The effects of dolutegravir on creatinine clearance in children and adolescents living with HIV: a retrospective cohort study in Johannesburg

Student: Dr. Chiara Sewnarain

Student number: 445977

Student email: chiarasewnarain@gmail.com

Degree: Master of Medicine in paediatrics (MMed)

Supervisor: Assoc. Prof. Karl-Gunter Technau

Supervisor email: karl-gunter.technau@wits.ac.za

Table of contents:

Declaration:

I, Dr Chiara Sewnarain, student number 445977 do hereby declare that I am aware that plagiarism (the use of someone else's work without their permission and or without acknowledging the original source, is wrong. without acknowledging the original source) is wrong. I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise. I have followed the required conventions in referencing the thoughts and ideas of others. I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Dr Chiara Sewnarain

Dedication:

This MMed is dedicated from the bottom of my heart to all the children I have the privilege of interacting with on a daily basis. I am grateful for my loving mom and sister for their constant support, encouragement and love.

Acknowledgments:

I appreciate my supervisor and co-author Prof. Technau for his unwavering dedication to this project.

List of figures:

List of tables:

The effects of dolutegravir on creatinine clearance in children and adolescents living with HIV: a retrospective cohort study in Johannesburg

Chiara Sewnarain [1], Karl - Gunter Technau [2]

1. Department of Paediatrics and Child Health, Rahima Moosa Mother and Child Hospital, Faculty of Health Sciences, University of Witwatersrand, South Africa
2. Empilweni Services and Research Unit, Department of Paediatrics and Child Health, Rahima Moosa Mother and Child Hospital, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, South Africa

Corresponding author:

Chiara Sewnarain

Corner Fuel & Oudtshoorn St, Johannesburg, Gauteng 2093

Email: chiarasewnarain@gmail.com

Cell phone number: 072 640 6104

Keywords: Dolutegravir, renal functioning, children, adolescent

Word count: Abstract: 263/250 Main text: 3394/5000

Abstract:

Background: Dolutegravir (DTG) can result in serum creatinine (SC) elevation that should be less than 15% from the baseline and remain stable after initial rise. We wanted to explore whether DTG's effects on SC were similar in our patients.

Objectives: We investigated the effect of DTG on renal function and if there were any adverse renal effects when paired with tenofovir (TDF).

Methods: Adolescents on anti-retroviral treatment were divided into the number of patients on TDF only, those that had started TDF prior to DTG, and the number of patients started on DTG prior to or concurrent with TDF. SC values were compared to reference ranges and glomerular filtration rate (GFR) was calculated using either the modification of diet in renal disease (MDRD) formula or the Counahan Barratt formula. The renal functioning for these patients was then separated into those that had significant renal dysfunction (GFR<80 in under 16-year-olds and <50 in over 16-year-olds).

Results: The percentage change of SC between start of TDF and 12 months on TDF was > 15% in 50% cases. By 24 months of TDF 70% patients had >15% rise in SC, more so in the DTG concurrent group ($p<0.0001$). SC was above reference range in 4% at 12 months and 5% at 24 months while GFR was below recommended cut off in 3% at 12 and 24 months more so in adolescents also on DTG.

Conclusion: Our study showed that most of our patients had significant increases in SC, but few had significant renal dysfunction (low GFR), of note, many children had an increased GFR (glomerular hyperfiltration).

What this study adds:

Our study gives a detailed picture of SC monitoring and GFR calculations in our local population and highlights that the current guidelines do not give enough guidance and may need slight modification to prevent unnecessary drug switches but also encourage adequate monitoring. Our study shows that the increase in SC is generally greater than 15% in adolescence. Although renal functioning does not seem to be affected, this study does show that there may be a tendency for greater effects in males and individuals who switch to TDF earlier in life. As glomerular hyperfiltration predicts future renal dysfunction; it is important to note that our study displayed this.

Introduction:

South Africa has the largest anti-retroviral therapy (ART) programme in the world for the treatment and prevention of HIV. Providing early detection of the disease as well as early initiation of therapy and easy access to health care are the pillars for ensuring decreased morbidity and mortality. Combination therapy using different classes of drugs that act at different stages of the HIV life cycle ensures reduced resistance as well as rapid viral suppression. (1) The latest ART guidelines released in 2023 in South Africa have included dolutegravir, (DTG) an integrase strand transfer inhibitor (INSTI), as part of the first line

treatment for adults, adolescents, and children. This is available with tenofovir (TDF) and lamivudine (3TC) as a fixed dose combination (TLD) for children and adolescents ten years and older weighing more than 30kg. (1) For children who are under ten years old or weigh less than 30kg, abacavir, (ABC) lamivudine (3TC) and DTG is the recommended first line combination. It is important to note that guidelines have changed in terms of weight cut-offs for TDF; from >40kg in the 2015 guidelines, to >35kg in the 2019 guidelines (2) and >30kg in the 2023 guidelines; the reason for this seems to be earlier harmonization with adult guidelines; but special attention needs to be paid to whether exposing children and adolescents to a longer period of TDF is the best decision for renal functioning.

DTG has been shown to be well tolerated; available in a small tablet, with superior efficacy, demonstrating anti-HIV activity by inhibiting the enzyme responsible for incorporation of viral DNA into the host genome. It causes rapid viral suppression, has a high genetic barrier to resistance and mild side effects. (2) Known side effects that have been demonstrated include weight gain, insomnia, dizziness, and a mild, transient increase in serum creatinine. (1)

The renal effects of DTG have been studied in adults, but data is scarce in the paediatric population, and especially in the paediatric African population. As renal functioning can be compromised by HIV itself, concomitant diseases and drugs like TDF, it is important to know how DTG effects renal functioning when making the decision to switch regimens and place patients on this drug lifelong. Current guidelines suggest that DTG causes a non-progressive rise in SC (<15%) that stabilises over time without affecting the glomerular filtration rate (GFR). (1) However, a rising SC is considered a cause for concern. The monitoring of creatinine is already part of the management in children and adolescents

currently on TDF; however, with the addition of DTG to most fixed dose combinations, this could complicate this assessment. Due to anecdotal concerns and reports that the SC rise is >15%, and the concern about potentially unnecessary treatment switches, we wanted to assess patterns of SC and GFR change in our patients starting DTG; especially if paired with TDF. We assessed whether observed changes are adequately addressed in the guidelines. Of note, the guidelines do not mention the impact of glomerular hyperfiltration and as this is a predictor of future renal dysfunction, we think it is very important to possibly include this in future guidelines.

Research methods and design:

We conducted a retrospective longitudinal cohort study to describe the population of adolescents between the ages of 10 - 19 years who were treated with TDF with and without DTG and assessed the SC and GFR in these patients. The participants were all patients at Empilweni Services and Research unit (ESRU) clinic located within Rahima Moosa Mother and Child Hospital (RMMCH). ESRU is one of the larger paediatric HIV clinics in South Africa, with over 1400 children in active care. The clinic manages neonates, children and adolescents living with HIV, as well as neonates that are exposed but uninfected, daily. Management includes initiation of treatment-naïve patients on to first line ART, regular follow up appointments and those requiring 2nd or 3rd line treatment. At each follow up, BP and urine dipstick was measured by the nursing staff and recorded in the patient's file. The heights of patients were measured by stadiometer and recorded in cm. SC was done at 3 months after the commencement of treatment, followed by a 12-month creatinine and annually thereafter. All laboratory tests were processed at the National Health Laboratory

Services (NHLS) and SC reported in uMol/L. On average, each patient attended the clinic four times every year. All results were recorded in a flow sheet found in each patient's file.

All children/adolescents >10 years of age and </= 18 years of age initiated on or switched to a TDF-containing regimen, with or without DTG at RMMCH from January 2015 to November 2022 were included. We included all adolescents who had SC measurements done due to routine clinical guideline requirements (initiation of TDF) and we described the SC and GFR progression over time. According to the South African National ART guidelines estimated GFR (in mL/min/1.73m2) is calculated by the MDRD (modification of diet in renal disease) formula for adolescents older than 16 (https://www.kidney.org/mdrd-study-equation) where a value <50 is considered abnormal, and the GFR according to the Counahan Barratt formula for those aged 10-16 years (patient's height in cm multiplied by a constant (40) divided by the SC) where a value of <80 is considered abnormal. We also recorded adolescents who had SC levels above the reference ranges according to the NHLS. We described changes overall (related to anthropometric growth) and related to timing of switch to TDF and/or DTG and any associations of GFR changes >15% or above normal range SC with ART start characteristics and specific regimen switches. We subdivided our population into the number of patients on TDF only (TDF-only), those that had started TDF prior to DTG, (TDF-prior) and patients started on DTG prior to or concurrent with TDF (DTG-concurrent).

We used standard descriptive statistical methods. Continuous variables were analysed using median and interquartile range. Percentages and frequencies were used to describe categorical variables. De-identified data was analyzed using SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA). Fischer's exact and Chi square tests were used to compare groups of

categorical data while Wilcoxon and Student t-test were applied to continuous variables. Group based outcomes were created i.e. TDF-only, TDF-prior and DTG-concurrent.. Baseline (at the time of DTG switch) variables included sex, age, weight, regimen pre-switch, prior ART exposure, time on ART, CD4 count, CD4 percentage and VL at the time of switch. Creatinine and GFR were described at baseline (relative to TDF switch), 3 months (window 0.5-6 months), 12 months (window 6-16 months), and 24 months (16-30 months). A Cox proportional hazards model was constructed using the outcome of a GFR below the recommended cutoff for age.

