Clinical, pharmacokinetic, and genetic determinants of change in serum creatinine among Southern Africans on dolutegravir based antiretroviral therapy

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Name: Rephaim Mpofu
Student number: MPFREP001

E-mail: MPFREP001@myuct.ac.za

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Supervisor/s:

A/Prof Phumla Sinxadi, Division of Clinical Pharmacology (University of Cape Town), Supervisor

Prof Gary Maartens, Division of Clinical Pharmacology (University of Cape Town), Co-supervisor

Declaration

I, Rephaim Mpofu, hereby declare that the work on which this dissertation / thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to this or any other university. This work has not been reported or published prior to registration for the abovementioned degree.

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Format and contributions

This dissertation has been written and presented in a publication-ready format for submission to the British Journal of Clinical Pharmacology, in accordance with the University of Cape Town Master of Medicine minor dissertation guidelines.

This work is based on data collected from the ADVANCE clinical trial (Clinicaltrials.gov identifier: NCT03122262). N.C., S.S., W.D.F.V were involved in conduct of the original clinical trial that provided data for this analysis. G.A was involved in data curation of the original clinical trial data. R.M., the candidate, was responsible for conceptualisation, data curation and management specific to this study, data analysis, presentation, and interpretation of results, and manuscript development. P.S. and G.M. supervised and guided this research project during the conceptualization, data analysis and interpretation, and manuscript development stages. D.W.H and F.P. provided input during the study design and analysis stages. L.W. supervised the dolutegravir concentration assay procedures, and A.N.K., R.E.W, and P.D. performed the pharmacokinetic modelling. All authors reviewed and provided comments on the final manuscript.

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- 95% CI – 95% confidence interval
- ART – Antiretroviral therapy
- $AUC_{0\text{-}24h}$ – Area under the 24-hour concentration-time curve
- DTG - Dolutegravir
- IQR – Interquartile range
- LD – Linkage disequilibrium
- MAF - Minor allele frequency
- MATE1 – Multidrug and toxin extrusion transporter 1
- MATE2-K - Multidrug and toxin extrusion transporter 2-K
- OCT2 – Organic cation transporter 2
- PharmGKB - Pharmacogenomics Knowledgebase
- PWH – People with HIV
- R^2 – R-squared / Coefficient of determination
- SLC22A2 – Solute carrier 22A2 transporter gene
- SLC47A1 - Solute carrier 47A1 transporter gene
- SNP – Single nucleotide polymorphism
- TAF – Tenofovir alafenamide fumarate
- TDF – Tenofovir disoproxil fumarate
- UGT1A1 – Uridine 5'-diphospho-glucuronosyltransferase
- VANTAGE - Vanderbilt Technologies for Advanced Genomics
- β – Regression coefficient

Abstract

Introduction: Dolutegravir increases serum creatinine by inhibiting renal secretion of creatinine, potentially resulting in inappropriate regimen switches. We investigated determinants of early changes in serum creatinine in a Southern African cohort starting dolutegravir-based antiretroviral therapy.

Methods: We conducted a secondary analysis of data from participants in a randomised controlled trial of dolutegravir with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF) plus emtricitabine (ADVANCE, NCT03122262). We assessed clinical, pharmacokinetic, and genetic factors associated with the change in serum creatinine from baseline to week 4 using linear regression adjusting for age, sex, baseline serum creatinine, HIV-1 RNA viral load, CD4 T-cell count, total body weight, and co-trimoxazole use.

Results: We included 689 participants, of whom 470 had pharmacokinetic data and 315 had genetic data. Mean change in serum creatinine was 11.3 $\mu mol.L^{-1}$. Dolutegravir area under the 24-hour concentration-time curve (change in creatinine regression coefficient [β] = 2.78 [95% confidence interval 0.54, 5.01]) and male sex (β = 5.20 [2.92, 7.48]) were associated with an increased change in serum creatinine at week 4, while higher baseline serum creatinine (β = -0.22 [-0.31, -0.12]), use of TAF (β = -2.30 [-4.06, -0.53]) and *Uridine glucuronosyltransferase 1A1* (*UGT1A1*) polymorphism rs929596 (β = -2.33 [-4.49, -0.17]; not significant after adjustment for multiple comparisons) were associated with a decreased change in serum creatinine.

Conclusion: We identified clinical and pharmacokinetic determinants of change in serum creatinine in participants starting a dolutegravir-based regimen. *UGT1A1* polymorphisms may play a role, but further research on genetic determinants is needed.

Publication ready manuscript

Full title: Clinical, pharmacokinetic, and genetic determinants of change in serum creatinine among Southern Africans on dolutegravir based antiretroviral therapy

Running title: Dolutegravir effect on creatinine in Africans

Authors: Rephaim Mpofu[1], Aida N. Kawuma[1], Roeland E. Wasmann[1,2], Godspower Akpomiemie[3], Nomathemba Chandiwana[3], Simiso Sokhela[3], W. D. Francois Venter[3], Paolo Denti[1], Lubbe Wiesner[1], Frank Post[4], David W. Haas[5,6], Gary Maartens[1], and Phumla Sinxadi[1]

Affiliations:

[1]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

[2]Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa

[3]Ezintsha, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[4]King's College London School of Medicine, London, United Kingdom

[5]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[6]Department of Internal Medicine, Meharry Medical College, Nashville, Tennessee, USA

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

What is already known about this subject:

- Dolutegravir increases serum creatinine due to the inhibition of renal transporters such as organic cation transporter 2 and multidrug and toxin extrusion protein 1.
- Clinical, pharmacological, and genetic determinants of dolutegravir mediated increases in serum creatinine are not well characterized.

What this study adds:

- Increased dolutegravir exposure, male sex, lower baseline creatinine, and TDF use were associated with increased serum creatinine change in participants on dolutegravir.
- *UGT1A1* polymorphisms may affect the magnitude of creatinine change.
- Investigation may be considered for those with creatinine changes ≥30 $\mu mol.L^{-1}$ more than 4 weeks after treatment initiation.

Introduction

Dolutegravir increases serum creatinine by an average of 10-15%. This typically occurs within the first week of treatment initiation and plateaus by the fourth week.[1-3] This does not reflect nephrotoxicity; rather, it is due to the inhibition of renal tubular cell transporters that facilitate creatinine elimination by dolutegravir, including organic cation transporter 2 (OCT2), multidrug and toxin extrusion transporter 1 (MATE1), and multidrug and toxin extrusion transporter 2-K (MATE2-K).[1, 4, 5] There is considerable interindividual variability in the change in serum creatinine after starting dolutegravir – in the ADVANCE trial, the median change in creatinine at week 48 was 12 $\mu mol.L^{-1}$ with an interquartile range (IQR) of -29 $\mu mol.L^{-1}$ to 39 $\mu mol.L^{-1}$.[6] This variability may be due to multiple factors including concomitant medications, improvement of HIV-associated nephropathy by antiretroviral therapy (ART), intercurrent illness, or genetic factors including those that affect plasma dolutegravir exposure and renal tubular cell transporter function.[7] Individuals who experience greater increases in serum creatinine may unnecessarily change their antiretroviral regimen, particularly when tenofovir is co-administered.[8]

Dolutegravir is primarily metabolized in the liver by uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1)[9], and frequent *UGT1A1* variants are associated with increased dolutegravir exposure. In a Southern African population, *UGT1A1* single nucleotide polymorphisms (SNPs) rs887829 and rs28899168 were associated with increased plasma dolutegravir exposure.[10] A moderate exposure-response relationship has been reported between dolutegravir and change in creatinine clearance over time.[2] It is possible to suggest that *UGT1A1* genetic variants that affect dolutegravir exposure could explain some of the variability in changes in creatinine with dolutegravir. Rs316019, a non-synonymous polymorphism in *SLC22A2* that encodes OCT2 has been associated with reduced creatinine secretion.[11, 12] Additional transporters MATE1 and MATE2-K are encoded by *SLC47A1* and *SLC47A2,* respectively, and are also involved in creatinine excretion.[13, 14] While few studies have assessed the role of MATE transporter polymorphisms and dolutegravir pharmacokinetics/pharmacodynamics, a MATE1 polymorphism (rs2252281) was associated with an enhanced response to metformin in a study of patients with

diabetes.[15] It is therefore important to understand the role of these genetic variants on substrate transport.

Populations of African ancestry have greater genetic diversity than other ancestral groups. Most pharmacogenetic studies to date have been conducted in non-African populations, and novel genetic variants that affect treatment responses may be found in African populations.[16, 17] The present study aimed to identify associations between dolutegravir exposure, selected genetic polymorphisms, and early changes in serum creatinine concentrations in a Southern African cohort of treatment-naive people with HIV (PWH) who initiated dolutegravir-containing ART.

Methods

Study population

We conducted a secondary analysis of clinical, laboratory, pharmacokinetic, and genetic data collected from the ADVANCE clinical trial (Clinicaltrials.gov trial identifier: NCT03122262). ADVANCE was a phase 3, single-centre, open-label, non-inferiority, clinical trial conducted in Johannesburg, South Africa, in which treatment naïve PWH were randomly assigned to one of 3 treatment arms: 1) tenofovir disoproxil fumarate (TDF), emtricitabine, and dolutegravir; 2) tenofovir alafenamide fumarate (TAF), emtricitabine, and dolutegravir; or 3) TDF, emtricitabine, and efavirenz.[6] The present analysis included ADVANCE participants that 1) were assigned to dolutegravir-containing arms, and 2) had available serum creatinine measurements from baseline (defined as the period between study entry and treatment initiation) and week 4 after starting therapy.

Pharmacokinetic sampling

Pharmacokinetic samples were collected from a subgroup of participants who provided informed consent. A subset of participants (N = 41) were invited to enrol in an intensive pharmacokinetic sub-study after 96 weeks, and were sampled pre-dose, and at 1, 2, 4, 6, 8, as well as 24 hours post dose. The samples were stored at -80°C until analysis.

Pharmacokinetic analysis and modelling

Plasma dolutegravir concentrations were measured by liquid chromatography with mass tandem spectrometry detection using an AB SCIEX API 4000 instrument in the Division of Clinical Pharmacology at the University of Cape Town, as described elsewhere.[10] A population pharmacokinetic model was developed from the intensively sampled cohort using non-linear mixed-effects modelling. Individual, 24-hour dolutegravir area under the concentration-time curve ($AUC_{0\text{-}24h}$) values were estimated from sparse samples collected from the other ADVANCE participants using a post-hoc Bayesian estimation method that accounted for participant characteristics. Details are described elsewhere.[10]

Genotyping and quality control

Whole blood samples were obtained from participants who consented to genetic testing. DNA was extracted from whole blood using a simple salting out procedure. Genotyping for this project was conducted using the Illumina Infinium Multi-Ethnic Global BeadChip ($MEGA^{EX}$) at Vanderbilt Technologies for Advanced Genomics (VANTAGE), and quality control was performed as described elsewhere.[10]

For the genetic association analyses, we *a priori* selected 39 polymorphisms in *UGT1A1* (rs1042640, rs10929302, rs11891311, rs12474441, rs28946889, rs3755319, rs3771341, rs4148324, rs4148325, rs6431630, rs6742078, rs8330, rs887829, rs929596)*; SLC22A2* (encoding OCT-2; rs12207180, rs2279463, rs28495851, rs3101823, rs3119304, rs3119311, rs3127573, rs3127575, rs316009, rs316019, rs316020, rs476235, rs515140, rs596881, rs77648599, rs79370442); and *SLC47A1* (encoding MATE-1; rs11871125, rs12451696, rs2018675, rs2440164, rs2440165, rs2453580, rs2453583, rs2453584, rs894680). These polymorphisms were selected based on previously reported associations with renal traits in the GWAS catalogue[18] with p-values $<5.0 \times 10^{-8}$, as well as polymorphisms associated with drug-related phenotypes in the Pharmacogenomics Knowledgebase (PharmGKB)[19] with levels of evidence of 1 or 2A.

