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ORIGINAL ARTICLE

Determinants of early change in serum creatinine after initiation of dolutegravir-based antiretroviral therapy in South Africa

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Aims: Dolutegravir increases serum creatinine by inhibiting its renal tubular secretion and elimination. We investigated determinants of early changes in serum creatinine in a southern African cohort starting first-line dolutegravir-based antiretroviral therapy (ART).

Methods: We conducted a secondary analysis of data from participants in a randomized controlled trial of dolutegravir, emtricitabine and tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF) (ADVANCE, NCT03122262). We assessed clinical, pharmacokinetic and genetic factors associated with change in serum creatinine from baseline to Week 4 using linear regression models adjusted for age, sex, baseline serum creatinine, HIV-1 RNA concentration, 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 (SD 9.9) μmol.L^{-1}. Factors that were positively associated with change in serum creatinine at Week 4 were increased log dolutegravir area under the 24-h concentration–time curve (change in creatinine coefficient [β] = 2.78 μmol.L^{-1} [95% confidence interval (CI) 0.54, 5.01]), TDF use (β = 2.30 [0.53, 4.06]), male sex (β = 5.20 [2.92, 7.48]),

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baseline serum creatinine ($\beta = -0.22$ [−0.31, −0.12]) and *UGT1A1* rs929596 A→G polymorphism with a dominant model ($\beta = -2.33$ [−4.49, −0.17]). The latter did not withstand correction for multiple testing.

Conclusions: Multiple clinical and pharmacokinetic factors were associated with early change in serum creatinine in individuals initiating dolutegravir-based ART. *UGT1A1* polymorphisms may play a role, but further research on genetic determinants is needed.

KEYWORDS

cytochrome P450 enzymes, drug transporters, HIV/AIDS, pharmacogenomics, pharmacokinetic-pharmacodynamic

1 | INTRODUCTION

Dolutegravir, an integrase strand transfer inhibitor and recommended component of first-line antiretroviral regimens, increases serum creatinine by an average of 10% to 15%.[1] This typically occurs within the first week of treatment initiation and plateaus by the fourth week.[2–4] This does not reflect nephrotoxicity, but is instead 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).[2,5,6] There is considerable interindividual variability in the change in serum creatinine after starting dolutegravir: dolutegravir-based antiretroviral therapy (ART) has previously been associated with a mean change in creatinine of 11 μmol.L^{-1} (standard deviation, SD 8) after 4 weeks of treatment.[7] This variability may be due to multiple factors including concomitant medication, remission or resolution of HIV-associated nephropathy with ART, intercurrent illness or genetic factors including those that affect plasma dolutegravir exposure or renal tubular cell transporter function.[8] Improved understanding of factors associated with greater increases in serum creatinine when using dolutegravir could reduce the likelihood of unnecessarily changing ART regimens, particularly when dolutegravir is co-administered with other drugs that may cause nephrotoxicity such as tenofovir disoproxil fumarate (TDF).

Dolutegravir is primarily metabolized in the liver by uridine 5′-diphospho-glucuronosyltransferase 1A1 (UGT1A1),[9] and frequent genetic *UGT1A1* variants are associated with increased dolutegravir exposure. In a southern African population, *UGT1A1* polymorphisms 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.[3] It is possible that *UGT1A1* variants that affect dolutegravir exposure could explain some of the variability in changes in creatinine with dolutegravir. A non-synonymous polymorphism in *SLC22A2* that encodes OCT2 (rs316019) has been associated with reduced creatinine secretion.[11,12] Additional transporters, MATE1 and MATE2-K, encoded by *SLC47A1* and *SLC47A2*, respectively, are also involved in creatinine excretion.[13,14] While few studies have assessed

What is already known about this subject

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

What this study adds

- Plasma dolutegravir exposure, use of tenofovir disoproxil fumarate, male sex and baseline serum creatinine were associated with change in serum creatinine in participants initiating dolutegravir.
- Investigations for renal dysfunction may be most appropriate for patients experiencing early creatinine increases of ≥30 μmol.L^{-1}.

the role of *MATE* transporter polymorphisms in dolutegravir pharmacokinetics/pharmacodynamics (PK/PD), a *MATE1* polymorphism (rs2252281) has been associated with enhanced response to metformin in patients with diabetes.[15] It is important to consider the role of these genetic variants on substrate transport.

African populations exhibit a higher degree of genetic diversity than other ancestral groups.[16] As most pharmacogenetic studies to date have been conducted in non-African populations, novel genetic variants that affect treatment responses may be discovered in African populations.[16,17] The present study aimed to investigate associations between dolutegravir exposure, selected genetic polymorphisms and early changes in serum creatinine concentrations in a southern African cohort of treatment-naïve people with HIV (PWH) who initiated dolutegravir-containing ART.