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee. (ref: M230248) All data was kept in a password protected de-identified spreadsheet. Only the researcher and supervisor had access to this spreadsheet. The cohort is prospectively captured under the protocol, Cohort Study of HIV-infected and exposed Children receiving care at Rahima Moosa Mother and Child Hospital was supported by the Empilweni Services and Research Unit and participation in the International epidemiological Databases to Evaluate AIDS (IeDEA) Collaboration (M170778 – M220559). Data are routinely collected from patient hospital records and entered into the database. The database is hosted on the University of the Witwatersrand REDCAP platform. (19) Children or adolescents being cared for at RMMCH who refused or whose parents refused consent for the use of routine data for research purposes were excluded from the study.

Results:

A total number of 1747 patients were seen at the Empilweni clinic between 01 January 2015 and 30 November 2022. After exclusions (Figure 1) our total study population of 1179 was

divided into three groups; those on TDF only (n=232), those started on DTG after TDF therapy (n=476) and those on DTG prior to or concurrent with TDF therapy (n=471). Table 1 shows the characteristics of the total population of these three groups. We found that the age at ART start as well as the years of birth declined across these groups, showing that these groups represent three distinct periods in terms of TDF and DTG exposure. The groups also had different starting regimens with most of the TDF-only group starting on NNRTI based regimens and the majority of the DTG-concurrent group having started on PI based treatment. Anthropometry at ART start showed that the three groups had similarly low levels of height-for-age with medians close to -2. There was a rise in the nadir CD4 measurement across the three groups. There were greater levels of underweight for age in the younger population.

There was a total of 5812 creatinine tests included for which 5546 (95%) GFR values could be calculated by the CB formula and all of which had a calculated MDRD GFR value. Out of 3429 creatinine values done in adolescents or children under 16, 3241 (95%) had an associated GFR value calculated according to the CB formula, while all of the 2383 creatinine values done in adolescents older than 16 had an associated GFR value according to the MDRD formula. Amongst the 1179 patients there was a median of 5 (IQR: 3-6) creatinine values per person included and the age at creatinine test was a median of 15 years (IQR: 14-17). The upper limit of normal was available for 5764 (99%) of cases and the SC value was above the normal limit in 291 (5%) of cases.

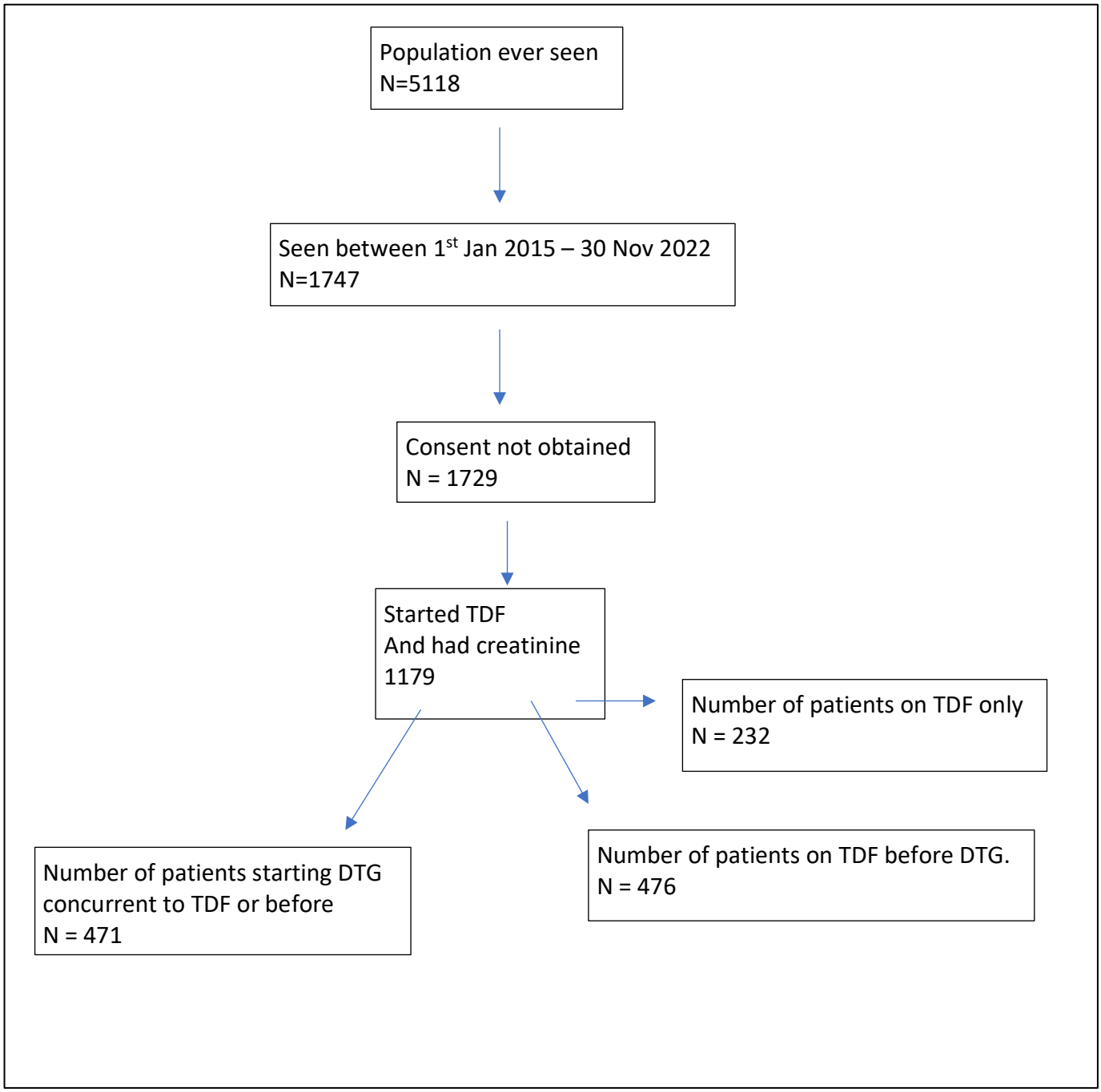


Figure 1: Study population with inclusion and exclusion criteria. TDF: Tenofovir; DTG: Dolutegravir; N: number

Table 1: Baseline characteristics of the population stratified by ART baseline regimens.

	TOTAL:	TDF-only	TDF-prior	DTG-concurrent	P value
	1179	232	476	471	
Gender female, N (%)	609 (51)	141 (59)	246 (52)	222 (46)	0.0085
Median Age at first visit in years (IQR)	4.6 (1.8-7.7)	6.8 (4.0-10.1)	5.0 (2.0-7.6)	3.0 (0.8-6.0)	<0.0001
Year of birth (IQR)	2005 (2002-2007)	2000 (1999-2002)	2004 (2002 - 2005)	2007 (2006-2009)	<0.0001
Age at ART start (IQR)	4.0 (1.1-7.6)	7.4 (5.3-9.8)	4.0 (1.6-7.3)	1.6 (0.5-4.8)	<0.0001
Time on ART (years) (IQR)	13.1 (10.4-15.3)	11.2 (8.8-13.3)	14.3 (11.6-16.3)	12.9 (9.9-14.4)	<0.0001
First regimen: N(%)					
INSTI based	13 (1.1)	0 (0)	0 (0)	13 (1.1)	<0.0001
NNRTI based	665 (58.0)	20 (17.4)	305(26.6)	160 (14.0)	PI and NNRTI only <0.0001
PI based	456 (40.0)	21 (1.8)	166 (14.5)	269 (23.5)	
Other	13 (1.1)	6 (0.5)	2 (0.2)	5 (0.4)	
Lowest CD4 (IQR)	413 (205-597)	219 (69-410)	416 (245-568)	490 (285-684)	<0.0001
Highest viral load (log)	4.9 (3.7-5.7)	5.2 (4.5-5.7)	4.7 (3.5-5.6)	5.0 (3.6-5.9)	0.0010
Anthropometry at ART start: (IQR)					
Height Z score	-1.8 (-2.7 --0.8)	-1.9 (-2.6 - -1)	-1.8 (-2.6 - -0.7)	-1.8 (-3.0 - -0.8)	0.44
Weight Z score	-0.6 (-2.0-0.5)	0.0 (-1.8 – 0.8)	-0.3 (-1.5 – 0.7)	-0.9 (-2.6 - -0.3)	0.0006
BMI Z score	-0.5 (-1.8-0.4)	-0.6 (-1.7 – 0.4)	-0.3 (-1.5 – 0.5)	-0.8 (-2.3 – 0.2)	0.0010
Year of last visit (IQR)	2022(2022-2022)	2019 (2017-2021)	2022 (2022 – 2022)	2022 (2022 – 2022)	<0.0001
Current age in 2022 (IQR)	18 (16-20)	19 (18-20)	19 (18-20)	15 (14-17)	<0.0001
ART exposure: (IQR)					
D4T	4.7 (3.1-6.7)	4.3 (2.5 – 6.1)	4.8 (3.5 – 7.0)	4.7 (2.9 – 6.6)	0.035
AZT	3.7 (1.9-5.9)	3.9 (1.9 – 5.9)	3.2 (1.2 – 4.8)	4.3 (2.1 – 6.1)	0.078