Three polymorphisms were excluded during the quality control process as their minor allele frequencies (MAFs) were less than the required threshold (5%), leaving 36

polymorphisms (12 *UGT1A1*, 15 *SLC22A2*, 9 *SLC47A1*) among 315 participants that were available for analysis. MAFs are reported in **Table S1**.

Statistical and genetic association analyses

The primary outcome was a change in serum creatinine from baseline to week 4. Study baseline characteristics and changes in serum creatinine were summarized with descriptive statistics. Data distributions were assessed by visual inspection of distribution patterns with histograms, quantile-quantile plots, and the Shapiro-Wilk test. Continuous, non-parametric data were log-transformed. Univariable and multivariable linear regression models were developed to assess relationships between change in serum creatinine and various factors in three separate analyses. First, in a clinical association analysis, we assessed relationships between change in serum creatinine and the following clinical and laboratory variables: age, sex, and serum creatinine at baseline, allocation to the TDF or TAF treatment group (with TDF as variable reference), baseline CD4 T-cell count, baseline HIV-1 RNA viral load, baseline total body weight, and co-trimoxazole use (co-trimoxazole is also known to inhibit tubular secretion of creatinine[4]) during the first 4 weeks of treatment. Second, in the pharmacokinetic association analysis, we assessed relationships between change in serum creatinine at week 4 and dolutegravir $AUC_{0\text{-}24h}$ while adjusting for the clinical covariates noted above. Third, in the genetic association analysis, we assessed relationships between change in serum creatinine at week 4 and *a priori* selected genetic polymorphisms. Multivariable linear regression models were used to explore potential relationships between genetic polymorphisms and change in serum creatinine at week 4, using additive, dominant, and recessive assumptions of allelic effects. To adjust for population stratification, we included principal components that were derived as described elsewhere.[20] The first two principal components were included as these accounted for a substantial proportion of variability. The above-mentioned clinical covariates were also included in genetic association analyses. To exclude the potential additive influence of dolutegravir exposure on relationships between genetic polymorphisms and change in creatinine, we conducted sensitivity analyses by including dolutegravir $AUC_{0\text{-}24h}$ in genetic regression models examining polymorphisms in *SLC22A2* and *SLC47A1*.

To further assess potential relationships between polymorphisms in *UGT1A1*, *SLC22A2* and *SLC47A1* and change in creatinine, we considered linkage disequilibrium (LD). Polymorphisms with R-squared (R^2) coefficients greater than 0.8 were excluded from sensitivity analyses. LD and statistical significance of associations between change in creatinine and examined polymorphisms were illustrated with heatmaps and scatter plots of negative, log-transformed p-values obtained from the linear regression models, respectively.

Thresholds for statistical significance in the genetic association analyses were adjusted using the Bonferroni method by dividing the overall threshold of 0.05 by the number of polymorphisms included in the analyses. Statistical and genetic analyses were conducted in STATA 16 IC[21], R Studio[22], and PLINK v1.90[23] software.

Results

The two dolutegravir arms of ADVANCE enrolled 702 participants in total, of whom 689 were included in the clinical association analysis after excluding 13 participants who lacked serum creatinine concentration data from week 4. Of the 689 participants evaluable for the clinical association analysis, 470 were included in the pharmacokinetic association analysis after excluding 219 participants who did not undergo pharmacokinetic sampling. Similarly, 315 of the 689 participants evaluable for clinical variables were included in the genetic association analysis after excluding 362 participants who did not provide consent for genetic testing, and 12 that failed genetic data quality checks. Participant characteristics at study entry are shown in **Table 1**.

Analysis of clinical variables

At week 4, the mean change in serum creatinine was 11.3 µmol.L^{-1} (95% confidence interval 10.5, 12.0), as indicated in **Table 2.** The mean change in serum creatinine was similar among participants in the TDF/DTG treatment group (12.1 µmol.L^{-1}; 95% CI 11.0, 13.2) and the TAF/DTG arm (10.4 µmol.L^{-1}; 95% CI 9.4, 11.4). These changes corresponded to a relative mean percent change in serum creatinine of 19% overall, 20% in the TDF/DTG group, and 17% in the TAF/DTG group. Substantial variability

was noted in the change in serum creatinine as evidenced by an IQR of -14 to 45 $\mu mol.L^{-1}$ (absolute range = -25 to 67).

Univariable and multivariable linear regressions of change in serum creatinine at week 4 are shown in **Table 3**. In the multivariable analysis, male sex ($p<0.001$) was independently associated with an increased change in serum creatinine, while higher baseline serum creatinine ($p<0.001$) and TAF use ($p = 0.008$) were independently associated with a decreased change in serum creatinine.

Pharmacokinetic analyses

Univariable and multivariable linear regression showed that higher dolutegravir AUC_{0-24h} values were independently associated with an increased change in serum creatinine at week 4 (**Table 4**). The relationship between dolutegravir AUC_{0-24h} and change in serum creatinine is presented in **Figure 1.** The multivariable analysis also found an independent association between male sex and an increased change in serum creatinine, while a higher baseline serum creatinine and TAF use were independently associated with a decreased change in serum creatinine.

Genetic analysis

Of the 36 evaluable polymorphisms, none were associated with change in serum creatinine when analysed using additive (**Figure 2**) or recessive models (**Figure S1, Table S1**). Using a dominant model, rs929596 A>G from the *UGT1A1* locus was nominally associated with change in serum creatinine, but this association was not significant after adjusting for multiple comparisons (**Figure S2, Table S2**). In contrast to the clinical and pharmacokinetic analyses, increasing age ($p = 0.007$) and baseline CD4 T-cell count ($p = 0.039$) were associated with an increased change in serum creatinine. Other covariates associated with change in serum creatinine in the model assessing *UGT1A1* rs929596 A>G were baseline serum creatinine, male sex, and the use of TAF, in keeping with the clinical and pharmacokinetic analyses. The average change in serum creatinine, when stratified by *UGT1A1* rs929596 genotype, was 12.5 $\mu mol.L^{-1}$, 9.5 $\mu mol.L^{-1}$, and 12.4 $\mu mol.L^{-1}$ for the A/A (major homozygous), A/G (heterozygous), and G/G (minor homozygous) genotypes, respectively (**Figure 3**).

We conducted 2 sensitivity analyses: 1) We included dolutegravir $AUC_{0\text{-}24h}$ as an additional covariate in models evaluating *SLC22A2* and *SLC47A1* polymorphisms (282 participants; **Table S3**), and 2) we excluded polymorphisms in high LD > 0.8 (13 polymorphisms; **Figure S3-Figure** S5). The results from these analyses were similar to those from the main analyses.

Discussion

This study found that mean serum creatinine increased by 11 µmol.L^{-1} from baseline to week 4 in participants treated with dolutegravir containing ART. Additionally, higher dolutegravir exposure and male sex were independently associated with an increased change in serum creatinine, while higher baseline serum creatinine and use of TAF were associated with a reduced change in serum creatinine. These findings emphasize the importance of monitoring renal function and suggest that patients with these characteristics may be at increased risk of changes in serum creatinine requiring closer attention.

The early increase in serum creatinine in our participants after dolutegravir initiation is similar to observations from other trials.[1, 24, 25] A phase I, placebo-controlled study that included healthy participants who were treated with 50 mg of dolutegravir given once or twice daily for two weeks, found a 10% and 14% decrease in creatinine clearance respectively by the end of the 2 week period.[1] Similarly, a phase IIb dose-ranging study that included treatment-naïve adults found that dolutegravir 50 mg once daily was associated with a mean increase in serum creatinine of 12.2 mmol.L^{-1} after one week of therapy that persisted over the course of the trial.[26] Importantly, these studies did not find evidence of nephrotoxicity associated with these changes in creatinine. The large variability observed in this analysis and previous studies confirm that clinicians can expect that most patients will experience modest increases in serum creatinine on dolutegravir, however, some patients may experience relatively higher increases in serum creatinine that are not necessarily indicative of impaired renal function.

Our finding that TAF use was associated with a reduced change in serum creatinine when compared with TDF is in keeping with its reduced nephrotoxic profile. Interestingly, this difference occurred early, within the first 4 weeks of treatment. A

single-arm study of PWH that were switched from a previous TDF-containing ART regimen to a regimen of elvitegravir, emtricitabine, cobicistat, and TAF, observed increases in creatinine-estimated glomerular filtration in as little as 4 weeks.[27] This observation is not limited to PWH: HIV-negative participants that were randomised to receive pre-exposure prophylaxis in the form of daily TDF/emtricitabine also experienced a greater decline in estimated glomerular filtration and increased proteinuria as early as 4 weeks after treatment initiation, when compared with those treated with TAF/emtricitabine.[28] These early changes in creatinine are likely mediated by an inhibitory process of creatinine elimination.[29] Tenofovir is a substrate of additional renal transporters that facilitate creatinine clearance such as organic anion transporters 1 and 3 (located on the basolateral membrane), and multidrug resistance protein transporter 4 (located on the luminal membrane), while TAF is not a significant substrate of these transporters.[30, 31] TDF also increases plasma tenofovir exposure by 90% compared to TAF.[32] Competitive inhibition of these transporters by tenofovir is the probable mechanism of reduced creatinine clearance, as opposed to altered glomerular filtration during this short period of observation in our study.[33] This interaction is likely compounded by the relatively high tenofovir exposure associated with TDF compared to TAF.

The pharmacokinetic analysis in this study confirmed that dolutegravir exposure is associated with modest changes in serum creatinine that occur early after the initiation of ART. Few studies have assessed this exposure-response relationship, and to our knowledge, this is the largest study to date to evaluate pharmacokinetic-pharmacodynamic associations between dolutegravir exposure and early changes in creatinine. As inhibitors of OCT-2, patients with factors resulting in increased dolutegravir concentrations are more likely to experience higher changes in serum creatinine. While the small changes seen here are unlikely to impact clinical care for most of the population, a subset of people remains at risk of further declines in renal function due to other causes. Patients exhibiting persistently rising trends in serum creatinine after 4 weeks should be evaluated further for other potential causes of renal dysfunction.

We found a possible association between change in serum creatinine and *UGT1A1* rs929596 A>G polymorphism when dominant allelic effects were assumed. Patients

with the A/A genotype for this SNP showed an increased change in creatinine levels in comparison to those with an A/G or G/G genotype. While this was not significant after adjusting for multiple comparisons, it lends support to the idea that *UGT1A1* polymorphisms may contribute to the variability in serum creatinine changes due to elevated dolutegravir concentrations. This polymorphism has been associated with increased bilirubin concentrations, likely due to reduced glucuronidation activity of variant UGT1A1 enzymes compared to those encoded by the common genotype.[34] A recent genome-wide association study found that the *UGT1A1* polymorphism rs887829 was also associated with a decrease in dolutegravir clearance, with the homozygous minor allele carriers exhibiting a 26% reduction in dolutegravir clearance compared to those homozygous for the major allele.[10] Rs929596 and rs887829 have been mapped to a *UGT1A* cluster located on chromosome 2 that houses multiple protein-coding, and non-encoding, genes.[34] These polymorphisms were in moderate LD in this population ($r^2 = 0.75$), which suggests that their effects may not be entirely independent. However, it is plausible that each polymorphism may also have independent, additive effects on creatinine clearance. By contrast, we did not find any significant associations between change in serum creatinine and the genetic variants of *SLC22A2* or *SLC47A1*. Prior studies have reported relationships between *SLC22A2* variants and the risk of neuropsychiatric adverse effects of dolutegravir, while *SLC47A1* variants have been linked to enhanced metformin responses in patients with diabetes. The lack of association in our study could be attributed to several factors including small effect sizes requiring larger samples, or the absence of polymorphisms in the population that influence renal transporter function.[15, 35]

It has been suggested that creatinine increases due to dolutegravir are unlikely to exceed 20 $\mu mol.L^{-1}$ and that greater increases should prompt consideration for alternative causes.[36, 37] However, 20% of our participants on TDF and dolutegravir had serum creatinine increases higher than this. We propose that a higher threshold of 30 $\mu mol.L^{-1}$ should be considered, based on the addition of 1.96 standard deviations from the mean to guide the need for further diagnostic investigations. Alternatively, methods to assess renal function using other, freely filtered endogenous markers such as cystatin C, should be considered for patients on dolutegravir as they are not dependent on OCT-2 transport and are therefore less susceptible to dolutegravir's effects on creatinine elimination.[38, 39].