2 | METHODS

2.1 | Study population

We conducted a secondary analysis of clinical, laboratory, pharmacokinetic and genetic data collected in the ADVANCE clinical trial (Clinicaltrials.gov identifier: NCT03122262). ADVANCE was a phase 3, single-centre, open label, non-inferiority trial conducted in Johannesburg, South Africa. Treatment-naïve PWH were randomly assigned to one of three treatment arms: (1) TDF, emtricitabine (FTC) and dolutegravir; (2) TAF, FTC and dolutegravir; or (3) TDF, FTC and efavirenz.[18] The present analysis included ADVANCE participants who (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.

2.2 | Pharmacokinetic sampling

Pharmacokinetic samples were collected from a subgroup of participants who provided written informed consent. A subset of participants ($n = 41$) underwent intensive pharmacokinetic sampling after 96 weeks, and were sampled pre-dose, and at 1, 2, 4, 6, 8, as well as 24 h post dose. The remaining participants underwent sparse sampling at one of 12, 24, 36 or 48 weeks. The samples were stored at −80°C until analysis.[10]

2.3 | 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-h dolutegravir area under the concentration–time curve (AUC_{0-24h}) values were estimated from sparse samples using a post hoc Bayesian estimation method that accounted for participant characteristics. Details are described elsewhere.[10]

2.4 | Genotyping and quality control

Whole blood samples were obtained from participants who consented to genetic testing. DNA was extracted from whole blood using a salting out procedure. Genotyping was conducted using the Illumina Infinium Multi-Ethnic Global BeadChip ($MEGA^{EX}$) at Vanderbilt Technologies for Advanced Genomics (VANTAGE), with quality control performed as described elsewhere.[10] For 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 renal trait associations with *P*-values $<5.0 \times 10^{-8}$ in the GWAS Catalog,[19] as well as polymorphisms associated with drug-related phenotypes with levels of evidence of 1 or 2A in the Pharmacogenomics Knowledgebase (PharmGKB).[20]

We excluded three polymorphisms with minor allele frequencies less than 5%, leaving 36 evaluable polymorphisms (12 in *UGT1A1*, 15 in *SLC22A2*, 9 in *SLC47A1*).

2.5 | Statistical and genetic association analyses

The primary outcome was change in serum creatinine from baseline to Week 4. Study baseline characteristics and change in serum creatinine were summarized with descriptive statistics. We assessed the proportion of participants who had a clinically significant increase in serum creatinine using 20 $\mu mol.L^{-1}$ and 15% as pre-defined upper limits of expected increases based on literature and national treatment guidelines.[21–23] We calculated the upper 95% confidence interval of the absolute change in serum creatinine, as such confidence intervals are widely used in determining normal ranges.[24] Data distributions were assessed by visual inspection using histograms, quantile–quantile plots, and were also assessed using 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 in years, sex (male or female), serum creatinine at baseline, tenofovir

prodrug allocation group (TDF or TAF, with TAF as reference), baseline CD4 T-cell count, plasma HIV-1 RNA concentration, baseline total body weight and use of co-trimoxazole (a known inhibitor of creatinine tubular secretion[5]) in the first 4 weeks of treatment. Second, in a pharmacokinetic association analysis, we assessed relationships between change in serum creatinine and dolutegravir AUC_{0-24h} while adjusting for the clinical covariates noted above. Third, we conducted a genetic association analysis by assessing relationships between change in serum creatinine and pre-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 the first two genetic principal components that were derived as described elsewhere.[10,25] The above-mentioned clinical covariates (excluding dolutegravir PK estimates) were also included in the genetic association analysis. To exclude a potential additive influence of dolutegravir exposure on relationships between genetic polymorphisms and change in creatinine, we conducted sensitivity analyses by including dolutegravir AUC_{0-24h} in genetic regression models examining polymorphisms in *SLC22A2* and *SLC47A1*.

To further assess potential relationships between change in creatinine and polymorphisms in *UGT1A1*, *SLC22A2* and *SLC47A1*, 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 polymorphisms and change in creatinine were illustrated with heatmaps and scatter plots of negative, log-transformed *P*-values from the linear regression models, respectively.

Thresholds for statistical significance in genetic association analyses were adjusted using the Bonferroni method by dividing the overall threshold of 0.05 by the number of polymorphisms included per genetic model. Statistical and genetic analyses were conducted in STATA 16 IC,[26] R version 4.2.2[27] and PLINK v1.90[28] software.