ABC	6.1 (3.8-8.5)	5.0 (3.0 – 6.9)	6.3 (3.8 – 8.3)	6.6 (4.3 – 9.5)	<0.0001
EFV	6.2 (3.8-9.9)	6.8 (4.0 – 10.6)	8.2 (4.8 – 11.1)	5.1 (3.1 – 7.9)	<0.0001
PI	6.6 (3.8-9.5)	4.9 (2.3 – 8.8)	7.0 (3.8 – 9.7)	7.0 (4.4 – 9.6)	0.0012
Year started TDF (IQR)	2019 (2018-2020)	2016 (2015-2018)	2019 (2018-2019)	2021 (2020-2021)	<0.0001
Age started TDF(IQR)	14.7 (13 – 15.8)	16.2 (15.3 – 17.4)	14.9 (13.7 – 15.4)	13.3 (12 – 14.8)	<0.0001
Year started DTG (IQR)	2020 (2020 – 2021)	-	2020 (2020 – 2020)	2020 (2020 – 2021)	0.0016
Age started DTG	14.7 (12.5 – 17.1)	-	16.6 (14.8 – 18.3)	12.8 (11.4 – 14.7)	<0.0001

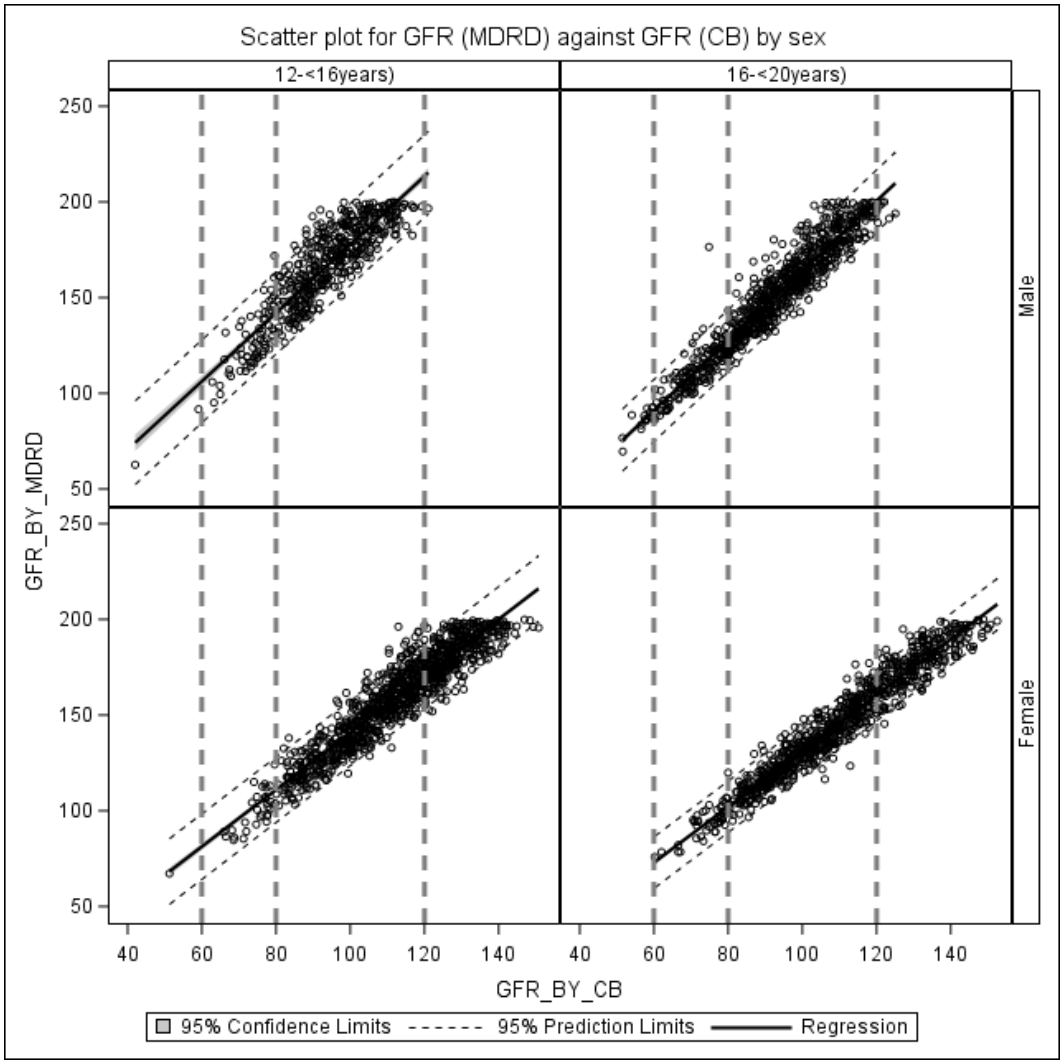
BMI: Body mass index; ART: Antiretroviral disease; D4T: Stavudine; AZT: Zidovudine; EFV: Efavirenz; N: number; IQR: interquartile range; INSTI: integrase strand transfer inhibitor; NNRTI: non-nucleoside reverse transcriptor inhibitor; PI: protease inhibitor

Table 2 shows the dynamics of creatinine and GFR changes in the population stratified by the three groups of DTG exposure in relation to TDF commencement. SC levels above laboratory cutoff remained relatively constant at a rate of 5% at 3-, 12- and 24-months post TDF initiation. Similarly, the proportion of patients with a GFR level beyond the recommended cutoff for age (<80 in <16 years and <50 above 16 years) remained 3%. SC above lab cutoff was consistently more common in the DTG-concurrent group. GFR level below recommended cutoff was more common in the DTG-concurrent group at 3, 12 months but not 24 months post DTG start.

Over the first 24 months of TDF exposure the prevalence of a GFR less than the recommended cutoff increased from 0.2% at baseline to 1.8% at three months, 2.3% at 12 months and 2.9% at 24 months. Over the first 24 months of DTG exposure the prevalence of a GFR below the recommended cutoff increased from 0.2% (1/605) at baseline to 2.9% (15/496) at 3 months, 3.3% (22/664) at 12 months and 3.3% (18/551) at 24 months. The percentage change of SC between start of TDF and 12 months on TDF was > 15% in 50%

cases, more commonly in the DTG-concurrent or TDF-prior group as opposed to the TDF-only group. By 24 months of TDF 70% patients had a >15% rise in SC, again more so in the DTG-concurrent group. Of 208 patients not exposed to DTG, 3 of 36 (8%) under 15 years old, developed a low GFR compared to 1 of 172 (0.6%) older than 15 years (p=0.017, Fisher exact test).

Supplemental Figure 1 displays the relationship between the GFR by CB vs the GFR by the MDRD formula by age groups and sex. It shows distinct patterns for male and female with little variation by age group (<16 vs ≥ 16 years). GFR by MDRD was lower than CB by 62 mL/min/1.73m2 (IQR: 44-92) and the difference was significantly greater in males than females (86 vs 48; p<0.0001) and in adolescents younger than 16 than those 16 and older (72 vs 50; p<0.0001).



Supplemental Figure 1: MDRD GFR against CB GFR by sex. GFR_BY_MDRD: glomerular filtration rate by Modification of Diet in Renal Disease; GFR_BY_CB: glomerular filtration rate by Counahan Barratt

Table 2: Description of creatinine and GFR changes over 24 months relative the start of TDF

	TOTAL:	TDF only	DTG after TDF	DTG concurrent / before TDF
nine and GFR	1179	232	476	471
Creatinine available N (%)	983 (83)	193 (83.2)	411 (86.3)	379 (80.5)
Median Creatinine (IQR)	48 (42-56)	50 (43-58)	47 (41-55)	48 (42-56)
GFR available N (%)	952 (80.8)	188 (81.0)	392 (82.4)	372 (78.9)
Median GFR (IQR)	135 (117-156)	147 (124-189)	137 (121-155)	126 (110-145)
Creatinine high N (%)	17 (1.7)	0	2 (0.5)	15 (3.9)
GFR < recommended cut-off	2 (0.2)	0	0	2 (0.5)
nine and GFR				
Creatinine available	839 (71.2)	160 (69.0)	381 (80.0)	298 (63.3)
Median Creatinine (IQR)	53 (46-61)	52 (45-62)	51 (45-56)	55 (49-65)
GFR available	821 (69.6)	155 (66.8)	374 (78.6)	292 (62.0)
Median GFR	127 (110-155)	159 (126-193)	131 (117-157)	112 (99-131)
Creatinine high	39 (4.7)	2 (1.3)	5 (1.3)	32 (10.7)
GFR < recommended cut-off	15 (1.8)	2 (1.3)	2 (0.5)	11 (3.8)
ne increased by >15% compared to baseline	262 (37.6)	46 (35.1)	96 (28.8)	120 (51.5)
ced by >15% compared to baseline	299 (45.1)	59 (48)	110 (35)	130 (58)
tinine and GFR				
Creatinine available	824 (69.9)	146 (62.9)	374 (78.6)	304 (64.5)
Median Creatinine (IQR)	55 (49-63)	53 (46-62)	55 (49-62)	58 (50-68)
GFR available	811 (68.8)	143 (61.6)	370 (77.7)	298 (63.2)
Median GFR (IQR)	129 (107-164)	168 (130-199)	132 (112-170)	113 (98-132)
Creatinine high	37 (4.5)	0	7 (1.9)	30 (9.9)
GFR< recommended cutoff	19 (2.3)	0 (0)	2 (0.5)	17 (5.7)
sed by >15% compared to baseline	345 (49.9)	36 (30.0)	167 (49.6)	142 (60.8)
>15% compared to baseline	356 (54.7)	63 (55.7)	166 (52.5)	127 (57.2)
tinine and GFR				
Creatinine available	692 (58.7)	101 (43.5)	421 (88.4)	170 (36.1)

Median Creatinine (IQR)	62 (53-71)	55 (48-65)	64 (55-74)	62 (51-70)
GFR available	689 (58.4)	101 (43.5)	419 (88.0)	169 (35.9)
Median GFR (IQR)	131 (107-160)	164 (139-192)	132 (109-158)	112 (97-130)
GFR< recommended cutoff	20	2 (2.0)	9 (2.2)	9 (5.3)
Creatinine high	35 (5.1)	1 (1.0)	15 (3.6)	19 (11.2)
Creatinine >by 15%	411 (71)	33 (39.8)	282 (77.5)	96 (71.1)
ced by >15% compared to baseline	361(64.7)	55(67.9)	224 (64.7)	82 (62.6)

All values are given as N (%) unless otherwise indicated GFR: Glomerular filtration rate; N: number; IQR: interquartile range. Denominators are calculated from the totals shown in the first row.