Our study has limitations. First, this was a secondary data analysis, therefore, we did not perform sample size estimations. As we used a convenience sampling strategy, only some participants had DNA extracted; the sample size may therefore have been inadequate to detect small, or uncommon, genetic associations. Secondly, administration of the dolutegravir dose before sparse pharmacokinetic sampling was not observed and therefore, may not have been a reliable estimate of exposure. In addition, the estimation of dolutegravir exposure was based on sparse samples obtained at 48 or 96 weeks, which may not adequately reflect exposure at the 4-week time point.

In conclusion, we identified clinical and pharmacokinetic determinants of early changes in creatinine in Southern Africans initiated on dolutegravir-containing ART. *UGT1A1* polymorphisms may play a role, but further research is needed. A higher threshold of change in creatinine to alert the clinician of the potential further investigations may be needed. We suggest that studies assessing the feasibility of renal function estimation using other endogenous substrates besides creatinine in patients on dolutegravir should be conducted. In addition, investigations examining gene-environment and SNP-SNP interactions may provide additional insight into the risk of changes in creatinine concentrations in the presence of multiple polymorphisms.

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Conflict of Interest Disclosure

Ezintsha receives funding from the Bill and Melinda Gates Foundation, SA Medical Research Council, National Institutes for Health, AIDS Fonds, Unitaid, Foundation for Innovative New Diagnostics and the Children's Investment Fund Foundation, has recently received funding from USAID, and receives drug donations from ViiV Healthcare, Merck and Gilead Sciences for investigator-led clinical studies. The unit does investigator-led studies with Merck and ViiV providing financial support and is doing commercial drug studies for Merck. The unit performs evaluations of diagnostic

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables and Figures

Table 1. Study baseline characteristics of ADVANCE participants included in association analyses of clinical, pharmacokinetic, and genetic variables

Variables	Clinical (n=689)	Pharmacokinetic (n=470)	Genetic (n=315)
Age (years)†	32 (8)	33 (8)	32 (8)
Sex			
Female	414 (60%)	280 (60%)	199 (63%)
Male	275 (40%)	190 (40%)	116 (37%)
Treatment group			
TDF	344 (50%)	234 (50%)	155 (49%)
TAF	345 (50%)	236 (50%)	160 (51%)
Total body weight (kg)†	69 (14)	69 (14)	68 (14)
Serum creatinine ($\mu mol.L^{-1}$) †	65 (14)	65 (14)	64 (13)
log_{10} HIV-1 RNA viral load ($cp.ml^{-1}$)*	4.4 (3.8, 4.9)	4.4 (3.8, 4.9)	4.4 (3.8, 4.9)
CD4 T-cell count ($cells.mm^{-3}$)*	292 (170, 457)	282 (170, 444)	292 (163, 459)
Concomitant co-trimoxazole			
No	573 (83%)	384 (82%)	265 (84%)
Yes	116 (17%)	86 (18%)	50 (16%)

Note: Continuous variables are presented as means† and standard deviations† or medians* and interquartile ranges*

Table 2. Summary of absolute and relative percent change in creatinine ($\mu mol.L^{-1}$) at week 4 in participants initiated on dolutegravir-containing antiretroviral therapy from the analysis of clinical variables, stratified by tenofovir treatment group

Treatment groups	Sample size	Mean (%)	Mean 95% CI	Min (%)	Max (%)	SD
TDF	344	12.1 (20%)	11.0, 13.2	-25.0 (-20%)	67.0 (120%)	10.4
TAF	345	10.4 (17%)	9.4, 11.4	-17.0 (-24%)	51.0 (160%)	9.4
Overall	689	11.3 (19%)	10.5, 12.0	-25.0 (-20%)	67.0 (120%)	9.9

Note: Relative percent change from baseline reported in brackets.

TDF = Tenofovir disoproxil fumarate; TAF = Tenofovir alafenamide fumarate; 95% CI = 95% confidence intervals; SD = Standard deviation

Table 3. Univariable and multivariable linear regression models of associations of clinical variables with change in serum creatinine from baseline to week 4 on dolutegravir

	Univariable regression		Multivariable regression	
Variables	**Beta (95% CI)**	**P-value[a]**	**Beta (95% CI)**	**P-value[a]**
Age (years)	-0.09 (-0.15, -0.03)	0.003	0.08 (-0.02, 0.18)	0.113
Male sex (ref = female)	0.06 (-0.04, 0.16)	0.254	4.37 (2.43, 6.31)	<0.001
TAF (ref = TDF)	1.05 (-0.50, 2.60)	0.185	-1.96 (-3.40, -0.52)	0.008
Baseline serum creatinine ($\mu mol.L^{-1}$)	-1.74 (-3.22, -0.26)	0.022	-0.20 (-0.27, -0.12)	<0.001
log_{10} HIV-1 RNA viral load ($cp.ml^{-1}$)	0.81 (-0.26, 1.87)	0.138	0.33 (-0.83, 1.50)	0.576
ln T-cell CD4 count ($cells.mm^{-3}$)	-0.55 (-1.40, 0.31)	0.209	0.07 (-0.94, 1.08)	0.895
Concomitant co-trimoxazole (ref = no)	1.64 (-0.61, 3.89)	0.152	0.77 (-1.76, 3.30)	0.549
Total body weight (kg)	-0.01 (-0.07, 0.04)	0.629	0.01 (-0.05, 0.07)	0.690

Note: A negative regression beta value (coefficient) indicates a decrease in change in creatinine per unit increase in variable value.

TDF = Tenofovir disoproxil fumarate; TAF = Tenofovir alafenamide fumarate; ln = Natural log; Ref = Reference variable value.

[a]P-values calculated with Student's t-tests.

Variables included in the multivariable regression: Age, sex, TAF use, baseline serum creatinine, log_{10} HIV-1 RNA count, ln T-cell CD4 count, concomitant co-trimoxazole use, and total body weight.

Table 4. Univariable and multivariable linear regression models from the pharmacokinetic association analysis assessing the association between dolutegravir $AUC_{0\text{-}24h}$ and change in serum creatinine from baseline to week 4

	Univariable regression		Multivariable regression	
Variables	**Beta (95% CI)**	**P-value[a]**	**Beta (95% CI)**	**P-value[a]**
ln Dolutegravir $AUC_{0\text{-}24h}$ ($mg.h.L^{-1}$)	2.56 (0.33, 4.80)	0.025	2.78 (0.54, 5.01)	0.015
Age (years)	-0.10 (-0.18, -0.02)	0.018	0.11 (-0.01, 0.24)	0.080
Male sex (ref = female)	0.06 (-0.07, 0.19)	0.370	5.20 (2.92, 7.48)	<0.001
TAF (ref = TDF)	1.39 (-0.51, 3.29)	0.151	-2.30 (-4.06, -0.53)	0.011
Baseline serum creatinine ($\mu mol.L^{-1}$)	-2.26 (-4.06, -0.47)	0.014	-0.22 (-0.31, -0.12)	<0.001
log_{10} HIV-1 RNA viral load ($cp.ml^{-1}$)	0.24 (-1.02, 1.50)	0.712	-0.38 (-1.73, 0.97)	0.579
ln CD4 T-cell count ($cells.mm^{-3}$)	-0.39 (-1.40, 0.62)	0.446	-0.08 (-1.29, 1.13)	0.899
Concomitant co-trimoxazole (ref = no)	1.39 (-1.26, 4.04)	0.304	0.82 (-2.07, 3.71)	0.578
Total body weight (kg)	-0.05 (-0.10, 0.01)	0.093	-0.01 (-0.08, 0.05)	0.682

Note: A negative regression beta value (coefficient) indicates a decrease in change in creatinine per unit increase in variable value.

TDF = Tenofovir disoproxil fumarate; TAF = Tenofovir alafenamide fumarate; ln = Natural log; Ref = Reference variable value.

[a]P-values calculated with Student's t-tests.

Variables included in the multivariable regression: ln Dolutegravir $AUC_{0\text{-}24h}$, Age, sex, TAF use, baseline serum creatinine, log_{10} HIV-1 RNA count, ln T-cell CD4 count, concomitant co-trimoxazole use, and total body weight.

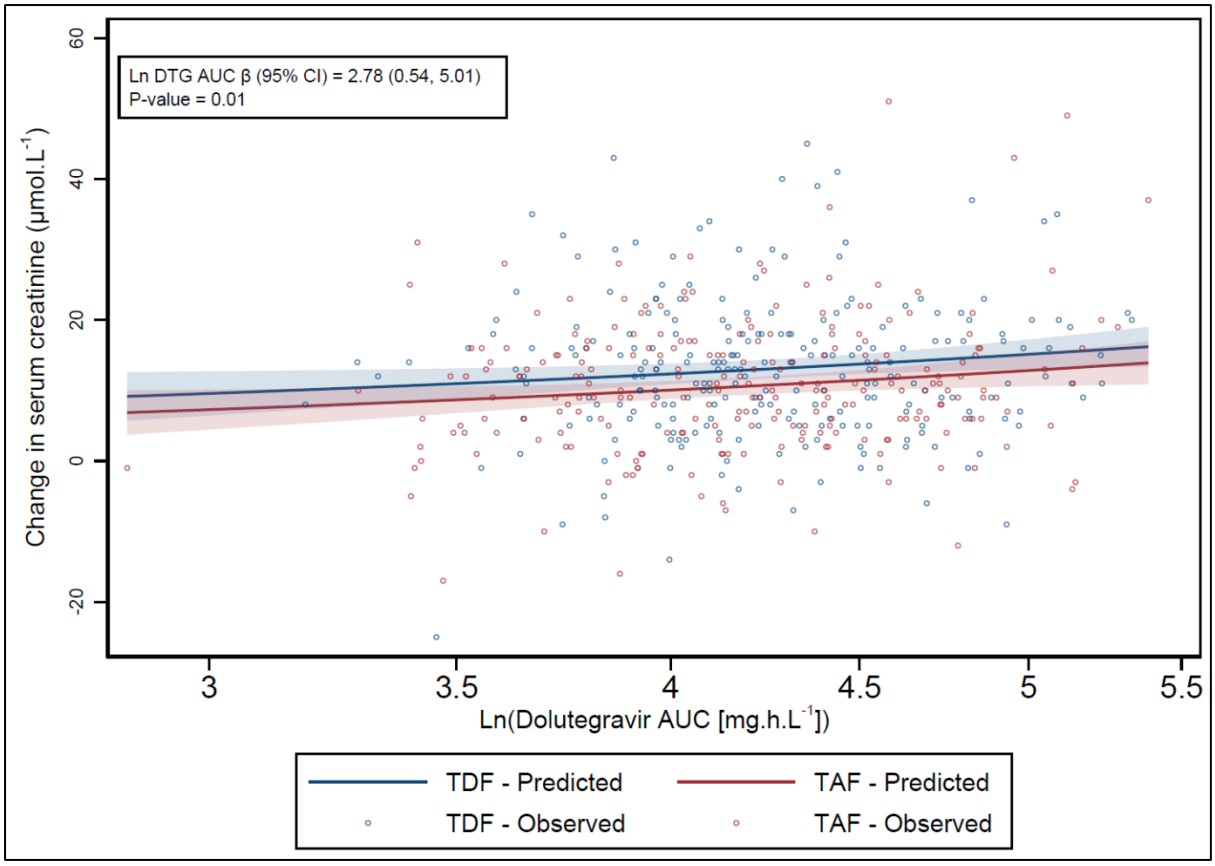

Figure 1. Observed and predicted values of change in serum creatinine plotted against incremental dolutegravir $AUC_{0\text{-}24h}$ values

The scatter plot graph illustrates the predicted values of change in serum creatinine, calculated using estimated marginal means based on a multivariable regression model from the pharmacokinetic association analysis. This involved incrementally increasing the estimated dolutegravir $AUC_{0\text{-}24h}$ values within the range of dolutegravir exposure estimates while keeping the other variables, namely age, sex, baseline serum creatinine, tenofovir treatment group (TDF or TAF use), HIV-1 RNA viral load, CD4 T-cell count, total body weight, and concomitant co-trimoxazole use, constant at their means. These predicted values were represented by a continuous line on the scatter plot, while the observed values were represented by circles. The p-value, determined through a Student t-test, indicated the statistical significance of the estimated dolutegravir $AUC_{0\text{-}24h}$ in the multivariable regression model.