3 | RESULTS

A total of 702 participants were enrolled in the two dolutegravir arms of ADVANCE, 689 of whom were included in the clinical association analysis (13 participants were excluded due to absence of serum creatinine data from Week 4). Of these 689 participants, 470 were included in the pharmacokinetic association analysis (219 who did not undergo pharmacokinetic sampling were excluded), and 315 were included in the genetic association analysis (362 who did not provide consent for genetic testing were excluded, as were 12 who failed genetic data quality checks). Participant baseline characteristics are shown in Table 1.

3.1 | Analysis of clinical variables

At Week 4, the mean change in serum creatinine was 11.3 $\mu mol.L^{-1}$ (95% confidence interval [95% CI] = 10.5, 12.0), as detailed in Table 2. Participants in the TDF/dolutegravir (TDF/DTG) treatment group experienced a greater increase in serum creatinine compared to those in the TAF/dolutegravir (TAF/DTG) group (12.1 and 10.4 $\mu mol.L^{-1}$, respectively; $P = .021$). These changes corresponded to a relative mean change in serum creatinine of 17% overall, 18% in the TDF/DTG group and 16% in the TAF/DTG group. Substantial variability was noted in the change in serum creatinine as evidenced by an interquartile range (IQR) of −14 to 45 $\mu mol.L^{-1}$ (range = −25 to 67). Among the 689 participants in the study, 96 (14%) had changes in serum creatinine greater than 20 $\mu mol.L^{-1}$, while 388 participants (56%) had treatment-emergent changes in creatinine greater than 15%. The upper bound of the 95% confidence interval for the change in serum creatinine was 31 $\mu mol.L^{-1}$, which we rounded down to 30 $\mu mol.L^{-1}$ for clinical application—23 (3%) of 689 participants (16 on TDF, 7 on TAF) exceeded this threshold.

Univariable and multivariable linear regression analyses of change in serum creatinine at Week 4 are shown in Table 3. In the multivariable analysis, male sex ($P < .001$) and TDF use ($P = .008$) were each positively associated with change in serum creatinine, while baseline serum creatinine was negatively associated with change in serum creatinine ($P < .001$).

3.2 | Pharmacokinetic analyses

Univariable and multivariable linear regression showed that higher dolutegravir AUC_{0-24h} was positively associated with change in serum creatinine at Week 4 ($\beta = 2.78$; 95% CI 0.54, 5.01; $P = .015$; Table 4). The modelled relationship between dolutegravir AUC_{0-24h} and change in serum creatinine is presented in Figure 1. The multivariable analysis also found a positive association between change in serum creatinine and male sex, TDF use and lower baseline serum creatinine, in keeping with the clinical association analysis (Table 4).

3.3 | Genetic analysis

When analysed using an additive genetic model, none of the 36 evaluable polymorphisms were associated with change in serum creatinine (Figure 2). The polymorphism with the lowest *P*-value was *UGT1A1* rs1042640 ($P = .108$; Figure 2; Table S1). Similarly, none of the evaluated polymorphisms were significant in recessive models (Figure S1; Table S1). Using a dominant genetic model, *UGT1A1* rs929596 A→G was nominally associated with change in serum creatinine, but this did not withstand correction for multiple testing ($P = .035$; Figure S2; Tables S1 and S2). The mean change in serum creatinine when stratified by *UGT1A1* rs929596 A→G genotype was 12.5, 9.5 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). *UGT1A1* polymorphism rs887829 C→T and *SLC22A2* polymorphism rs316019 C→A were not associated with change in serum creatinine (Figure 3). Polymorphisms with the lowest *P*-values are shown in Table S1. Assessment of the other covariates in genetic analyses found that TDF use, age, male sex and baseline CD4 T-cell count were

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

Variables	Clinical (SD/IQR) ($n = 689$)	Pharmacokinetic (SD/IQR) ($n = 470$)	Genetic (SD/IQR) ($n = 315$)
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%)
Nationality			
Malawi	7 (1%)	7 (1%)	5 (2%)
Mozambique	14 (2%)	8 (2%)	6 (2%)
South Africa	427 (62%)	285 (61%)	177 (56%)
Zimbabwe	222 (32%)	157 (33%)	119 (38%)
Other[a]	19 (3%)	13 (3%)	8 (3%)
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 concentration ($cp.mL^{-1}$)*	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† or medians*, and standard deviations† or interquartile ranges* in parentheses.
Abbreviations: TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.
[a]Nationalities of participants included in the 'other' category: Democratic Republic of the Congo, Eswatini, Lesotho, Nigeria and Zambia.

TABLE 2 Summary of absolute and relative per cent change in creatinine ($\mu mol.L^{-1}$) at Week 4 in participants initiated on dolutegravir-containing antiretroviral therapy, stratified by tenofovir treatment group.