The group with a GFR < recommended cutoff at 24 months of TDF was significantly more likely to be male, slightly younger at start of TDF with no difference in height z-score at the time (Table 3). None of the adolescents with GFR below recommended cut-off at 24 months had a GFR <50 and none had undergone a drug switch away from TDF or DTG. In 9 of the 20 adolescents the SC was above reference range but never >100. 4 of 14 with a value at 12 months had a GFR less than recommended cut-off at 12 months and 2 of 14 at 3 months post TDF switch. There were no differences in systolic blood pressure at 24 months between those with GFR below cut-off compared to normal GFR (median 115 mmHg [IQR 107-123]) and diastolic pressures were slightly lower in those with lower GFR who had median diastolic pressures of 61mmHg (IQR:53-72) compared to 68 (61-75) in those with normal GFR (0.044).

Table 3: Clinical outcomes of patients (n=689) stratified by GFR level according to age cutoff at 24 months after starting TDF

	Total	GRF < cutoff	GFR >
Total	689	20 (3)	669 (97
Sex female	362 (53)	5 (25)	357 (53

Age at ART start (IQR)	4 (1-8)	4 (1-7)	4 (1-8)
Age at TDF start (IQR)	15 (13-16)	13 (13-14)	15 (13-
TDF/DTG group	689		
TDF only	101 (15)	2 (10)	99 (15)
DTG only after	419 (61)	9 (45)	410 (61
DTG concurrent or before TDF	169 (35)	9 (45)	160 (24
Height Z-Score at 24 months (IQR)	-0.9 (-1.4;-0.3)	-0.7 (-1.3;-0.3)	-0.9 (-1
VL at 24 months	633		
0-<50 copies/ml	496 (78)	12 (75)	484 (78
50-<1000 copies/ml	89 (14)	3 (19)	86 (14)
>=1000 copies/ml	48 (8)	1 (6)	47 (8)

ART: Antiretroviral; IQR: Interquartile range; TDF: Tenofovir; DTG: Dolutegravir; VL: Viral load; ART: antiretroviral

Finally, we examined cox proportional hazards model of the associations with a GFR going below the recommended cutoff (Table 4). Of a total of 1084 patients with at least one SC value, 79 (7%) had an outcome of a GFR below the recommended cutoff at any time after TDF start which occurred at a median time on TDF of 12 months (IQR: 5-20). The model shows that the female sex was protective with a hazard ratio (HR) of 0.4 (95% Confidence Interval [CI] 0.2-0.6) and that the age of TDF commencement was very important with TDF start before 15 years associated with a HR of 7.9 (CI: 3.7-16.8). Exposure to DTG at the time of the event was associated with an increased risk: HR 3.0 (CI: 1.3-7.3) in the unadjusted model but this effect fell away in the adjusted model.

Table 4: Cox proportional hazards model for the outcome of GFR below recommended range (n/N=79/1084)

Variable	Outcome n/N (%)	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
DTG Exposure at time of event					
Yes	73/834 (9)	3.2 (1.4-7.3)	0.0067	1.5 (0.6-3.6)	0.38
No	6/250 (2)	Ref			
Sex					
Female	26/559 (5)	0.4 (0.3-0.7)	0.0007	0.4 (0.2-0.6)	0.0008
Male	53/525 (10)	Ref			
Nadir CD4					
<500	41/712 (6)	0.5 (0.3-0.8)	0.0046	0.7 (0.4-1.1)	0.13
≥500	36/363 (10)	Ref			
Missing	2/9 (22)	2.4 (0.6-10.2)	0.22	2.5 (0.6-11.3)	0.23
VL at event					
0-<50	55/805 (7)	1.4 (0.6-3.6)	0.43	0.9 (0.3-2.5)	0.89
50-<1000	19/162 (12)	2.8 (1.0-7.5)	0.040	2.4 (0.9-6.8)	0.09
≥1000	5/117 (4)	Ref			

Age at TDF					
<15 years	71/595 (12)	8.1 (3.9-16.8)	<0.0001	7.9 (3.7-16.8)	<0.0001
≥15 years	8/489 (2)	Ref		Ref	

N: number; CI: confidence interval; DTG: Dolutegravir; VL: viral load; TDF: Tenofovir; Ref: reference

Discussion:

Our study showed that there has been a great change in exposure to TDF and DTG over time; and this is due to changing guidelines with the introduction of DTG at different phases of life and different weight categories. TDF is known to cause renal impairment and is part of most of our fixed dose combination ART. (2, 3, 5, 23) Our study showed that patients experienced changes in both SC and GFR; these changes were significant from baseline but in general, it was less common to see an above normal range SC or a GFR that was below the recommended range. Our study showed that the changes observed were more pronounced in patients starting DTG with a relatively lower SC and higher GFR; after 2 years of exposure to DTG; these patients had a higher SC, and a lower GFR. In our study, we found that the percentage change of GFR between start of TDF and 12 months on TDF was > 15%. By 24 months of TDF, 66% of patients had a >15% drop in GFR. Male sex and earlier age of starting TDF were significantly associated with having a GFR below recommended range.

Our findings are in keeping with what the current guidelines state: there is indeed an increased SC in patients on DTG but even in those only on TDF. The percentage increase of SC is usually much greater than 15% and this cut-off stated in the guidelines may not be that useful. There was a very minor difference in diastolic but not systolic blood pressure at 24 months, but this was not clinically significant. The guidelines provide two different methods of calculating GFR, the MDRD and the CB method; after seeing the results from our study, we conclude that using different formulas around the age cut off of 16 years might be unnecessary. The relative difference between values obtained from the CB formula (generally lower values) compared to the MDRD formula may mean that adolescents <16 years of age may be unnecessarily classified as having low GFR (<80) which then resolves as they move to >16 years and the MDRD formula is used. We recommend adding GFR as well as SC

increases as side effects for DTG; as SC is a marker for renal function and not kidney injury and the current guidelines do not mention any increases or decreases in GFR which may be helpful. (17)

Our study showed that there seems to be a predominance of males and those with earlier switch to TDF with higher SC and GFR readings irrespective of DTG exposure; the reason for this is unknown and more research is required to assess the significance of this. The age at TDF start seems to play an important role; this is hard to distinguish from the role of DTG but potentially requires further research. The consolidated 2015 South African guidelines recommended that TDF only be commenced from the age of 15 years and weight of 40kg onwards. (2) The current guidelines recommend TDF use from 10 years and 30kg onwards. While this makes application easier, it is important to ensure that earlier TDF commencement does not cause harm (24).

According to the guidelines, there should be a regimen change if the SC >15%; we did not note any regimen changes in our patients despite levels of changes in SC being >15%. This suggests a real dilemma between what the guidelines say especially when clinically, we did not see any evidence of harm. Pill burden increases with a regimen switch away from TDF as well as DTG, so this is also something to consider in the guidelines.

Early investigations of DTG in the SPRING-1, SPRING-2 and the VIKING trials showed that patients had a mild, non-progressive increase in serum creatinine after one week of initiation and remained stable thereafter. (3, 5). These trials found that GFR does not appear to be affected by DTG, and this initial rise of SC is likely due to inhibition of the renal organic cation transporter 2 (OCT2) activity, leading to reduced secretion of creatinine.

The SPRING-1 trial compared raltegravir (RAL) with DTG, no renal associated withdrawals were recorded for either of these drugs. The use of DTG over 48 weeks does not appear to affect renal functioning, although the long-term effects of this drug on renal functioning are still to be determined. (4,5,6) As we can see; our study found a large disparity in comparison with these early trials.

DTG's effects were also studied in another trial that looked at actual GFR, creatine clearance and renal plasma flow. The participants of this trial took DTG 50mg daily or bidaily and some received a placebo for 14 days together with infusions containing iohexol and para-aminohippurate (PAH) on days 1-7 and day 14. Iohexol is a freely filtered (not secreted) solute that measures GFR. PAH is a maker of effective renal plasma flow. Both showed no effects of DTG on their clearance. (14) This is again in contrary to our study which showed a significant increase in GFR.

The strengths of the study are numerous; we included a large sample size as well as a long study period spanning over 8 years. Our study also had high quality data that had been recorded electronically. Our study had significant weaknesses; the study was conducted at a non-research site and as a consequence of this, data was missing. Not all adolescents had values for some of our variables. This could be secondary to poor capture or non-compliance in scheduled visits.

There are few markers of renal dysfunction – BP was available but did not show significant differences and a detailed analysis of blood pressure distribution was beyond the scope of this study. Urine dipstix was not as useful and not consistently captured. There are few other

ways of distinguishing whether diminished GFR is due to damage to the renal system or due to elevation of SC because of the displacement caused by DTG.

Conclusion:

Our findings show that contrary to the guidelines, the rise in SC is often >15%, but is less commonly associated with GFR below cutoff and SC above reference ranges. The use of two different formulae may be confusing for clinicians and a streamlined approach may be needed. Further consultation may be needed to adjust the guidelines.