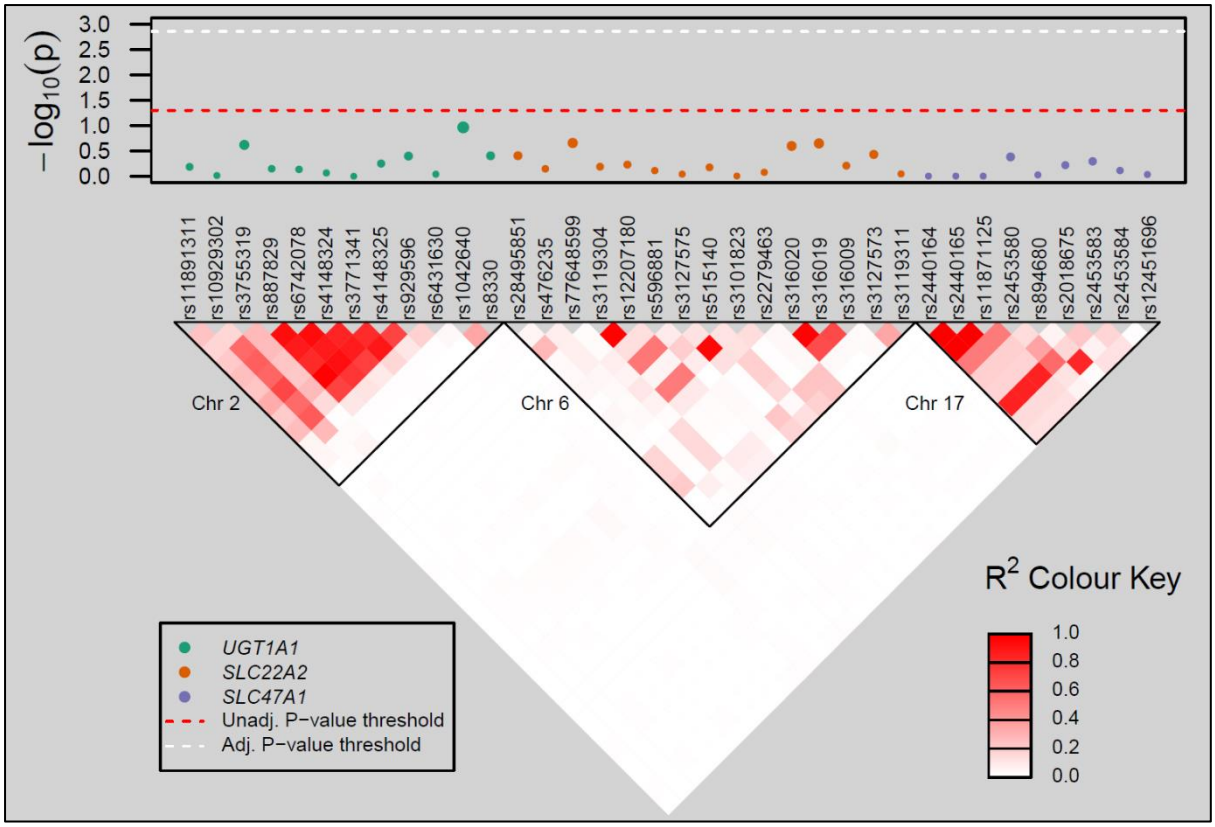

Figure 2. Linkage disequilibrium and significance of polymorphism associations within the *UGT1A1*, *SLC22A2*, and *SLC47A1* genes from the additive regression models of genetic association analyses

The white-red colour gradient in this heatmap illustrates the pairwise linkage disequilibrium (LD) measured by R^2, with red colour intensity indicating higher LD. Statistical significance of polymorphisms in the additive, multivariable regression models from the genetic association analyses are shown in the dot plot using negative log transformed p-values as determined by Student t-tests.

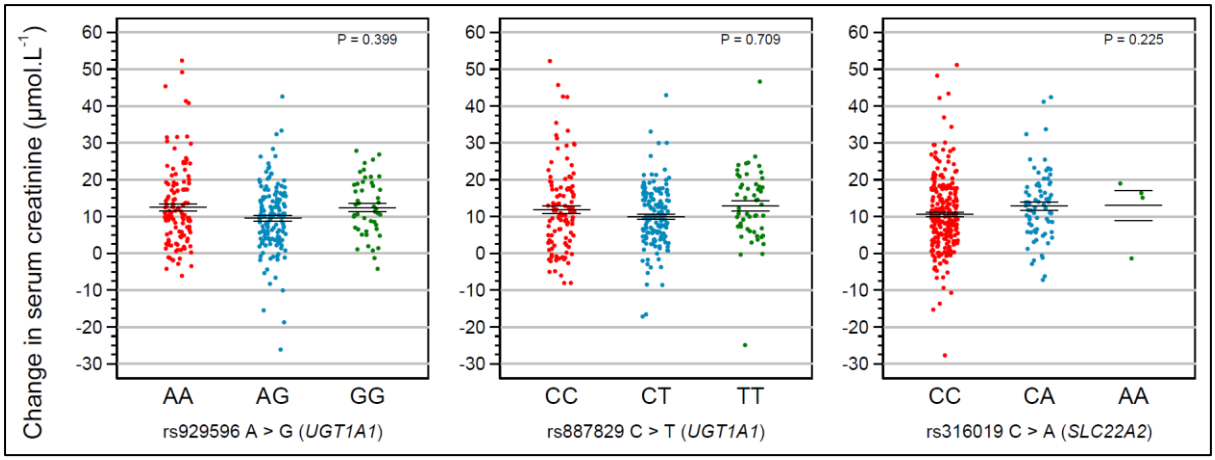

Figure 3. Observed change in serum creatinine at week 4 by rs929596 (*UGT1A1*), rs887829 (*UGT1A1*), and rs316019 (*SLC22A2*) genotypes in participants initiated on dolutegravir-containing antiretroviral therapy

A jitter plot of the observed change in serum creatinine at week 4 by rs929596 (*UGT1A1*), rs887829 (*UGT1A1*), and rs316019 (*SLC22A2*) genotypes in participants initiated on dolutegravir-containing antiretroviral therapy is shown. The plot displays the impact of *UGT1A1* and *SLC22A2* polymorphisms on the change in serum creatinine at week 4. The horizontal bars indicate means and standard errors. P-values indicate statistical significance of polymorphisms from the additive models and were calculated using Student t-test. The Bonferroni-adjusted significance threshold is 1.4×10^{-3}.

Appendix A: Manuscript supplementary tables and figures

Table S1. Univariable and multivariable linear regression models of associations of pharmacokinetic variables with change in serum creatinine from baseline to week 4 on dolutegravir containing ART

Model	Chromosome	Variant ID	Gene	Allele	MAF	Coef. (95% CI)	P-value[a]
Additive	2	rs1042640	*UGT1A1*	C > G	0.18	1.62 (-0.35, 3.59)	0.108
	2	rs3755319	*UGT1A1*	C > A	0.30	-1.01 (-2.70, 0.67)	0.240
	2	rs8330	*UGT1A1*	C > G	0.40	-0.68 (-2.23, 0.88)	0.393
	6	rs77648599	*SLC22A2*	T > G	0.11	1.42 (-0.84, 3.68)	0.22
	6	rs316019	*SLC22A2*	C > A	0.13	1.40 (-0.85, 3.65)	0.225
	6	rs316020	*SLC22A2*	G > A	0.13	1.32 (-0.93, 3.56)	0.251
	17	rs2453580	*SLC47A1*	T > C	0.42	-0.64 (-2.18, 0.90)	0.414
	17	rs2453583	*SLC47A1*	A > T	0.30	0.56 (-1.08, 2.19)	0.506
	17	rs2018675	*SLC47A1*	C > T	0.36	0.43 (-1.18, 2.05)	0.602
Dominant	2	rs929596	*UGT1A1*	A > G	0.38	-2.33 (-4.49, -0.17)	0.035
	2	rs1042640	*UGT1A1*	C > G	0.18	1.92 (-0.30, 4.14)	0.091
	2	rs3771341	*UGT1A1*	G > A	0.37	-1.18 (-3.34, 0.98)	0.285
	6	rs316019	*SLC22A2*	C > A	0.13	1.55 (-0.89, 4.00)	0.213
	6	rs316020	*SLC22A2*	G > A	0.13	1.45 (-0.98, 3.88)	0.242
	6	rs77648599	*SLC22A2*	T > G	0.11	1.20 (-1.38, 3.79)	0.362
	17	rs2018675	*SLC47A1*	C > T	0.36	0.83 (-1.33, 3.00)	0.452
	17	rs2453584	*SLC47A1*	G > C	0.07	0.88 (-2.27, 4.03)	0.585
	17	rs2453583	*SLC47A1*	A > T	0.30	0.41 (-1.68, 2.51)	0.70
Recessive	2	rs887829	*UGT1A1*	C > T	0.41	2.55 (-0.23, 5.32)	0.073
	2	rs4148325	*UGT1A1*	C > T	0.41	2.55 (-0.23, 5.32)	0.073
	2	rs6742078	*UGT1A1*	G > T	0.40	2.37 (-0.42, 5.17)	0.097
	6	rs3101823	*SLC22A2*	T > G	0.11	-8.04 (-18.70, 2.62)	0.140
	6	rs3127575	*SLC22A2*	C > T	0.11	-8.04 (-18.70, 2.62)	0.140
	6	rs77648599	*SLC22A2*	T > G	0.11	5.60 (-2.02, 13.22)	0.150
	17	rs2453580	*SLC47A1*	T > C	0.42	-1.52 (-4.33, 1.30)	0.292
	17	rs2453583	*SLC47A1*	A > T	0.30	1.62 (-2.15, 5.39)	0.399
	17	rs2453584	*SLC47A1*	G > C	0.07	-4.08 (-14.80, 6.65)	0.457

[a]Unadjusted P-values. Adjusted p-values are not statistically significant. The genome-wide significance threshold was 1.4×10^{-3}. P-values determined by Student t-test. Listed SNPs were limited to the top three SNPs with the lowest probability for type I error by model assumption and gene were displayed in the table.

Note: Covariates included in each model: patient age (years), sex, treatment group (TDF or TAF), baseline serum creatinine ($\mu mol.L^{-1}$), total body weight (kg), HIV-1 RNA viral load ($cells.ml^{-1}$), CD4 T-cell count ($cells.mm^{-3}$), and concomitant use of co-trimoxazole.