Treatment groups	Sample size	Mean (%)	95% CI	Min (%)	Max (%)	SD	*P*-value[a]
TDF	344	12.1 (18%)	11.0, 13.2	−25.0 (−21%)	67.0 (120%)	10.4	.021
TAF	345	10.4 (16%)	9.4, 11.4	−17.0 (−19%)	51.0 (159%)	9.4	
Overall	689	11.3 (17%)	10.5, 12.0	−25.0 (−21%)	67.0 (120%)	9.9	

Note: Relative per cent change from baseline reported in brackets.
Abbreviations: 95% CI, 95% confidence interval; SD, standard deviation; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.
[a]*P*-value was calculated to evaluate the significance of change in serum creatinine between treatment group using a Student's two sample *t*-test with unequal variance.

positively associated with change in serum creatinine, while baseline serum creatinine was negatively associated with change in serum creatinine (Table S2).

We conducted two sensitivity analyses: (1) We included dolutegravir AUC_{0-24h} as an additional covariate in models evaluating *SLC22A2* and *SLC47A1* polymorphisms (24 variants among 282 participants were included; Table S3), and (2) we excluded 11 polymorphisms with LD $R^2 > .8$ (leaving 25 polymorphisms for assessment; Figures S3–S5). Results from these sensitivity analyses were similar to those from the main analyses.

4 | DISCUSSION

Among participants who were randomized to receive dolutegravir-containing ART during participation in ADVANCE, we found that mean serum creatinine increased by 11 $\mu mol.L^{-1}$ from baseline to Week 4. Increased dolutegravir exposure, TDF use, older age, higher baseline CD4 T-cell count and male sex were independently associated with an increase in serum creatinine, while higher baseline serum creatinine and *UGT1A1* polymorphism rs929596 A→G were independently associated with a decrease in serum creatinine, though the

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**	**Beta (95% CI)**	***P*-value[a]**
Age (years)	0.06 (−0.04, 0.16)	.254	0.08 (−0.02, 0.18)	.113
Male sex (ref = female)	1.05 (−0.50, 2.60)	.185	4.37 (2.43, 6.31)	<.001
TDF use (ref = TAF)	1.74 (0.26, 3.22)	.022	1.96 (0.52, 3.40)	.008
Baseline serum creatinine ($\mu mol.L^{-1}$)	−0.09 (−0.15, −0.03)	.003	−0.20 (−0.27, −0.12)	<.001
log_{10} HIV-1 RNA concentration ($cp.mL^{-1}$)	0.81 (−0.26, 1.87)	.138	0.33 (−0.83, 1.50)	.576
ln CD4 T-cell count ($cells.mm^{-3}$)	−0.55 (−1.40, 0.31)	.209	0.07 (−0.94, 1.08)	.895
Concomitant co-trimoxazole (ref = no)	1.64 (−0.61, 3.89)	.152	0.77 (−1.76, 3.30)	.549
Total body weight (kg)	−0.01 (−0.07, 0.04)	.629	0.01 (−0.05, 0.07)	.690

Note: A negative regression beta value (coefficient) indicates a decrease in change in creatinine per unit increase in variable value. Variables included in the multivariable regression: age, sex, TDF use, baseline serum creatinine, log_{10} HIV-1 RNA concentration, ln CD4 T-cell count, concomitant co-trimoxazole use and total body weight.
Abbreviations: TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.
[a]*P*-values calculated with Student's *t*-tests.

TABLE 4 Univariable and multivariable linear regression models assessing association between pharmacokinetic variables (including dolutegravir AUC_{0-24h}) and change in serum creatinine from baseline to Week 4.

	Univariable regression		Multivariable regression	
Variables	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value[a]**
ln dolutegravir AUC_{0-24h} ($mg.h.L^{-1}$)	2.56 (0.33, 4.80)	.025	2.78 (0.54, 5.01)	.015
Age (years)	0.06 (−0.07, 0.19)	.370	0.11 (−0.01, 0.24)	.080
Male sex (ref = female)	1.39 (−0.51, 3.29)	.151	5.20 (2.92, 7.48)	<.001
TDF use (ref = TAF)	2.26 (0.47, 4.06)	.014	2.30 (0.53, 4.06)	.011
Baseline serum creatinine ($\mu mol.L^{-1}$)	−0.10 (−0.18, −0.02)	.018	−0.22 (−0.31, −0.12)	<.001
log_{10} HIV-1 RNA concentration ($cp.mL^{-1}$)	0.24 (−1.02, 1.50)	.712	−0.38 (−1.73, 0.97)	.579
ln CD4 T-cell count ($cells.mm^{-3}$)	−0.39 (−1.40, 0.62)	.446	−0.08 (−1.29, 1.13)	.899
Concomitant co-trimoxazole (ref = no)	1.39 (−1.26, 4.04)	.304	0.82 (−2.07, 3.71)	.578
Total body weight (kg)	−0.05 (−0.10, 0.01)	.093	−0.01 (−0.08, 0.05)	.682