DTG has many benefits and its introduction to ART regimens has no doubt caused rapid viral suppression and shown excellent tolerance. It is imperative to monitor any adverse effects of ART; especially since ART is lifelong and childhood and adolescent exposure to ART is a prolonged period. Careful attention to renal function is needed especially because guidelines have moved towards earlier initiation of TDF and DTG. Monitoring of these renal side effects needs to be ongoing, and clinicians need to be aware of the different methods of monitoring renal functioning in children and what norms to compare these to; especially in relation to drugs such as DTG. Our study was an interesting one to perform as ART use is widespread and integral at prolonging longevity with children and adolescents living with HIV. We often prescribe drugs with known side effects and although routine monitoring of these side effects is happening – is it suggestive of what our guidelines are saying and in keeping with what we are teaching clinicians to be aware of?

Acknowledgements:

We acknowledge the families and adolescents who are part of the clinic and provided their data. We appreciate the assistance of the data collection team on site including nursing staff and data capturers. We gratefully acknowledge the National and Gauteng Provincial Department of Health for funding of HIV treatment and investigations. The study was supported in part by the National Institutes of Health through the International epidemiology Databases to Evaluate AIDS (IeDEA) (grant number 5U01-AI069924-05).

Competing interests: None

Author contributions: CS was involved in all phases of the study and drafted the manuscript, KT assisted with data collection, data analysis and revision of the manuscript. All the author's approved the final version of the paper.

Funding: None

Disclaimer: All views expressed in this article are our own and not an official position of the institution.

References:

1. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd ed [Online]. Who.int. 2023 [cited 01 January 2025].
2. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd ed [Online]. Who.int. 2019 [cited 30April 2024].
3. Gutiérrez F, Fulladosa X, Barril G, Domingo P. Renal tubular transporter-mediated interactions of HIV drugs: Implications for patient management.: Semantic scholar [Internet]. undefined. 1970 [cited 13 March 2022]. Available from: https://www.semanticscholar.org/paper/Renal-tubular-transporter-mediated-interactions-of-Guti%C3%A9rrez-Fulladosa/48ca933fedab4bea28be480b30de3b330c1edb5b
4. Reese MJ, Savina PM, Generaux GT, Tracey H, Humphreys JE, Kanaoka E, Webster LO, Harmon KA, Clarke JD, Polli JW. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor [Internet]. Drug metabolism and disposition: the biological fate of chemicals. U.S. National Library of Medicine; [cited 14 March 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/23132334/
5. van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, Rockstroh JK, Almond S, Song I, Brothers C, Min S. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: Planned interim 48-week results from spring-1, a dose-ranging, randomised, phase

2b trial [Internet]. The Lancet. Infectious diseases. U.S. National Library of Medicine; [cited 13 March 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/22018760/

6. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, Bloch M, Podzamczer D, Pokrovsky V, Pulido F, Almond S, Margolis D, Brennan C, Min S. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48-week results from the randomised, double-blind, non-inferiority spring-2 study [Internet]. Lancet (London, England). U.S. National Library of Medicine; [cited 12 March 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/23306000/
7. What are HIV and AIDS? [Internet]. HIV.gov. [cited 13 March 2022]. Available from: https://www.hiv.gov/hiv-basics/overview/about-hiv-and-aids/what-are-hiv-and-aids
8. Global health observatory (GHO) Data. World Health Organization. [Online] 2020 [cited 13 March 2022]. Available from: https://www.who.int/data/gho
9. Guidelines for the use of Antiretroviral Agents in adults and Adolescents with HIV. AIDSinfo. [Online] Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/37/whats-new-in-the-guidelines- [Accessed 05 April 2022]
10. Fletcher C. Overview of antiretroviral agents used to treat HIV. UpToDate. [Online] 2020. [Accessed 14 March 2022] Available from: https://www.uptodate.com contents/overview-of-antiretroviral-agents-used-to-treat-hiv?csi=220ef98c-15fe-43fc-859f-18aaa19d27df&source=contentShare

11. Mckenzie L, Hadzic T. Clinical pharmacokinetic, pharmacodynamic and drug interaction profile of the integrate inhibitor Dolutegravir. Clin Pharmacokinet. 2013 November; 52(11): 981–994. doi:10.1007/s40262-013-0093-2.

12. Barata R, Costa BMda, Navarro D, Mendes M, Silva C, Góis M, et al. Acute interstitial nephritis due to dolutegravir: The first case reported: Semantic scholar [cited 14 March 2022]. Available from: https://www.semanticscholar.org/paper/Acute-interstitial-nephritis-due-to-dolutegravir%3A-Barata-Costa/0906a4cd83ef19864e3e57e3cff7cc1f3b0128c4

13. Maggi P, Montinaro V, Mussini C, Di Biagio A, Bellagamba R, Bonfanti P, Calza L, Cherubini C, Corsi P, Gargiulo M, Montella F, Rusconi S. Novel antiretroviral drugs and renal function monitoring of HIV patients [Internet]. AIDS reviews. U.S. National Library of Medicine; [cited 14 April 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/25102336/

14. Sutherland SM, Kwiatkowski DM. Acute kidney injury in children. Advances in Chronic Kidney Disease. 2017; 24(6):380–7.

15. Khwaja A. KDIGO clinical practice guidelines for Acute Kidney Injury. Nephron Clinical Practice. 2012;120(4):c179–c184.

16. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin C: The New England journal of medicine. U.S. National Library of Medicine; [20 April 2022] Available from: https://pubmed.ncbi.nlm.nih.gov/22762315/

17. Bjornstad P, Karger AB, Maahs D. DM; BPKABM. Measured GFR in routine clinical practice-the promise of dried blood spots [Internet]. Advances in chronic

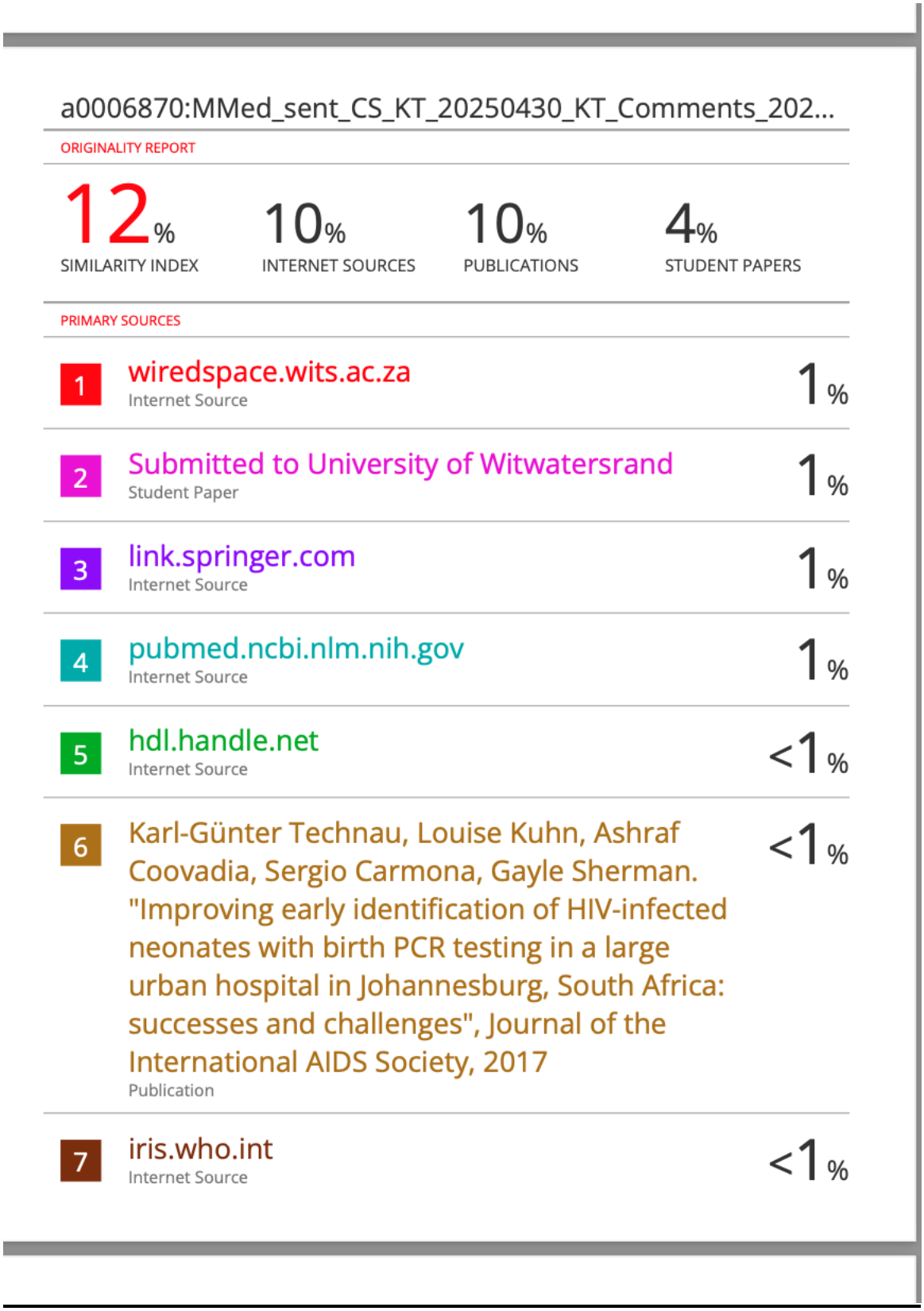
kidney disease. U.S. National Library of Medicine; [cited 20 May 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/29499891/

18. Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, Warady BA. Blood pressure in children with chronic kidney disease: A report from the chronic kidney disease in children study [Internet]. Hypertension (Dallas, Tex.: 1979). U.S. National Library of Medicine; [cited 2022Oct20]. Available from: https://pubmed.ncbi.nlm.nih.gov/18725579/
19. Utsch B, Klaus G. Urinalysis in children and adolescents. Deutsches Ärzteblatt international. 2014
20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support [Internet]. J Biomed Inform. 2009;42(2):377
21. Stevens, L. A., Coresh, J., Greene, T, Levey, A. S. (AS; SLACJGTL. Assessing kidney function--measured and estimated glomerular filtration rate [Internet]. The New England journal of medicine. U.S. National Library of Medicine; [cited 2022Oct20]. Available from: https://pubmed.ncbi.nlm.nih.gov/16760447/
22. Chuang G-T, Tsai I-J, Tsau Y-K. Serum creatinine reference limits in pediatric population—a single center electronic health record-based database in Taiwan. Frontiers in Pediatrics. 2021;9.
23. Kliegman R. Nelson textbook of Paediatrics. Edition 21. Philadelphia, PA: Elsevier (202)

24. Mtisi, T.J., Ndhlovu, C.E., Maponga, C.C. *et al.* Tenofovir-associated kidney disease in Africans: a systematic review. *AIDS Res Ther* **16**, 12 (2019). https://doi.org/10.1186/s12981-019-0227-1

Appendix A: Ethics clearance

Appendix B: Plagiarism declaration



a0006870:MMed_sent_CS_KT_20250430_KT_Comments_202...

ORIGINALITY REPORT

12%	10%	10%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	wiredspace.wits.ac.za Internet Source	1%
2	Submitted to University of Witwatersrand Student Paper	1%
3	link.springer.com Internet Source	1%
4	pubmed.ncbi.nlm.nih.gov Internet Source	1%
5	hdl.handle.net Internet Source	<1%
6	Karl-Günter Technau, Louise Kuhn, Ashraf Coovadia, Sergio Carmona, Gayle Sherman. "Improving early identification of HIV-infected neonates with birth PCR testing in a large urban hospital in Johannesburg, South Africa: successes and challenges", Journal of the International AIDS Society, 2017 Publication	<1%
7	iris.who.int Internet Source	<1%

Appendix C: Submission format guideline: Southern African Journal of HIV medicine:

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative changes or differences on answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)

Do not cite references and do not use abbreviations excessively in the abstract.

What this study adds: What key insights into the research results and its future function are revealed? How do these insights link to the focus and scope of the journal? It should be a concise statement of the primary contribution of the manuscript; and how it fits within the scope of the journal.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by the use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the

knowledge gap that this study will address. Your argument should be supported by the use of evidence from the literature.

- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.

- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Appendix D: Research protocol

The effects of dolutegravir on creatinine clearance in children and adolescents living with HIV: a retrospective cohort study in Johannesburg

Student: Dr. Chiara Sewnarain

Student number: 445977

Student email: chiarasewnarain@gmail.com

Degree: Masters of medicine in paediatrics (MMed) - research protocol

Supervisor: Assoc. Prof. Karl-Gunter Technau

Supervisor email: karl-gunter.technau@wits.ac.za

Summary:

In 2013, the FDA approved dolutegravir (DTG) for treatment of human immunodeficiency virus (HIV) infection in combination with other drugs. In 2019, South Africa revised its anti-retro viral therapy (ART) guidelines to include DTG as a fixed dose combination drug with tenofovir (TDF) and lamivudine (3TC) as well as a single formulation for patients above 20kg. DTG is a second-generation integrase inhibitor; a newer class of ART drug and works by blocking the incorporation of HIV DNA into the host genome, thus preventing replication. It has widely publicised benefits; superior tolerability, mild side effects, a high genetic barrier to resistance and enables rapid viral suppression.

DTG has been noted to result in a serum creatinine (SC) rise of no more than 15% from the baseline creatinine; an observation that has been found to stabilise without any adverse renal outcomes. It therefore can be safely used in patients with significant renal dysfunction. DTG is often used with other nephrotoxic drugs and therefore determining the cause of the increase in creatinine can be challenging.

Clinicians have voiced concerns that the rise in SC may be more than 15% and are faced with uncertainty especially when DTG is used with TDF. DTG is a relatively new drug, and we would like to explore whether its effects on SC are similar in our patients as described in other studies as well as if these effects are addressed adequately in the current guidelines.

Our objectives are:

I. To describe the population of children between the ages of 10 - 18 years (who switched to TDF and/or DTG after 2015) who had SC measurements done due to routine clinical guideline requirement (initiation of TDF).
II. To describe the SC and eGFR progression over time, describing changes overall (related to anthropometric growth) and related to timing of switch to TDF and/or DTG (3 months post switch and annually post switch noting changes exceeding and not exceeding 15% from baseline over time in SC and eGFR and above normal range SC).
III. To evaluate for any associations of SC or eGFR changes >15% or above normal range SC with ART start characteristics and specific regimen switches.

This is a retrospective data analysis of data that has already been prospectively collected. This data will be collected from an existing database from the Empilweni Services and Research Unit at Rahima Moosa Mother and Child Hospital.

Table of contents:

List of abbreviations:

ABC: Abacavir

ART: Antiretroviral therapy

BMI: Body mass index

CLHIV: Children living with HIV

DTG: Dolutegravir

EFV: Efavirenz

ESRU: Empilweni Services and Research Unit

FTC: Emtricitabine

HIV: Human immunodeficiency virus

IMPAACT: International Maternal Paediatric Adolescent AIDS Clinical Trials

INSTI: Integrase strand transfer inhibitor

MTCT: Mother-to-child transmission

NNRTI: Non-nucleotide reverse transcriptase inhibitor

PI: Protease inhibitor

PLHIV: People living with HIV

RMMCH: Rahima Moosa Mother and Child Hospital

SC: Serum creatinine

TAF: Tenofovir alafenamide fumarate
TDF: Tenofovir disoproxil fumarate
TEE: Tenofovir, Emtricitabine, Efavirenz
TLD: Tenofovir, Lamivudine, Dolutegravir
WHO: World Health Organization
3TC: Lamivudine

1.0 Introduction:

Human immunodeficiency virus (HIV) is a blood borne virus and transmitted via sexual intercourse, vertical transmission via the birth process, via breast milk and the sharing of needles. The virus is a retrovirus in the Retroviridae family within the *Lentivirus* genus. (7) Patients with HIV infection often present with symptoms representing various phases of the disease, ranging from acute seroconversion to acquired immune deficiency syndrome (AIDS). HIV causes immune system compromise by replicating itself using the host's CD4 cells thereby making opportunistic infections a major contributing factor to mortality in these patients. (7) The diagnosis of HIV is no longer a death sentence, however the number of people diagnosed with HIV seems to be on an increasing trend. In 2021, the World Health Organisation reported a total number of 38,4 million people living with HIV globally, as compared to 26 million people in 2000. This shows that the transmission of HIV is ongoing. (8) In South Africa in 2021, an estimated 13.7% of the total population was living with HIV. The total number of individuals living with this disease has increased exponentially from an estimate of 3.8 million in the year 2002 to 8.2 million by 2021, of which an estimated 280 000 were children under the age of 14 years. (8)

South Africa has the largest anti-retroviral therapy (ART) programme in the world. Providing early detection of the disease as well as early initiation of therapy and easy access to health care are the cornerstone pillars for ensuring decreased morbidity and mortality. Combination

therapy using different classes of drugs that act at different stages of the HIV life cycle ensures reduced resistance as well as rapid viral suppression. (10) The ART guidelines released in 2019 in South Africa have included dolutegravir, (DTG) an integrase strand transfer inhibitor (INSTI), as part of the first line treatment for adults, adolescents and children over the age of 6 years and weighing more than 35kg. This is available with tenofovir (TDF) and lamivudine (3TC) as a fixed dose combination (TLD). For children who are between 20kg and 35kg, abacavir, (ABC) lamivudine (3TC) and DTG is the recommended first line combination. (8)

DTG has been shown to be well tolerated, demonstrating anti-HIV activity by inhibiting the enzyme responsible for incorporation of viral DNA into the host genome. It causes rapid viral suppression and mild side effects. (3) Known side effects that have been demonstrated include weight gain, insomnia, dizziness and a mild, transient increase in serum creatinine. (SC)

It is important to establish the severity of renal dysfunction whilst using DTG and how congruent this is with current studies and guidelines, so as to ensure adverse effects are being pre-empted and treated.