Table S2. Multivariable linear regression model assessing the genetic association between *UGT1A1* polymorphism rs929596 assuming dominant allelic effects, and change in serum creatinine from baseline to week 4 on dolutegravir containing ART

Variable	Beta (95% CI)	P-value
rs929596	-2.33 (-4.49, -0.17)	0.035
Age (years)	0.19 (0.05, 0.33)	0.007
Sex (ref = female)	4.54 (1.70, 7.37)	0.002
Treatment group (ref = TDF)	-2.11 (-4.18, -0.04)	0.047
Baseline serum creatinine ($\mu mol.L^{-1}$)	-0.20 (-0.30, -0.10)	<0.001
log_{10} baseline HIV-1 RNA viral load ($cp.ml^{-1}$)	0.55 (-0.94, 2.04)	0.471
ln baseline CD4 T-cell count ($cells.mm^{-3}$)	1.59 (0.09, 3.10)	0.039
Concomitant co-trimoxazole (ref = no)	1.63 (-1.68, 4.94)	0.334
Total body weight (kg)	-0.06 (-0.14, 0.02)	0.136
Principal component 1	206.40 (-1614.00, 2027.00)	0.824
Principal component 2	1236.00 (-2178.00, 4650.00)	0.479

Table S3. Sensitivity analysis of genetic association analyses between polymorphisms in *SLC22A2* and *SLC47A1*, and change in serum creatinine from baseline to week 4 with dolutegravir $AUC_{0\text{-}24h}$ included

Model	Chromosome	Variant ID	Gene	Allele	MAF	Coef. (95% CI)	P-value[a]
Additive	6	rs28495851	SLC22A2	A > C	0.08	-2.24 (-5.15, 0.66)	0.131
	6	rs316019	SLC22A2	C > A	0.13	1.26 (-1.12, 3.65)	0.299
	6	rs316020	SLC22A2	G > A	0.13	1.12 (-1.26, 3.50)	0.357
	17	rs2453583	SLC47A1	A > T	0.30	0.96 (-0.73, 2.65)	0.266
	17	rs2453584	SLC47A1	G > C	0.07	1.09 (-1.82, 3.99)	0.465
	17	rs2018675	SLC47A1	C > T	0.36	0.57 (-1.12, 2.27)	0.508
Dominant	6	rs28495851	SLC22A2	A > C	0.08	-2.18 (-5.31, 0.94)	0.172
	6	rs316019	SLC22A2	C > A	0.13	1.49 (-1.13, 4.11)	0.266
	6	rs316020	SLC22A2	G > A	0.13	1.31 (-1.30, 3.92)	0.325
	17	rs2453584	SLC47A1	G > C	0.07	1.84 (-1.42, 5.09)	0.269
	17	rs2018675	SLC47A1	C > T	0.36	1.11 (-1.15, 3.37)	0.338
	17	rs2453583	SLC47A1	A > T	0.30	1.04 (-1.16, 3.24)	0.354
Recessive	6	rs3101823	SLC22A2	T > G	0.11	-7.12 (-17.72, 3.48)	0.189
	6	rs3127575	SLC22A2	C > T	0.11	-7.12 (-17.72, 3.48)	0.189
	6	rs77648599	SLC22A2	T > G	0.11	4.90 (-2.65, 12.46)	0.204
	17	rs2453580	SLC47A1	T > C	0.42	-1.39 (-4.26, 1.48)	0.343
	17	rs2453584	SLC47A1	G > C	0.07	-5.07 (-15.69, 5.55)	0.350
	17	rs894680	SLC47A1	G > A	0.07	-5.07 (-15.69, 5.55)	0.350

[a]Unadjusted P-values. Adjusted p-values are not statistically significant. The genome-wide significance threshold was 1.4×10^{-3}. P-values determined by Student t-test. Listed SNPs were limited to the top three SNPs with the lowest probability for type I error by model assumption and gene were displayed in the table.

Note: Covariates included in each model: patient age (years), sex, treatment group (TDF or TAF), baseline serum creatinine ($\mu mol.L^{-1}$), total body weight (kg), HIV-1 RNA viral load ($cells.ml^{-1}$), CD4 T-cell count ($cells.mm^{-3}$), and concomitant use of co-trimoxazole.

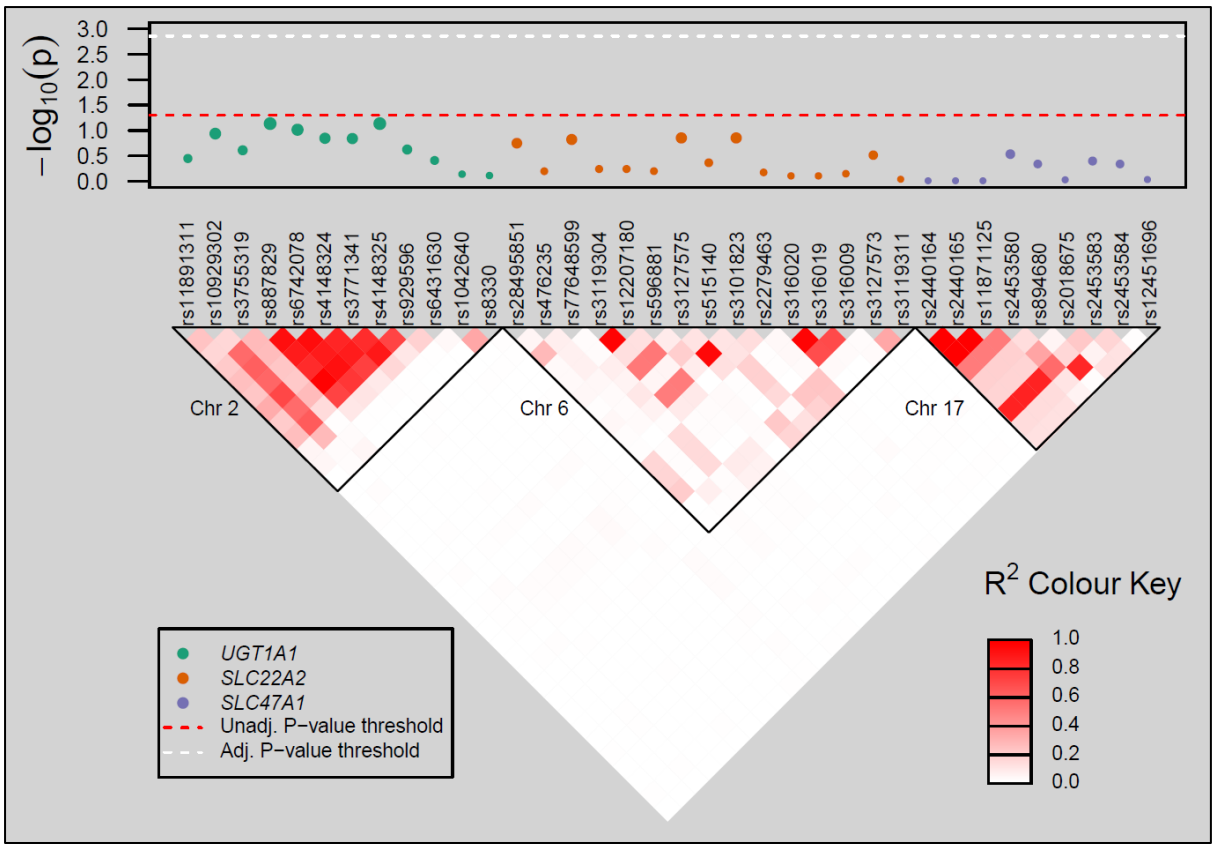

Figure S1. Heatmap and scatter plot of linkage disequilibrium (LD) over the *UGT1A1*, *SLC22A2*, and *SLC47A1* genes with p-values of polymorphisms from the recessive regression models of genetic association analyses

The white-red colour gradient of the cells illustrates the pairwise LD measured by r^2, with red colour intensity indicating strength of LD. Statistical significance of polymorphisms in the recessive regression models are illustrated in the scatter plot using negative log transformed p-values as determined by Student t-tests.

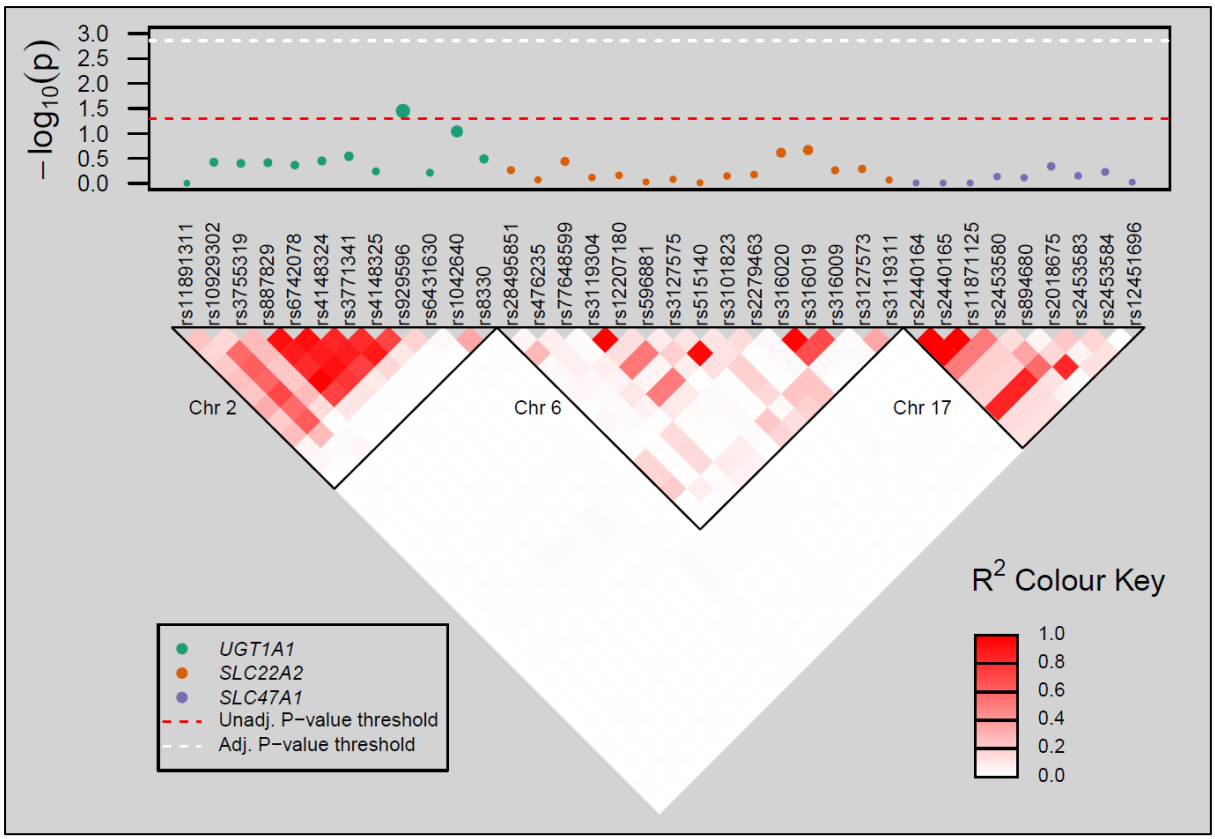

Figure S2. Heatmap and scatter plot of linkage disequilibrium (LD) over the *UGT1A1*, *SLC22A2*, and *SLC47A1* genes with p-values of polymorphisms from the dominant regression models of genetic association analyses

The white-red colour gradient of the cells illustrates the pairwise LD measured by R^2, with red colour intensity indicating strength of LD. Statistical significance of polymorphisms in the dominant regression models are illustrated in the scatter plot using negative log transformed p-values as determined by Student t-tests.