Note: A negative regression beta value (coefficient) indicates a decrease in change in creatinine per unit increase in variable value. Variables included in the multivariable regression: dolutegravir AUC_{0-24h}, age, sex, TDF use, baseline serum creatinine, log_{10} HIV-1 RNA concentration, ln CD4 T-cell count, concomitant co-trimoxazole use and total body weight.
Abbreviations: TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.
[a]*P*-values calculated with Student's *t*-tests.

latter did not withstand correction for multiple testing. These findings help interpret the magnitude of change in renal function at Week 4 in individuals initiating dolutegravir-based ART.

The early increase in serum creatinine in participants after dolutegravir initiation is similar to that observed in other clinical trials.[2,28,29] A phase I, placebo-controlled study that included healthy participants who were treated with 50 mg of dolutegravir given once or twice daily for 2 weeks, found a 10% and 14% decrease in creatinine clearance, respectively, by the end of Week 2.[2] Similarly, a phase IIb dose-ranging study that included treatment-naïve adults with HIV found that dolutegravir 50 mg once daily was associated with a mean increase in serum creatinine of 12.2 $\mu mol.L^{-1}$ after 1 week of therapy that persisted over the course of the trial.[30] 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 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 dolutegravir exposure is associated with increases in serum creatinine is consistent with previous studies.[3] Novel features of our analysis include the relative contribution of TDF to change in serum creatinine compared with TAF, the potential contribution of genetic variability, and that the study involved an African

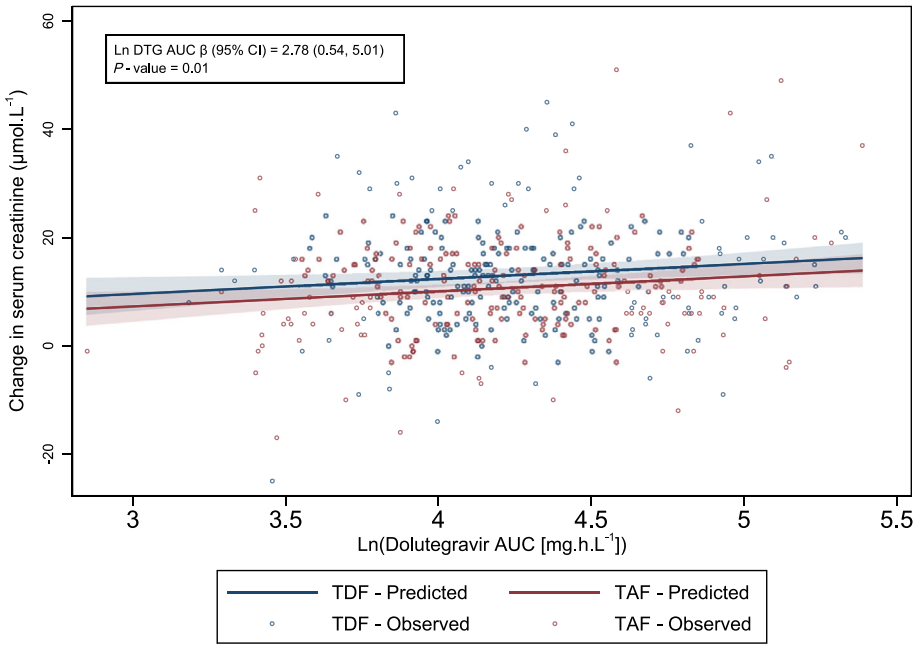

FIGURE 1 Linear relationship between change in serum creatinine and dolutegravir AUC_{0-24h} based on the multivariable linear regression analysis. The scatter plot graph illustrates the predicted values of change in serum creatinine, calculated with estimated marginal means based on a multivariable linear regression model from the pharmacokinetic association analysis. Dolutegravir area under the concentration–time curve (AUC_{0-24h}) values were incrementally increased within the range of observed dolutegravir exposure estimates, while holding constant at their means other variables, namely, age, sex, baseline serum creatinine, tenofovir treatment group (TDF or TAF use), HIV-1 RNA concentration, CD4 T-cell count, total body weight and concomitant co-trimoxazole use. The continuous lines on the scatter plot depict associations between natural log-transformed dolutegravir AUC_{0-24h} values and model-based predictions of change in serum creatinine, while the observed changes in creatinine values are illustrated with circles. The *P*-value, determined with a Student's *t*-test, indicates the statistical significance of the estimated dolutegravir AUC_{0-24h} variable in the multivariable linear regression model described in Table 4.

