Hepatotoxicity (not lactic acidosis)	2.2%
Lactic Acidosis	1.7%
Pancreatitis	1.5%
Peripheral Neuropathy	1.2%
NNRTI-Associated	
Cutaneous Hypersensitivity Reaction / Rash	2.9%
Neuropsychiatric Symptoms	1.1%
Total	**20.9%**

Table 1: NRTI and NNRTI-associated treatment modifying toxicities among Botswana adult antiretroviral treatment and drug resistance ("*Tshepo*") study participants. The proportions displayed in the table are out of total 650 study participants.

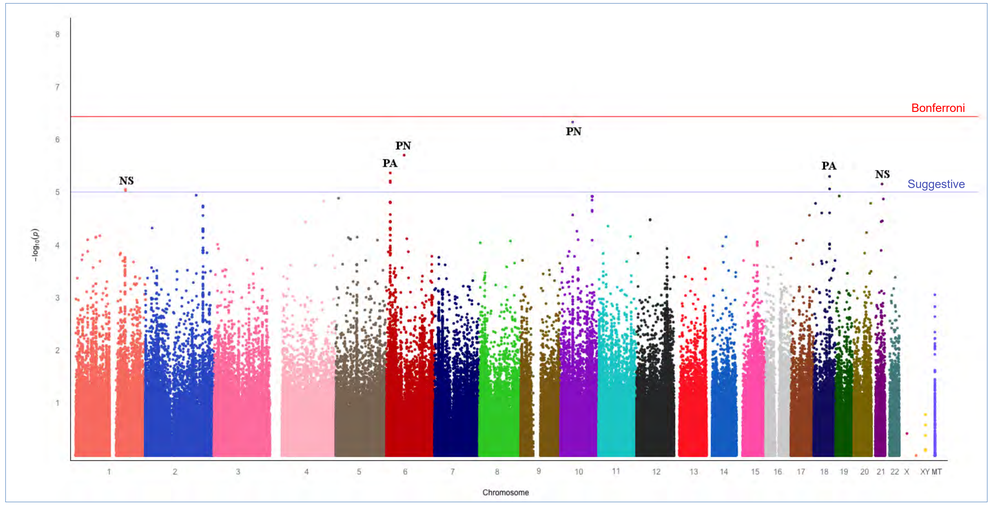


Figure 1: Combined Manhattan plot. Distribution along the chromosomes of -$\log_{10}$(*P*-values) in each of the 5 NRTI/NNRTI-related toxicities association studies. The red line marks the Bonferroni study-wide significance threshold ($P=3.7\times10^{-7}$), and the blue line marks the suggestive significance threshold ($P=10^{-5}$). PA=pancreatitis, PN=peripheral neuropathy, and NS=NVP-associated hypersensitivity cutaneous reaction.

Chr	SNP	A1	A2	NRTI/NNRTI-related toxicity	A1 frequency		*P*-value	OR	95%CI	Location
					Cases	Controls				
10	rs2503875	A	G	Peripheral Neuropathy	12.10%	2.47%	4.70E-07	6.79	3.2-14.3	intergenic
6	rs7767230	C	A		8.87%	1.29%	2.00E-06	9.10	3.7-22.6	*KHDRBS2*
6	rs115680577	A	G	Pancreatitis	26.32%	6.47%	4.34E-06	10.54	3.9-28.8	*PHACTR1*
6	rs115355199	A	G		23.68%	4.74%	6.16E-06	8.89	3.4-22.9	*PHACTR1*
6	rs34367742	A	G		23.68%	5.74%	6.58E-06	10.09	3.7-27.6	*PHACTR1*
18	rs1943220	A	G		21.05%	3.10%	5.06E-06	11.03	3.9-30.9	intergenic
18	rs55810853	A	C		23.68%	4.10%	8.71E-06	8.66	3.3-22.4	intergenic
21	rs702864	A	G	NVP-associated hypersensitivity cutaneous reaction	35.00%	9.85%	7.05E-06	5.90	2.7-12.8	*KCNJ6*
1	rs2902211	A	C		42.50%	14.32%	8.89E-06	4.95	2.4-10.0	intergenic
1	rs11589503	C	A		32.50%	9.03%	9.36E-06	6.05	2.7-13.4	intergenic

Table 2: Top signals associated with NRTI/NNRTI-related toxicities. The allelic frequency is indicated for the *Tshepo* cases and controls for each clinical outcome, as well as the *P*-values, Odds-Ratios (OR), 95% confidence interval (CI), and gene location.

CONCLUSIONS

- **This is the first large genetic study evaluating severe ART-associated toxicities in sub-Saharan Africa.**
- Although power to reach genome-wide significance was reduced due to the limited number of cases for each toxicity, our study revealed several **noteworthy putative candidate loci**.
- We identified 10 SNPs associated with 3 potentially life-threatening and/or debilitating NRTI/NNRTI-related toxicities with **very robust effect sizes** (**5<OR<11**, $P<9.4\times10^{-6}$).
- These preliminary findings warrant **validation** and **further investigation.**