2.0 Literature review:

2.1 DTG and renal functioning:

DTG exhibits rapid absorption as well as extensive protein binding. Because DTG is primarily metabolised by the UDP glucuronosyltransferase (UGT1A1) pathway, it is >99% bound to protein and excreted primarily in faeces and bile, with <1% excreted unchanged in the urine. Early investigations of DTG in SPRING-1, SPRING-2 and the VIKING trials showed a mild, non-progressive increase in serum creatinine after one week of initiation and remained stable thereafter. (3, 5) The SPRING-1 trial compared raltegravir (RAL) with DTG, no renal associated withdrawals were recorded for either of these drugs. GFR does not appear to be affected by DTG and this initial rise of SC is likely due to inhibition of the renal organic cation transporter 2 (OCT2) activity, leading to reduced secretion of creatinine. The use of DTG over 48 weeks does not appear to affect renal functioning, although the long-term effects of this drug on renal functioning are still to be determined. (4,5,6) One case of acute interstitial nephritis has been described in a 44-year-old female patient who developed

eosinophila and worsening renal functioning after starting treatment with DTG. Her renal functioning subsequently improved after cessation of the drug and commencement of steroids. This, however, has not been described in children. (13)

DTG's effects were also studied in another trial that looked at actual GFR, creatine clearance and renal plasma flow. This was done in healthy individuals. The participants of this trial took DTG 50mg daily or bidaily and some received a placebo for 14 days together with infusions containing iohexol and para-aminohippurate (PAH) on days 1-7 and day 14. Iohexol is a freely filtered (not secreted) solute that measures GFR. PAH is a maker of effective renal plasma flow. Both showed no effects of DTG on their clearance. A marker of quantitative proteinuria, protein - creatinine ratio, was measured and none of the patients in both groups displayed altered proteinuria at any point. (14)

2.2 Abnormal renal functioning in children living with HIV disease:

As ART has become more available, there is improved survival of children living with this disease and treating children with kidney complications has improved. (25) Without access to ART, many African children <2 years of age previously died of diarrhoea associated dehydration and respiratory infections prior to renal disease even being diagnosed. HIV associated nephropathy (HIVAN) in children has certain unique features such as rapid progression of the disease as well as focal segmental glomerular sclerosis (FSGS) with microcytic changes in the tubules. FSGS in young, HIV positive children supports the idea that HIV-1 is capable of causing renal disease that is independent of drug use. (26) Other common presentations of renal disease in HIV infected children include an increased incidence of urinary tract infections, acute renal failure secondary to diarrhoeal disease, HIV-associated haemolytic uraemic syndrome (HUS) which can be a fatal form of HUS that is not preceded by diarrhoea, has an insidious onset and preserved urinary output. HIV infected children can also present with a typical picture of nephrotic syndrome and histological features herein include minimal change disease, lupus-like lesions and HIV immune complex disease. (HIVICK) (26)

Tenofovir (TDF) is a nucleotide reverse transcription inhibitor (NRTI) and is used in combination with other ART in the treatment of HIV disease in both children and adults. An important complication of TDF is renal toxicity which seems to be related to its clearance. Studies have shown that many children treated with TDF over a period of time have

experienced a decrease in GFR. (26) The use of TDF in pre-pubertal patients was initially not recommended and according to previous guidelines, its use was reserved for those >15 years. There is still anxiety about changing large-scale guidelines to include it in younger individuals.

2.3 Measures of renal functioning in children:

Glomerular filtration rate (GFR) is generally the best measure of renal functioning in children and adolescents. Unfortunately, it is often impractical to measure GFR directly, so it is often estimated using serum creatinine and serum Cystatin C. This however lacks precision and accuracy until GFR <60ml/min/l/1.73m2, a point at which half of renal functioning is already lost. Creatinine is a marker of kidney function and not kidney injury. (17) Accurate calculation of GFR is important to determine the burden of CKD in our HIV population, especially to guide drug dosing and to monitor toxicity. Creatinine is derived from its metabolism in skeletal muscle as well as from dietary meat. It is then released into the circulation at a stable rate. A way of calculating the creatinine clearance is by looking at the total amount of filtered creatinine, this is equal to the product of the GFR and serum creatinine concentration (SC) will be excreted (equal to the product of the urine creatinine concentration [UCr] and the urine flow rate or volume. [V]) (22) (GFR = [UCr X V] / SCr) eGFR can be measured by using the Counahan Barrett formula, which calculates eGFR (in mL/min/1.73m2) by using the patient's height in cm multiplied by a constant (40) divided by the creatinine in micromols / litre. (22)

From 1 month of age, serum creatinine usually increases gradually with age in response to an increase in muscle mass. These levels will therefore differ every year related to the child's growth. It is important to establish serum creatinine level reference limits for specific paediatric populations. (23) For example, The Nelson textbook of Paediatrics states the serum creatinine upper reference limit is 0.5mg/dL for children under 4 years of age. (24)

Urine output has been a growing measure of renal functioning in children. The problem with using urine output is that without urinary catheterisation, the volume of urine is very difficult to determine. There has been a move towards avoidance of catheterisation of children in hospital to prevent urinary tract infections. (UTI) Despite this, it has been proven that disregarding the urine output often leads to the under-diagnosis of AKI. (18)

Blood pressure (BP) is often used as a measure of chronic kidney disease as it is generally elevated in advanced disease. An elevated blood pressure is determined as a BP >= 90th percentile for age, gender and height whereas hypertension is defined as a BP>= 95th percentile for age, gender and height. (19)

Urine dipstick helps to determine the presence of proteinuria and is the most common bedside test in determining abnormalities of renal functioning. The timing and mode of collecting the urine sample can affect the assessment of proteinuria, haematuria, leucocyturia and nitrituria. It is important to note that abnormal urinalysis can be found in healthy children. (20)

3.0 Aims and objectives:

3.1 Problem statement:

The renal effects of DTG have been studied in adults, but data is scarce in the paediatric population, and especially in the paediatric African population. As renal functioning can be compromised by HIV itself, concomitant diseases and drugs (especially TDF), it is important to know how DTG effects renal functioning when making the decision to switch regimens and place patients on this drug for potentially long periods of their lives. Current guidelines suggest that DTG causes a non-progressive rise in SC (<15%) that stabilises over time without affecting the GFR. Due to anecdotal concerns and reports that the SC rise is >15%, we would like to assess this in our patient population and see if our findings are congruent with other literature that has been published and whether the current South African guidelines adequately address the commonly observed SC values.

3.1 Aim:

This descriptive study aims to evaluate SC and eGFR in children and adolescents switched to TDF formulations at Rahima Moosa Mother and Child Hospital, in the presence or absence of DTG.

3.2 Objectives:

III. To describe the population of children between the ages of 10 years to 18 years (who switched to TDF and/or DTG after 2015) who had SC measurements done due to routine clinical guideline requirement (initiation of TDF) in terms of:

- Their baseline renal function: evidence of abnormal SC, eGFR, elevated blood pressure, abnormal urine dipstix results, as well as their blood pressure for age.
- Their ART start (first disease presentation) characteristics. (Sex, age, CD4 count, clinical stage and anthropometric measures).
- Their regimen switches (specifically switch to TDF and switch to DTG) and background regimen (INSTI/ PI/ NNRTI).

II. To describe the SC and eGFR progression over time, describing changes overall (related to anthropometric growth) and related to timing of switch to TDF and/or DTG (3 months post switch and annually post switch noting changes exceeding and not exceeding 15% from baseline SC/eGFR and above normal SC and below normal eGFR over time)

III. To evaluate for any associations of SC and above normal SC or eGFR changes >15% with ART start characteristics and specific regimen switches.

4.0 Study design and methods:

4.1 Study design:

This is a retrospective data analysis of data that has already been prospectively collected at Rahima Moosa Mother and Child Hospital in Johannesburg. This is an urban academic provincial hospital specialising in maternal, paediatric and neonatal patient services. This study will be a sub-study of the existing study, "Cohort study of HIV-infected and exposed children receiving care at Rahima Moosa Mother and Child Hospital supported by Empilweni Services and Research Unit and participation in IeDEA-SA" (Site-PI Technau.M220559).

The Empilweni Services and Research unit (ESRU) clinic is one of the larger paediatric HIV clinics in South Africa, with over 1400 children in active care. On a daily basis, the clinic manages neonates, children and adolescents living with HIV, as well as neonates that are exposed but uninfected. Management includes initiation of treatment naïve patients on to first line ART, regular follow up appointments and managing those requiring 2nd or 3rd line

treatment. At each follow up, BP and urine dipstick is measured by the nursing staff and recorded in the patient's file. Renal functioning biomarkers (creatinine) is done three monthly for the first six months and thereafter at 12 months and then annually. Patients are then seen by the doctors and counsellors. Phlebotomy staff are available for taking the relevant and necessary blood tests. All results are recorded in a flow sheet in the patients file (Appendix 1).

4.2 Participants:

Inclusion criteria:

All children/adolescents >10 years of age and </= 18 year of age initiated on or switched to a TDF or a DTG-based regimen at RMMCH from January 2015 to November 2022.

Exclusion criteria:

1) Children/adolescents being cared for at RMMCH who refuse/whose parents refuse consent for the use of routine data for research purposes.

4.3 Study procedures:

The following data will be requested as an extract from the existing database for each patient fulfilling the inclusion criteria. Table 1 shows how this data will be collected:

Demographic data:	**Calculated data:**
Sex	Male/ Female
Age at ART start	Categorized as children >10 years, 10-12 years, 12-15 years and >15 years
ART regimen (initial), date of switch to TDF and / or DTG	**Age at DTG switch**
Anthropometry: value and date of visit (from 2015 and at ART start)	
- height (cm)	Z-score / BMI

- weight (kg)	Z-score / BMI
Bloods	
- CD4	<200, 200-349, 350-499 (cells/µl)
- VL	<50, 50-1000, >1000
- Creatinine	Normal, high, low

4.4 Data collection:

Data is usually collected from patient's files and entered into Empilweni's database. This database is hosted on the University of Witwatersrand REDCAP platform. (21) Application to the electronic gatekeeper of the database will have been made for data to be extracted. This data will be received in a way that is not identified.