population. To our knowledge, this is the largest study to date to evaluate PK/PD associations between dolutegravir exposure and early changes in serum creatinine. As dolutegravir is an inhibitor of OCT-2, one of the main renal transporters responsible for creatinine elimination, individuals with factors that increase dolutegravir concentrations are more likely to experience greater changes in serum creatinine. The modest changes observed in this study should not impact clinical care. Rather, they should serve as a reference against which subsequent creatinine measurements can be compared, thus allowing individuals with progressive decline in renal function due to other causes to be identified.

Our finding that TDF was independently associated with an increase in serum creatinine when compared to TAF is in keeping with TAF's improved renal safety profile. Interestingly, this difference occurred early, within the first 4 weeks of treatment. A single arm study of PWH that were switched from a TDF-containing ART regimen to one containing elvitegravir/cobicistat, FTC and TAF, observed increases in creatinine-estimated glomerular filtration rate (eGFR) and reductions in low molecular weight proteinuria in as few as 4 weeks.[31] This observation is not limited to PWH: HIV-negative participants that were on pre-exposure prophylaxis and randomized to receive daily TDF/FTC also experienced a decline in eGFR and increased proteinuria within 4 weeks of treatment initiation compared to those on daily TAF/FTC.[32] There are a few potential explanations for this: These early changes in creatinine may be mediated by further inhibition of creatinine elimination due to tenofovir.[33] 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).[34,35] TDF results in a 10-fold increase in plasma tenofovir exposure compared to TAF, and this may be associated with increased competitive inhibition of renal transporters that normally facilitate creatinine elimination.[36,37] Additionally, tenofovir may have modest potential for mitochondrial toxicity, though data are conflicting.[37–39] As creatinine secretion is facilitated by energy-dependent transporters, a relative increase in mitochondrial toxicity in individuals receiving TDF may contribute towards further alterations in creatinine secretion. Therefore, exposure-dependent inhibition of these transporters by tenofovir may explain the increased serum creatinine during this short period of observation in our study.

We found a possible association between changes in serum creatinine and *UGT1A1* rs929596 A→G polymorphism when dominant allelic effects were assumed. Participants with either an A/G or G/G genotype for this polymorphism were independently associated with a decrease in serum creatinine concentrations compared to those with the A/A genotype. While this was not significant after correcting for multiple testing, it lends support to the concept that *UGT1A1*