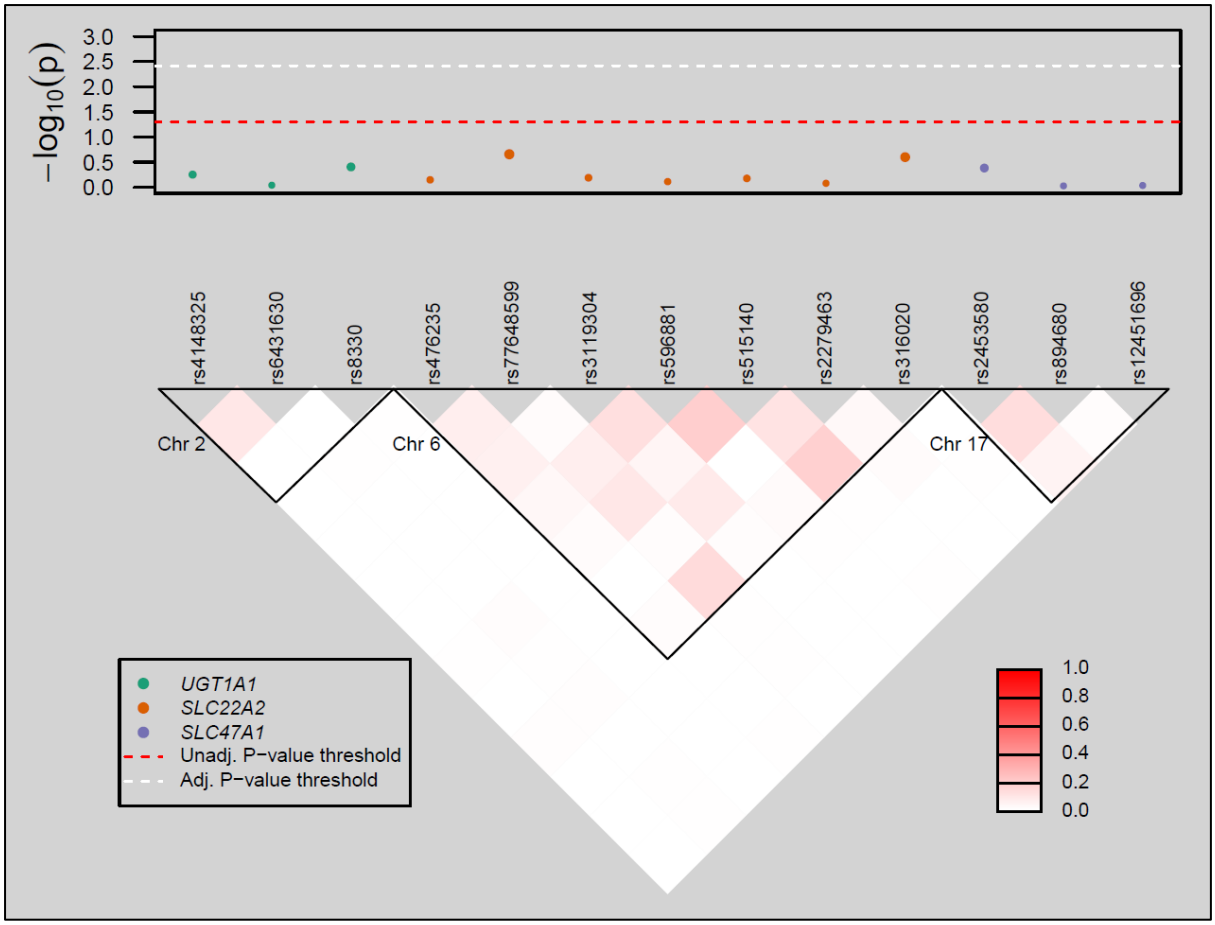

Figure S3. Sensitivity analysis - Heatmap plot of linkage disequilibrium (LD) for *UGT1A1*, *SLC22A2*, and *SLC47A1* genes with association p-values of polymorphism from the additive genetic linear regression models graphed above. Polymorphisms in high LD with R^2 value > 0.8 have been omitted.

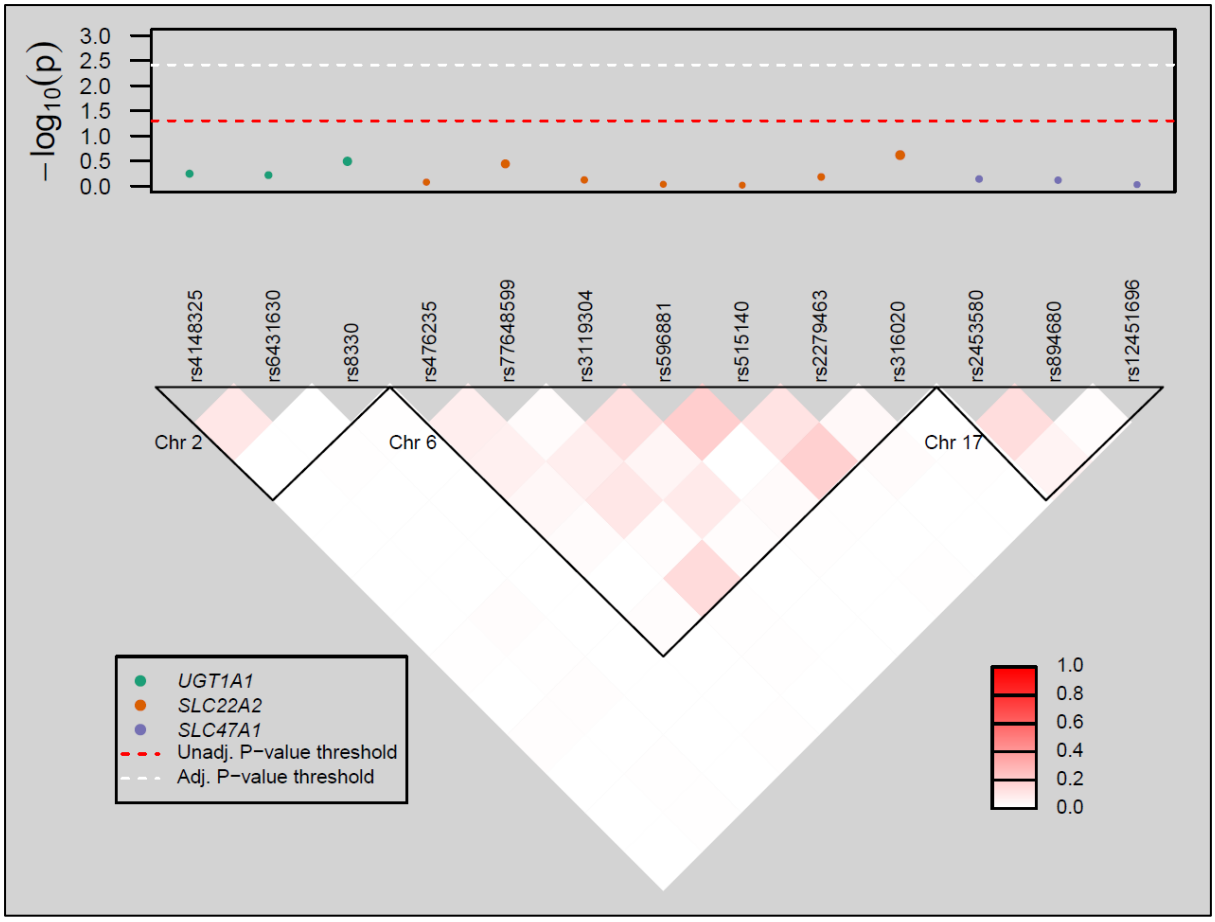

Figure S4. Sensitivity analysis - Heatmap plot of linkage disequilibrium (LD) for *UGT1A1*, *SLC22A2*, and *SLC47A1* genes with association p-values of polymorphisms from the dominant genetic linear regression models graphed above. Polymorphisms in high LD with R^2 value > 0.8 have been omitted.

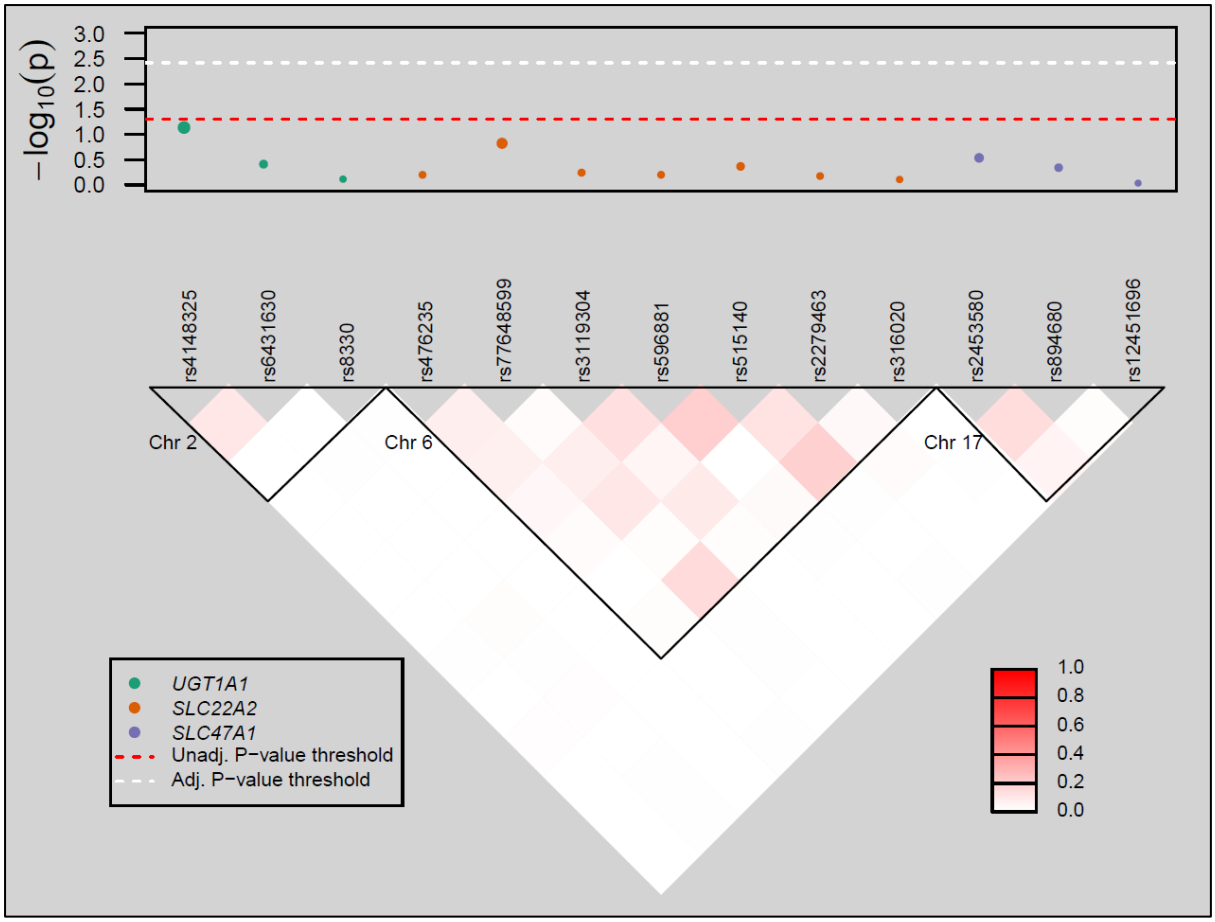

Figure S5. Sensitivity analysis - Heatmap plot of linkage disequilibrium (LD) for *UGT1A1*, *SLC22A2*, and *SLC47A1* genes with association p-values of polymorphisms from the recessive genetic linear regression models graphed above. Polymorphisms in high LD with R^2 value > 0.8 have been omitted.

BJCP British Journal of Clinical Pharmacology

Author Guidelines for *British Journal of Clinical Pharmacology*

Sections

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Appendix C: Ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

08 November 2022

HREC REF: 716/2022

A/Prof P Sinxadi
Division of Clinical Pharmacology
K-45 , OMB
Email: phumla.sinxadi@uct.ac.za
Student: Rephaim.mpofu@uct.ac.za

Dear A/Prof Sinxadi

PROJECT TITLE: PHARMACOKINETICS AND PHARMACOGENETICS OF EARLY CHANGES IN CREATININE AMONG SOUTHERN AFRICANS LIVING WITH HIV THAT HAVE INITIATED DOLUTEGRAVIRBASED ANTIRETROVIRAL THERAPY-
(MASTERS CANDIDATE-DR REPHAIM MPOFU)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Rephaim Mpofu will also be involved in this study.

Please quote the HREC REF 716/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC/ref 716.2022

Appendix D: Research protocol

Pharmacokinetics and pharmacogenetics of early changes in creatinine among Southern Africans living with HIV that have initiated dolutegravir-based antiretroviral therapy

Master of Medicine (MMed) research protocol

Version 1.0

01 November 2022

Name: Dr Rephaim Mpofu

Student number: MPFREP001

Supervisor/s:

A/Prof Phumla Sinxadi, Division of Clinical Pharmacology (University of Cape Town), Supervisor

Prof Gary Maartens, Division of Clinical Pharmacology (University of Cape Town), Co-supervisor

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Introduction

Dolutegravir is a second generation integrase strand inhibitor that has largely replaced efavirenz in first-line antiretroviral regimens due to it improved efficacy, tolerability, and higher barrier to resistance. [1] Commonly reported adverse events include gastrointestinal disturbances, neuropsychiatric disturbances such as headache and insomnia, and renal abnormalities such as increased serum creatinine and a reduced estimated glomerular filtration rate (eGFR). This change in serum creatinine, typically an increase of 10-15% that occurs within 1 week of treatment initiation that plateaus by the fourth week, has been observed among HIV-negative volunteers as well as people living with HIV (PLWH) that are on dolutegravir containing antiretroviral therapy (ART) regimens. [2-4] This effect is mediated by the inhibition of renal transporters involved in creatinine excretion. Importantly, this apparent decrease in estimated glomerular filtration rate is not reflective of a true decline in glomerular filtration and is rather due to inhibition of creatinine clearance.