4.5 Data management:

The dataset will be reviewed and cleaned. Outliers will be identified. These outliers will be values that are not in keeping with the patient's other information for example an aberrant weight or sudden high viral load or creatinine or a sudden low CD4 count. These will not be removed from the dataset but rather identified as outliers in a tabular form and analysed as either having an effect on the research question for that particular patient. If there are any concerns, these files will be reviewed in order to verify entries, to ensure it was not an error in capturing during routine capture. Once this data has been extracted, it will be kept in a password-protected spreadsheet. The only people to have access to this spreadsheet is the researcher and the supervisor. An anonymised clean final dataset will be agreed upon and locked.

4.6 Data analysis:

Overall:

ART regimen pre-switch will be categorised into non-nucleotide reverse transcriptase inhibitor (NNRTI) vs PI based and classified at switch as ABC/3TC/DTG vs. TLD. The CD4 count results at baseline and those closest to the time of DTG switch/start will be noted and immune status will be classified according to the WHO immunological classification (mild:

350-499, moderate: 200-349 and severe: < 200cells/µl). Weight and height will be collected from the data sheet and anthropological measures (body mass index, weight for age Z-scores, weight for height Z-scores and height for age Z-scores) recorded. VL measures will be considered as a proxy for adherence.

Data analysis per objective:

I. Descriptive statistics such as univariate, bivariate or multivariate statistics will be used to describe data - standard statistical methods. Categorical variables will assess data such as anthropometry and will be described using frequencies and percentages, while mean and standard deviation or median and interquartile range will be used for continuous variables such as creatinine values and body mass index, depending on the distribution of the data.
II. eGFR will be calculated by the Counahan Barrett formula. Changes in eGFR and SC will be calculated as percentage from baseline (switch to TDF and/ or DTG) at 3 months, 6 months and annually. SC values that are above the normal laboratory reference range will also be coded as high vs normal.
III. Univariate and multivariate logistic regression will be used to assess associations of the outcome. (Change >15%)

5.0 Ethical considerations:

If children are <18 years, parents or caregivers will sign a data sharing consent form. (Appendix 2) Adolescents will re-consent once they have turned 18 years. Prior ethics approval of the Empilweni database will be obtained from the University of Witwatersrand. Institutional permissions to conduct research at RMMCH will be sought from the hospital CEO and an application for this study will be made to The University of Witwatersrand Faculty Graduate Studies Committee and the Human Research Ethics committee of the University of the Witwatersrand.

6.0 Limitations:

Data analysis depends on the capturing of information and correct transcription, and this can sometimes be captured incorrectly. Some patients might be a loss to follow up, which may

affect the outcome of the study. Interpretation of urinalysis is also user-dependent, and we might find inconsistencies with these results. It is difficult to assess adherence to ART consistently in this kind of cohort. VL measures at the time of SC measures will be able to assist in distinguishing good adherence from poor adherence. In cases of poor adherence, it may be hard to differentiate between effects on SC being from ART or from disease progression.

7.0 Timeline:

	Sept 2022	Oct 2022	Oct 2022	Nov 2022	Dec 2022	Jan 2023	Feb 20
Protocol Development	-	-					
Protocol Submission							
Protocol Amendments							
Data Collection							
Data Analysis							
Submission of final research report							

s

8. References:

1. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd ed [Online]. Who.int. 2019 [cited 13 March 2022]. Available from: https://www.who.int/publications/i/item/9789241549684
2. Gutiérrez F, Fulladosa X, Barril G, Domingo P. Renal tubular transporter-mediated interactions of HIV drugs: Implications for patient management.: Semantic scholar [Internet]. undefined. 1970 [cited 13 March 2022]. Available from: https://www.semanticscholar.org/paper/Renal-tubular-transporter-mediated-interactions-of-Guti%C3%A9rrez Fulladosa/48ca933fedab4bea28be480b30de3b330c1edb5b
3. Reese MJ, Savina PM, Generaux GT, Tracey H, Humphreys JE, Kanaoka E, Webster LO, Harmon KA, Clarke JD, Polli JW. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor [Internet]. Drug metabolism and disposition: the biological fate of chemicals. U.S. National Library of Medicine; [cited 14 March 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/23132334/
4. van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, Rockstroh JK, Almond S, Song I, Brothers C, Min S. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: Planned interim 48 week results from spring-1, a dose-ranging, randomised, phase 2b trial [Internet]. The Lancet. Infectious diseases. U.S. National Library of Medicine; [cited 13 March 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/22018760/
5. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, Bloch M, Podzamczer D, Pokrovsky V, Pulido F, Almond S, Margolis D, Brennan C, Min S. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48-week results from the randomised, double-blind, non-inferiority spring-2 study [Internet]. Lancet (London, England). U.S. National Library of Medicine; [cited 12 March 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/23306000/

6. What are HIV and AIDS? [Internet]. HIV.gov. [cited 13 March 2022]. Available from: https://www.hiv.gov/hiv-basics/overview/about-hiv-and-aids/what-are-hiv-and-aids
7. Global health observatory (GHO) Data. World Health Organization. [Online] 2020 [cited 13 March 2022]. Available from: https://www.who.int/data/gho
8. Guidelines for the use of Antiretroviral Agents in adults and Adolescents with HIV. AIDSinfo. [Online] Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/37/whats-new-in-the-guidelines- [Accessed 05 April 2022]
9. Fletcher C. Overview of antiretroviral agents used to treat HIV. UpToDate. [Online] 2020. [Accessed 14 March 2022] Available from: https://www.uptodate.com contents/overview-of-antiretroviral-agents-used-to-treat-hiv?csi=220ef98c-15fe-43fc-859f-18aaa19d27df&source=contentShare
10. South African National Department of Health. 2019 ART Clinical Guidelines. 2019; (May 2022).
11. Mckenzie L, Hadzic T. Clinical pharmacokinetic, pharmacodynamic and drug interaction profile of the integrate inhibitor Dolutegravir. Clin Pharmacokinet. 2013 November; 52(11): 981–994. doi:10.1007/s40262-013-0093-2.
12. Barata R, Costa BMda, Navarro D, Mendes M, Silva C, Góis M, et al. Acute interstitial nephritis due to dolutegravir: The first case reported: Semantic scholar [Internet]. undefined. 1970 [cited 14 March 2022]. Available from: https://www.semanticscholar.org/paper/Acute-interstitial-nephritis-due-to-dolutegravir%3A-Barata-Costa/0906a4cd83ef19864e3e57e3cff7cc1f3b0128c4
13. Maggi P, Montinaro V, Mussini C, Di Biagio A, Bellagamba R, Bonfanti P, Calza L, Cherubini C, Corsi P, Gargiulo M, Montella F, Rusconi S. Novel antiretroviral drugs and renal function monitoring of HIV patients [Internet]. AIDS reviews. U.S. National Library of Medicine; [cited 14 April 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/25102336/
14. Sutherland SM, Kwiatkowski DM. Acute kidney injury in children. Advances in Chronic Kidney Disease. 2017;24(6):380–7.
15. Khwaja A. KDIGO clinical practice guidelines for Acute Kidney Injury. Nephron Clinical Practice. 2012;120(4):c179–c184.

16. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS. Estimating glomerular filtration rate from serum creatinine and cystatin C [Internet]. The New England journal of medicine. U.S. National Library of Medicine; [20 April 2022] Available from: https://pubmed.ncbi.nlm.nih.gov/22762315/

17. Bjornstad P, Karger AB, Maahs D. DM; BPKABM. Measured GFR in routine clinical practice-the promise of dried blood spots [Internet]. Advances in chronic kidney disease. U.S. National Library of Medicine; [cited 20 May 2022]. Available from: https://pubmed.ncbi.nlm.nih.gov/29499891/

18. Flynn JT, Mitsnefes M, Pierce C, Cole SR, Parekh RS, Furth SL, Warady BA. Blood pressure in children with chronic kidney disease: A report from the chronic kidney disease in children study [Internet]. Hypertension (Dallas, Tex.: 1979). U.S. National Library of Medicine; [cited 2022Oct20]. Available from: https://pubmed.ncbi.nlm.nih.gov/18725579/

19. Utsch B, Klaus G. Urinalysis in children and adolescents. Deutsches Ärzteblatt international. 2014

20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support [Internet]. J Biomed Inform. 2009;42(2):377

21. Stevens, L. A., Coresh, J., Greene, T, Levey, A. S. (AS; SLACJGTL. Assessing kidney function--measured and estimated glomerular filtration rate [Internet]. The New England journal of medicine. U.S. National Library of Medicine; [cited 2022Oct20]. Available from: https://pubmed.ncbi.nlm.nih.gov/16760447/

22. Chuang G-T, Tsai I-J, Tsau Y-K. Serum creatinine reference limits in pediatric population—a single center electronic health record-based database in Taiwan. Frontiers in Pediatrics. 2021;9.

23. Kliegman R. Nelson textbook of Paediatrics. Edition 21. Philadelphia, PA: Elsevier (202)

24. Pardo V, Meneses R, Ossa L, Jaffe DJ, Strauss J, Roth D, et al. AIDS-related glomerulopathy: Occurrence in specific risk groups [Internet]. Kidney international.

U.S. National Library of Medicine; 1987 [cited 2022Oct20]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/3599656

25. McCulloch MI, Ray PE. Kidney disease in HIV-positive children. [Internet]. Seminars in nephrology. U.S. National Library of Medicine; [cited 2022Oct20]. Available from: https://pubmed.ncbi.nlm.nih.gov/19013330/

26. Pontrelli G, Cotugno N, Amodio D, Zangari P, Tchidjou HK, Baldassari S, et al. Renal function in HIV-infected children and adolescents treated with tenofovir disoproxil fumarate and protease inhibitors. BMC Infectious Diseases. 2012;12(1).