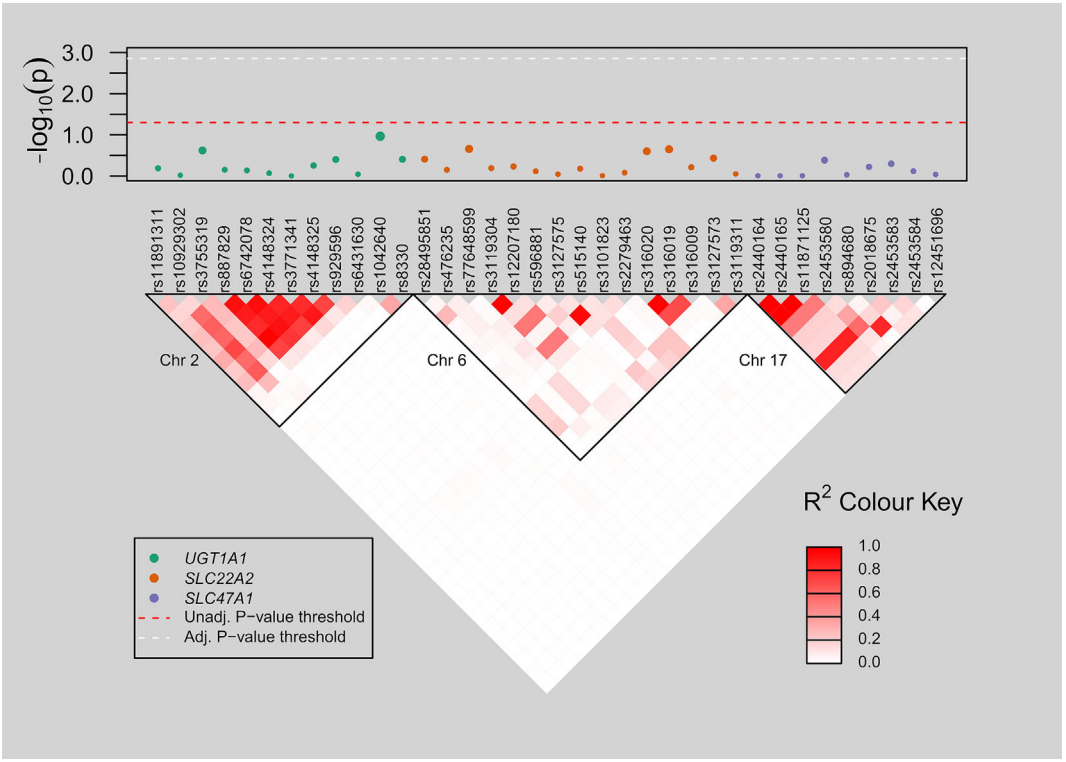

FIGURE 2 Linkage disequilibrium and significance of polymorphism associations within *UGT1A1*, *SLC22A2* and *SLC47A1* from additive regression models of genetic association analyses. The white-red colour gradient in this heatmap illustrates the pairwise linkage disequilibrium (LD) measured by R^2, with red colour intensity indicating higher LD. Statistical significance of polymorphisms in the additive regression models are illustrated in the scatter plot using negative log-transformed *P*-values as determined by Student's *t*-tests. Higher negative log-transformed *P*-values indicate increased probability of statistical significance. The thresholds of significance without (red dashed line) and with (white dashed line) correction for multiple testing by the Bonferroni method are 0.05 and 1.39×10^{-3} respectively. Chr 2 = Chromosome 2; Chr 6 = Chromosome 6; Chr 17 = Chromosome 17.

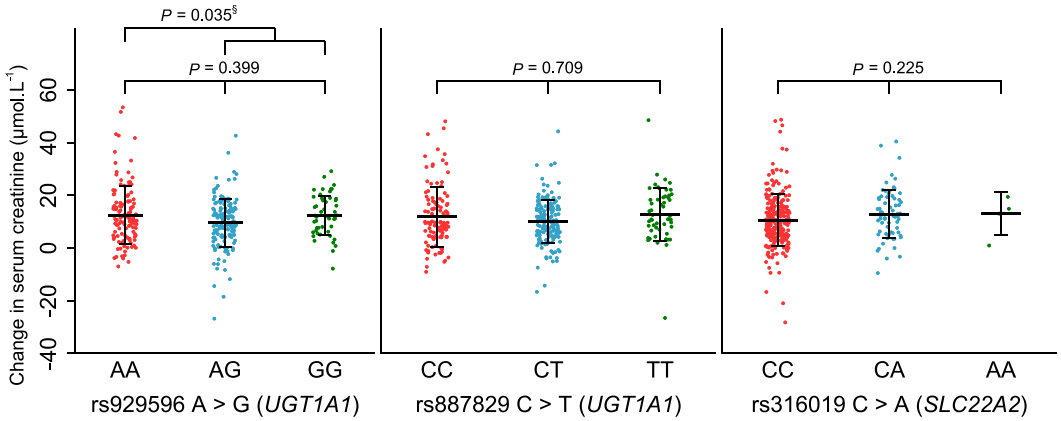

FIGURE 3 Observed change in serum creatinine at Week 4 by rs929596 (*UGT1A1*), rs887829 (*UGT1A1*) and rs316019 (*SLC22A2*) genotypes in participants initiated on dolutegravir-containing antiretroviral therapy. A jitter plot of the observed change in serum creatinine at Week 4 by rs929596 (*UGT1A1*), 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. Error bars are displayed using standard deviation. *P*-values indicate statistical significance of polymorphisms from the additive and dominant§ models and were calculated using Student's *t*-test.

polymorphisms may contribute to the variability in serum creatinine changes because of increased dolutegravir concentrations. This polymorphism has previously been associated with increased total bilirubin concentrations, likely due to reduced glucuronidation activity of variant UGT1A1 enzymes compared to those encoded by the common genotype.[40] A recent genome-wide association study found that

homozygous minor allele carriers of the *UGT1A1* polymorphism rs887829 exhibited a 26% reduction in dolutegravir clearance compared to those homozygous for the major allele.[10] The rs929596 and rs887829 polymorphisms have been mapped to a *UGT1A* cluster located on Chromosome 2 that houses multiple protein-coding, and non-encoding, genes.[40] These polymorphisms were in moderate LD in this population ($R^2 = .75$), which suggests that their effects may not be entirely independent. Our analysis did not find a significant association with the rs887829 polymorphism; however, it is possible that each polymorphism may have independent, additive effects on change in serum creatinine. We also did not find any significant associations between changes in serum creatinine and the genetic variants of *SLC22A2* or *SLC47A1*. Prior studies have reported relationships between *SLC22A2* variants (e.g., rs316019 C→A) and an increased risk for neuropsychiatric adverse effects on dolutegravir, while *SLC47A1* variants have been linked to enhanced metformin responses in patients with diabetes.[15,41] 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.