Creatinine is an endogenous cation produced by the metabolism of creatine, a major component of muscle tissue. Due to its chemical properties, it is eliminated solely by renal elimination. This involves a combination of passive glomerular filtration (approximately 80-90% of total creatinine clearance) and facilitated tubular secretion (10-20%). The relative contribution of each process can be affected by factors including age, the presence and severity of chronic kidney disease, or drugs. [5] Tubular secretion of creatinine is largely mediated by organic cation transporter 2 (OCT2) transporters that are located on the basolateral membrane, as well as multidrug and toxin extrusion 1 (MATE1) transporters and multidrug and toxin extrusion 2-K (MATE2-K) transporters that are located on the apical surface of renal tubular cells. [5, 6] OCT2 belongs to the solute carrier superfamily of transporters, and these proteins facilitate the transport of low molecular weight, hydrophilic, cationic compounds from blood to the intracellular compartment through an electrochemical gradient of their substrates. OCT2 is predominantly expressed in renal proximal tubular cells of the kidney but is also found in brain and lung tissues. MATE transporters are proton/cationic antiporters that are highly expressed in multiple tissues: MATE1 is expressed in the kidney, liver, adrenal gland, and skeletal muscle, while MATE2-K is specifically expressed in the kidney. [5, 7]

Drugs that alter the function of renal transporters can cause clinically significant drug interactions due to altered pharmacokinetics. Dolutegravir is a potent inhibitor of OCT2, with reported 50% inhibitory concentrations (IC_{50}) of 1.9 µM and 0.066 µM in two, separate studies. [2, 8] This is likely to exceed therapeutic concentrations with standard dolutegravir dosing by 3-7 fold. [9] Similarly, dolutegravir has been shown to inhibit MATE1 and MATE2-K mediated transport of solutes to varying degrees, with one *in-vitro* study reporting IC_{50} values of 3.6 µM and 12.5 µM when metformin was used as a probe substrate, while another reported IC_{50} values of 6.3-50 µM and >100 µM respectively. [5, 8, 10] Clinically, dolutegravir results in a 10-15% relative reduction in creatinine clearance, which largely corresponds to the proportion normally eliminated by tubular secretion. Importantly, this effect is not representative of a decline in renal function and did not require treatment discontinuation in clinical trials. [9, 11] This effect on serum creatinine varies widely between patients, as evidenced by the ADVANCE trial where a large difference can be noted between the median change in serum creatinine of 13 µmol/L overall (correlating with a reduction in eGFR of approximately 30 ml/min/1.73m^2, compared to a change in serum creatinine of 53 µmol/L among participants within the upper quartile. [12, 13] Factors that may contribute to this wide variability include pharmacokinetic, pharmacodynamic, and genetic predisposition.

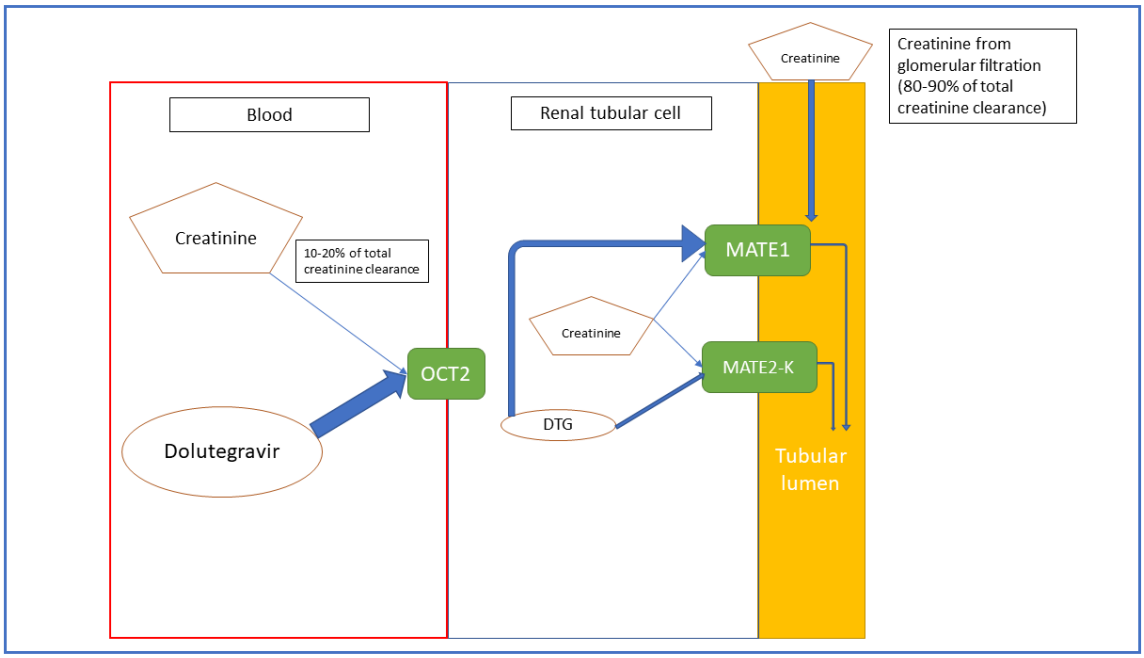

FIGURE 1. SCHEMATIC DIAGRAM DEMONSTRATING RELEVANT RENAL TRANSPORT OF CREATININE AND DOLUTEGRAVIR. ARROW THICKNESS INDICATES RELATIVE TRANSPORTER AFFINITY FOR DOLUTEGRAVIR COMPARED TO CREATININE, RESULTING IN COMPETITIVE INHIBITION OF CREATININE TRANSPORT

The OCT transporter subfamily is encoded by *SLC22A* genes. [14] Genetic diversity affects renal transporter structure or function, and this may contribute to inter-individual differences in drug disposition. [15] This has been evidenced by drugs such as metformin and cisplatin which undergo renal transport and have been associated with altered hypoglycaemic effects or nephrotoxicity, respectively. [16, 17] Pharmacogenetic data on dolutegravir-mediated creatinine secretion are sparse, but literature supports the hypothesis that genetic variation may influence the antagonistic effect exerted by dolutegravir on creatinine transport. One study reported an association between rs316019, a non-synonymous c.808G>T single nucleotide polymorphism (SNP) encoding *SLC22A2*, and an increased prevalence of neuro-psychiatric symptoms among PLWH on dolutegravir. [18] This SNP caused a non-synonymous change in amino acid at position 270 from alanine to serine. Patients with this genetic variant reported more features of anxiety and hostility, and scored higher on an objective neuro-psychiatric assessment test, which indicated potentially deranged neuro-psychiatric function. Interestingly, this SNP was not associated with differences in dolutegravir trough concentrations, which may suggest altered substrate transport at other sites such as the brain where OCT2 transporters are also found. [18] Previous studies have also demonstrated an association between this SNP and decreased creatinine secretion. [19, 20] This variant is well represented in almost all ethnicities studied including South African groups, with allelic frequency reports of up to 14%.[21] Other gene variants that have been reported to affect OCT2 function among populations of African ancestry include rs3127573, rs8177507, and rs8177516, among others. [22]

MATE1 and MATE2-K transporters, recently discovered in 2005, are encoded by *SLC47A1* and *SLC47A2* respectively. [7, 23] MATE2-K is a splice variant of MATE2, and is the predominant form expressed in the kidney. [7] They participate in creatinine efflux to the urinary filtrate with similar affinity, thereby creating multiple pathways for creatinine elimination. Thus far, no pharmacogenetic studies have been published that assess associations between MATE

transporter gene polymorphisms and dolutegravir pharmacokinetics/pharmacodynamics. Genetic variability in these transporters has been associated with altered disposition of other drugs such as metformin, which is also a MATE1 and MATE2-K transporter substrate. For example, a study published in 2013 demonstrated that the SNP rs2252281 was associated with an enhanced response to metformin in a cohort of patients with diabetes. This SNP is located in the 5' untranslated region and serves as a binding site for AP-1, a transcription factor. In the same study, participants with a genetic variant of MATE2 (rs12943590) displayed enhanced elimination of metformin compared to carriers of the normal allele. Inclusion of these genotypes in regression models improved the variability explained in metformin response from 7% when the model only included SNPs in either of the 2 genes, to 15% where SNPs in both genes were included. [24] These data underline two important concepts: First, it emphasizes the importance of understanding genetic variation within both exonic and intronic segments, as evidenced by the latter example where a SNP in an intronic region impacted metformin disposition. Evidence that introns contribute significantly to protein expression is increasing. [25] As a result, allelic variants in these regions may also affect substrate transport. Second, it demonstrates that individual gene effects interact with each other through additive mechanisms to produce variable phenotypes, and that the sum of individual effects should be considered to produce an accurate estimate of potential pharmacogenetic interactions.

Genetic variation that affects dolutegravir exposure may further alter its pharmacodynamic, inhibitory effect on creatinine secretion. Dolutegravir is primarily metabolized in the liver by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). *UGT1A1* variability has previously been associated with altered dolutegravir exposure. For example, one study noted a 27% increase in dolutegravir $AUC_{0\text{-}24}$ among homozygotes for rs8175347, a SNP that resulted in reduced UGT1A1 function, compared to homozygotes of the normal gene[26]. Another study recently showed that rs887829 and rs28899168 SNPs were associated with reduced dolutegravir clearance in a Southern African population. [27] Pharmacokinetic/pharmacodynamic studies further suggest that the degree of dolutegravir exposure may correlate with the magnitude of inhibition on creatinine clearance: A population pharmacokinetic model found a negative correlation between dolutegravir $AUC_{0\text{-}24h}$ and change in creatinine clearance over time with a correlation coefficient of -0.3177 ($p<0.001$). [3] On the basis of these findings, it is plausible to suggest that genetic variations in *UGT1A1* that alter dolutegravir exposure could have an exposure-response relationship with the inhibition of creatinine secretion, thus increasing the risk and magnitude of reduced creatinine clearance among populations with genetic polymorphisms.

Populations of African ancestry have more diverse genetic diversity compared to other populations. [28] This diversity has been linked to increased variability in drug response as well as adverse effects. [28] The majority of pharmacogenetic studies, however, have either been conducted in non-African cohorts, or in subgroups of African ancestry with limited diversity. Including Africans in research may reveal novel genetic factors. [29] Africa has a high prevalence of HIV infection, and the use of dolutegravir continues to increase due to its favourable drug profile. Dolutegravir associated elevations in serum creatinine can result in inappropriate switching of dolutegravir to other antiretrovirals. [30] Improving our understanding of potential pharmacogenetic interactions would increase the knowledgebase that permits safe and rational use of dolutegravir which could contribute to the reduction of unnecessary drug regimen alteration.

This analysis aims to assess potential relationships between dolutegravir exposure, relevant genetic polymorphisms that may affect renal transporters or UGT1A1, and early changes in serum creatinine concentrations among a Southern African cohort of treatment naïve PLWH who were initiated on ART.

Hypothesis

1. Dolutegravir has an exposure-dependent relationship with the inhibition of renal creatinine secretion.
2. Dolutegravir's inhibitory effect on renal creatinine secretion is modulated by genetic polymorphisms encoding renal transporters (OCT2, MATE1, and MATE2-K).
3. Dolutegravir's inhibitory effect on renal creatinine secretion is modulated by genetic polymorphisms encoding UGT1A1.

Aim

To assess pharmacokinetic-pharmacogenetic-pharmacodynamic relationships between dolutegravir exposure and early changes in serum creatinine when exposed to dolutegravir-containing ART among ART-naïve Southern African PLWH.

Study design

A post-hoc analysis of pharmacokinetic, pharmacogenetic, and pharmacodynamic data collected during the ADVANCE clinical trial. ADVANCE was an open-label, non-inferiority, randomized, controlled trial that evaluated the efficacy and safety of ART regimens composed of TDF or TAF when co-administered with emtricitabine (FTC) and dolutegravir (DTG) compared with a standard of care arm of TDF, FTC, and efavirenz. This study was conducted among 1,053 HIV-positive, treatment naïve Southern African PLWH that were treated and followed up for 48 weeks, with an extension study conducted to 96 weeks. Data collected from the ADVANCE clinical trial will be analysed to assess the effects of dolutegravir exposure and hepatic enzyme genetic polymorphisms that affect dolutegravir exposure, and renal transporter genetic polymorphisms on change from baseline in serum creatinine within the first 4 weeks of treatment.

Study population

The study population for this analysis will consist of participants randomized to the TAF-FTC-DTG or TDF-FTC-DTG arms in whom pharmacokinetic samples were collected. The sample will have a maximum size of 284 participants.

Objectives

- Assess relationship between dolutegravir exposure and early changes in creatinine clearance
- Assess the modulatory effect of genetic polymorphisms in *OCT2*, *MATE1*, and *MATE2-K* renal transporter genes on dolutegravir mediated inhibition of creatinine secretion.
- Assess the modulatory effect of genetic polymorphisms in *UGT1A1* on dolutegravir mediated inhibition of creatinine secretion

Endpoints and analyses

Endpoint: Change in serum creatinine from baseline (before starting dolutegravir therapy) to week 4 of treatment.

- Analysis 1: Analyse potential associations between change in serum creatinine, baseline characteristics, and treatment allocation (sample size = 700)

- Independent variables: age, sex, baseline serum creatinine, $\log_{10}$ HIV RNA, baseline BMI, CD4 T-cell count, co-trimoxazole use, and treatment group (TDF or TAF).

- Analysis 2: Analyse potential associations between change in serum creatinine and pharmacokinetic estimates of DTG exposure (sample size = 472):
  - Independent variables: age, sex, baseline serum creatinine, log HIV RNA, baseline BMI, CD4 T-cell count, co-trimoxazole use (Yes or no), treatment group (TDF or TAF), estimated dolutegravir $AUC_{0\text{-}24h}$.

- Analysis 3: Analyse potential associations between change in serum creatinine, clinical and DTG PK exposure variables, and genetic polymorphisms (sample size = 284):
  - Independent variables: age, sex, baseline serum creatinine, log HIV RNA, baseline BMI, CD4 T-cell count, co-trimoxazole use (Yes or no), treatment group (TDF or TAF), dolutegravir estimated $AUC_{0\text{-}24h}$, genetic principal components, and pre-specified gene polymorphisms (*SLC22A*2, *SLC47A1*, SLC*47A2,* and *UGT 1A1).*
  - Associations will be assessed in separate models (see statistical analysis plan below).

Inclusion and exclusion criteria

Inclusion criteria:

Inclusion criteria	Analysis 1	Analysis 2	Analysis 3
Enrolled in DTG containing arms	X	X	X
18 years of age or older	X	X	X
At least one pharmacokinetic dolutegravir measurement		X	X
Provided informed consent for genetic testing			X

Exclusion criteria:

- Participants without post-enrolment serum creatinine measurements

Sample collection

Blood samples for creatinine measurements were collected at baseline and at week 4 of ART. Intensive PK and PG specimens were collected from a subgroup of participants that provided informed consent. Intensive PK sampling was conducted at various time points: pre-dose, 1, 2, 4-, 6-, 8-, and 24-hours post-dose. The dose preceding PK sampling was directly observed. Participants also underwent sparse sampling at either 48- or 96-weeks. Upon collection, the times of last dose administration and sample collection were recorded. The samples were stored at -80°C until analysis.

Pharmacokinetic analyses

Plasma DTG concentrations were measured from the PK samples using liquid chromatography with mass tandem spectrometry by the Division of clinical pharmacology laboratory at the University of Cape Town using an AB SCIEX API 4000 instrument. A population pharmacokinetic (PopPK) model was developed from the intensive PK sampling cohort using non-linear mixed-effects modelling. Individual pharmacokinetic parameter (estimated DTG $AUC_{0\text{-}24h}$) values at steady state were estimated from collected sparse samples using a post-hoc Bayes estimation method that took individual PK data and characteristics into account. Individual $AUC_{0\text{-}24h}$ values were estimated using administered dose, bioavailability, and estimated clearance. Additional details are provided elsewhere. [27]

Genetic testing

Whole blood was collected from participants that provided consent, and DNA was extracted and genotyped using the Illumina Infinium Multi-Ethnic Global BeadChip ($MEGA^{EX}$) at Vanderbilt Technologies for Advanced Genomics (VANTAGE). Post-genotype quality control checks were performed, which included sex checks, call rates by marker and sample, identity by descent plots, batch effect assessments, duplicate sample checks, and HapMap controls. Genome data imputation was performed using the TOPMed reference panel after data transformation using LiftOver and stratification by chromosome to parallelize the imputation process. [31-34] Additional details on genetic testing have been described in a prior publication. [27]

Principal Components

Genetic data were previously projected onto the 1000Genomes database, and principal component screen plots were visually inspected to determine how many components to include in analyses. Based on this, the first two principal components will be included.

Variables

- Demographic data: age, sex
- Body weight
- Serum creatinine (µmol/L) and estimated glomerular filtration rate (CKD-EPI 2021)
- Baseline plasma HIV-1 viral load and CD4 T-cell count
- Co-trimoxazole use (Yes or no)
- Dolutegravir pharmacokinetic exposure data – estimated individual 24-hour dolutegravir $AUC_{0\text{-}24h}$ from dolutegravir population pharmacokinetics model
- Pharmacogenetic polymorphism data for the following genes: *SLC22A2* (OCT2), *SLC47A1* (MATE-1)*, SLC47A2* (MATE2-K)*,* and *UGT1A1*
- Treatment group arm (TDF or TAF)
- The first 2 principal components

Statistical analysis plan

Baseline characteristics will be summarized with descriptive statistics. Univariable and multivariable regression models will be used to assess relationships between change in serum creatinine (outcome variable) and the following variables: dolutegravir exposure (using estimated dolutegravir $AUC_{0\text{-}24h}$) and genetic polymorphisms. For genetic association analyses, *a priori* selected SNPs in *SLC22A2*, *SLC47A1*, *SLC47A2,* and *UGT1A1* will be

included. Polymorphisms in these genes will be selected based on previously reported genome-wide associations ($p<5.0x10^{-8}$) with renal traits in the GWAS Catalog, and associations with drug-related phenotypes in the PharmGKB with 1 or 2A levels of evidence. The first multivariable regression analysis will include the clinical covariates (adjusting for age, sex, baseline body weight, baseline CD4 cell count, baseline HIV viral load, and tenofovir prodrug allocation group (TDF or TAF), and baseline serum creatinine concentration). The second analysis will include all previously included variables, as well as estimated dolutegravir pharmacokinetic variables (dolutegravir $AUC_{0\text{-}24h}$). Subsequent analyses will include all clinical, pharmacokinetic, and genetic variables which will consist of individual SNPs and genetic principal components. Regression diagnostic tests assessing relationships between independent variables may reveal high collinearity between UGT1A1 polymorphisms and estimated DTG $AUC_{0\text{-}24h}$ due to the enzyme's role in metabolizing DTG. If this occurs, the final regression model that includes UGT1A1 SNPs as a covariate will be run without estimated DTG $AUC_{0\text{-}24h}$.

Statistical tests will be performed using parametric or non-parametric tests as appropriate. Normality will be assessed using visual inspection of distributions and the Shapiro-Wilk test. Non-parametric data will be log-transformed. All variables chosen *a priori* will be included in the multivariable regression. We will use the Holm-Bonferroni procedure to control for multiple hypothesis testing with an overall alpha value of 0.05. STATA 16 and/or PLINK software will be used for data analysis.

This analysis is likely to have sufficient power to detect a relationship between the pharmacokinetic and genetic variables. A template model which includes 11 predictors from 8 baseline variables (see variables section), one pharmacokinetic estimate variable (i.e., estimated DTG $AUC_{0\text{-}24h}$), and one gene with 5 SNPs will have an estimated power of 90% to detect a relationship with 284 participants and an r-squared value of 0.1 (Figure 2).

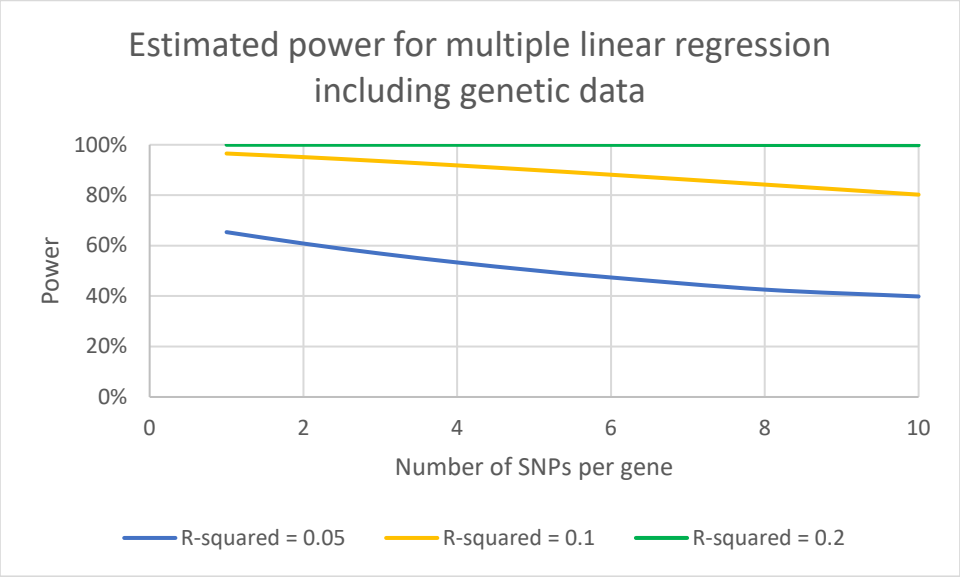

FIGURE 2. ESTIMATED POWER FOR MULTIPLE LINEAR REGRESSION MODELS THAT INCLUDE GENETIC DATA

Ethical considerations

This study will be conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation, and South African Good Clinical Practice

guidelines. Ethical approval for the conduct of the parent study (ADVANCE), as well as this analysis have been obtained by Human Research Ethics Committees at the University of Witwatersrand and the University of Cape Town, and participant informed consent was obtained during study conduct.

Potential risks

This study poses minimal additional risk to the study population as no further study procedures will be performed. All data and samples have been de-personalised, thus minimizing the risk of breach of confidentiality or privacy. All patient data will be kept on an electronically secured database which will be password protected and access controlled. Confidentiality will be maintained at all times to the best of the investigator's ability. Only the research team will have access to the data.

Potential benefits

While the research findings generated from this study may not necessarily benefit the study population directly, they may generate generalisable knowledge that may provide future benefit.

Limitations

The administration of ART was not directly observed for participants that underwent sparse sampling. Thus, it is possible that AUC parameters may be inaccurate if the medication schedule was not adhered to.

Results dissemination

This research project is an academic requirement for completion of a Master of Medicine degree in Clinical Pharmacology. From this research project, a minor dissertation will be written for submission to the University of Cape Town. In addition, any results generated will be reported in a peer-reviewed academic journal. Any communications and presentations that may stem from this research will be reviewed and approved by the contributing authors and supervisors.

Funding

This research study will receive funding from internal research funds.

Journal article publication fee	R 25 000.00
Total	**R 25 000.00**

Timing

Months from start	Jun 2022	Jul 2022	Aug 2022	Sep 2022	Sep 2022	Oct 2022	Nov-Dec 2022	Jan 2023	Feb-Mar 2023
Literature review									
Preparing Protocol									
Protocol Review									
Ethics application									
Data collection									
Data analysis									
Publication manuscript formulation									
Mini-thesis submission									
Journal article submission									

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