We identified associations between changes in serum creatinine and four participant characteristics: age, sex, serum creatinine at baseline and CD4 cell count. Regarding age, similar magnitudes of association were noted within all sets of multivariable regression analyses; however, this factor was only significant in the genetic analyses. Older adults experience physiological changes to renal tubular handling of creatinine that may modify the magnitude of dolutegravir's inhibitory effect.[42] Sex-related differences in creatinine clearance are well documented, with males generally demonstrating higher creatinine clearance compared to females.[43,44] HIV-associated nephropathy and opportunistic diseases that can cause renal impairment become more common as the CD4 cell count declines. Previous studies have reported associations between CD4 cell count and improved renal function within the first few weeks of initiating ART.[45]

Our study has limitations. First, this was a secondary data analysis, therefore, we did not perform sample size calculations. As we used a convenience sampling strategy, only some participants had DNA extracted; the sample size may therefore have been inadequate to detect weak genetic associations, or with infrequent variants, and may have been subject to selection bias. Secondly, dolutegravir dosing in the group that underwent sparse pharmacokinetic sampling was not observed, and, therefore, pharmacokinetic modelling of its exposure may have been inaccurate. In addition, the estimation of dolutegravir exposure was based on sparse samples obtained after 4 weeks of treatment, which may not adequately reflect exposure at the 4-week time point. However, it is expected that dolutegravir concentrations would have reached steady state by Week 4, and would remain stable until pharmacokinetic sampling occurred, thus reducing the impact of this limitation on these results. While our study focused on the systemic exposure of dolutegravir and its relationship with changes in serum creatinine, it is important to consider the potential role of dolutegravir metabolites in renal function. Approximately 31% of the total oral dose of dolutegravir is excreted in urine, mostly through either glucuronide or hydroxyl metabolites.[46] We did not measure dolutegravir metabolites and could not investigate their potential effects on change in creatinine. Furthermore, the use of a population pharmacokinetic or physiologically-based PK/PD model that incorporates the disposition of the parent drug and its metabolites, pharmacogenetics and the observed pharmacodynamic changes may have improved the robustness of these findings. This is an area worthy of future study.

Our findings provide clinicians with reassurance regarding the implications of these modest changes in creatinine. It has been suggested that creatinine increases due to dolutegravir are unlikely to exceed 20 μmol.L^{-1} and that greater increases should prompt consideration for alternative causes.[21–23] However, we found that a substantial proportion of participants on TDF and dolutegravir had changes in serum creatinine greater than this. We propose consideration of a higher threshold (e.g., 30 μmol.L^{-1}) based on the sample distribution and addition of 1.96 standard deviations from the mean, to guide the need for closer monitoring and further diagnostic investigations. We also suggest that alternative 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.[47–49]

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. Investigations examining gene–gene and gene–environment interactions may provide additional insight into the risk of clinically relevant changes in creatinine concentrations in the presence of multiple polymorphisms. Although the long-term significance of these early increases in serum creatinine remains uncertain, improved understanding of the underlying mechanisms and predisposing factors may avoid unnecessary changes to otherwise effective ART regimens.

AUTHOR CONTRIBUTIONS

Nomathemba Chandiwana, Simiso Mandisa Sokhela and Willem Daniel Francois Venter were responsible for the overall conduct of the clinical trial that provided data for this analysis. Godspower Akpomiemie was involved in the curation and management of the original clinical trial data. Rephaim Mpofu was responsible for conceptualization, data curation and management specific to this study, data analysis, presentation and interpretation of results and manuscript development. Phumla Sinxadi and Gary Maartens were responsible for conceptualization, data analysis and interpretation and manuscript development stages. David W. Haas and Frank A. Post provided input during study design, analysis and manuscript development and editing stages. Lubbe Wiesner supervised the dolutegravir concentration assay procedures, and Aida N. Kawuma, Roeland E. Wasmann and Paolo Denti performed the pharmacokinetic modelling. All authors reviewed the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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 devices for multiple biotech companies. Individually, W.D.F.V. receives honoraria for talks and advisory board membership for Gilead, ViiV, Mylan, Merck, Adcock-Ingram, Aspen, Abbott, Roche, J&J and Virology Education. S.S. and N.C. report grant support from ViiV Healthcare and Gilead Sciences during the conduct of the study. F.A.P. has received honoraria from ViiV Healthcare, Gilead Sciences and Merck, and research grants from ViiV Healthcare and Gilead Sciences. For the remaining authors, no conflicts of interest were declared.

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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SUPPORTING INFORMATION

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