Virological response in children and adolescents switching to dolutegravir based regimens in Johannesburg, South Africa – A Longitudinal Cohort Study

By

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirement for the degree of Master of Medicine in the Department of Paediatrics.

Johannesburg, 2023

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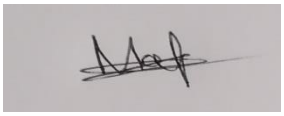
Declaration

I, Tshiamo Mafora, student number 358448 staff number A0037092, declare that this is my original work, submitted for the Master of Medicine in Paediatrics degree for the University of the Witwatersrand. It has not been submitted to any other university or for any other degree or examination. It has not yet been submitted for publication in any journal or presented at any conferences.



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Dr T Mafora

Letter from co-authors

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30th November 2023

Attention: PG Office, University of the Witwatersrand

Dear Dr Mafora

Re: Submission of Manuscript, permission to use as part of MMED

We would like to provide our consent and permission for Dr Tshiamo Mafora to include the following submitted work which was submitted for review to the Journal of the International AIDS Society (JIAS):

Mafora T, van Dongen N, Ferreira T, Sorour G, Technau K. Introduction of dolutegravir and the early viral response seen in South African children and adolescents

We, co-authors of the manuscript for review listed above do hereby give Dr Thsiamo Mafora (Student number: 358448) permission to include these publications in her MMED Research Report.

Yours faithfully

Karl Technau

Empilweni Clinic

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Introduction of dolutegravir and the early viral response seen in South African children and adolescents

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Abstract

Introduction: Dolutegravir (DTG) was introduced into South African HIV management guidelines in November 2019, and has since been the mainstay of both adult and paediatric first line antiretroviral treatment (ART) regimens. Following its rapid and widespread introduction we assessed the rate of virological suppression over two years in paediatric patients switching to DTG as part of first line treatment.

Methods: We performed a retrospective cohort study at Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa. Children and adolescents already on first line ART who switched to DTG (between November 2019 and November 2021) were included. Baseline characteristics (at DTG switch) included age, weight, gender, viral load (VL), CD4, and pre-switch regimen. Past ART exposure and past viraemic periods (years VL >1000 copies/ml) were assessed and VL suppression rates (< 50 copies/ml) were calculated at 6, 12 and 24 months post-switch. Associations with non-suppression were assessed using uni- and multivariate analysis.

Results: Of the 747 participants that were switched to DTG, 724 (97%) qualified for a VL and 697 (96%) of those had at least one VL done after switch. Overall, 83% (450/543) were suppressed at 6 months, 86% (434/504) at 12, 91% (487/534) at 24 months. Overall, at a median of 637 days after switch, 90% (624/697) were suppressed at their last VL. Factors associated with not being suppressed at the last VL included: missing a follow-up visit by more than 90 days post-switch to DTG (OR: 3.2 [CI:1.5-6.8], p=0.003), switching to DTG with a VL of 50-1000 rather than <50 copies/ml (OR 2.0 [CI:1.1-3.9], p=0.042), having the blood test done during July-December (OR 2.0 [CI:1.2-3.4], p=0.011), and having had exposure to viraemia ≥1000 copies/ml for more than two years between first ART start and DTG switch (OR: 1.9 [CI: 0.9-3.7], p=0.071).

Conclusion: In our population, similar to other studies, VL suppression was effectively maintained in the majority of patients after switching to DTG. The switch did however result in a loss of suppression in some patients and caution is needed in children and adolescents with missed visits and extensive prior viraemia.

Introduction

HIV contributes significantly to the burden of disease in South Africa. The Southern African region accounts for the majority of global HIV infections, with a prevalence of approximately 12.9% in 2021 in South Africa, and an incidence of 0.4% (1-3). There are 39 million people living with HIV globally including 1.5 million children (3). Ever improving low-cost once daily antiretroviral treatment (ART) with fewer side effects has improved outcomes for people living with HIV (PLHIV). Over the years multiple improved antiretroviral drugs have been discovered, resulting in new regimens and constantly evolving guidelines. South Africa currently has the largest ART programme in the world since its large-scale public introduction in 2004 (2).

The antiretroviral drug, dolutegravir (DTG), an integrase strand transfer inhibitor, was introduced as first line treatment for adults and children (≥20kg) living with HIV in the South African 2019 HIV treatment guidelines and the recent 2023 guidelines extended the weight cut-off to 3kg (4, 5). Recommendations on the preference for DTG as the backbone of first-line treatment are based on its low cost, once daily dosing, fewer side effects and drug interactions and a higher genetic barrier to resistance when compared to other drugs (6). It has been shown to be successful in both the adult and paediatric regimens, this was evident in the recent IMPAACT (International Maternal Pediatric Adolescent Aids Clinical Trial Network) P1093 trial (7). Data on dosing in children >20 kg are based on a sub-study of the Odyssey trial (8). There is unfortunately little data on the use of DTG and its effects on viral suppression in the paediatric population, particularly from routine implementation settings.

Children and adolescents present a vulnerable group as evidenced by the UNAIDS 95-95-95 indicators for children in South Africa (diagnosis of 95% of all PLHIV, achieving 95% on ART among those diagnosed and 95% virally suppressed among those being treated) between adults and children (9). Ninety four percent of adults living with HIV know their status, 74% of these are on ART and of those on treatment, 67% are virally suppressed. In comparison, 83% of children living with HIV know their status, of these, only 48% are on treatment, and a mere 33% of those on treatment are virally suppressed (10).

Adherence to ART in children and adolescents is dependent on their adult caregivers and can be a challenge due to factors such as pill burden, palatability, side effects and formulations that are difficult to administer (11). Infants and children living with HIV are exposed to a wider range of ART medication than adults and also use abacavir (ABC) rather than tenofovir (TDF) as the nucleoside reverse-transcriptase inhibitor(NRTI) given with lamivudine (3TC). This could result in different resistance patterns and could potentially result in resistance to DTG. The evidence for the preference of DTG in children ≥20kg is promising, but its introduction into the South African HIV program should be closely monitored to ensure that no untoward effects are seen. With the introduction of new regimens, particularly in large public health programs, strict and adequate monitoring needs to be in place to ensure that the regimens provide the same benefit during large-scale introduction as seen in clinical trials.

This study evaluated the viral response of ART-experienced children and adolescents who transitioned to first-line DTG-based regimen between December 2019 and October 2021, in the first 36 months of their DTG containing regimen.

Methods

This study is a retrospective cohort study based at Rahima Moosa Mother and Child Hospital, a paediatric referral hospital in Johannesburg. Follow-up for patients at the clinic depends on their clinical and immunological status and is based on national guidelines (4, 5). Patients that are virologically suppressed (HIV viral Load [VL] < 50 copies/ml) and stable are followed up three monthly, those not suppressed are followed up more frequently to address adherence challenges and other factors that might be affecting their virological and clinical outcomes.

Guidelines for the treatment of HIV during this time period, included two nucleoside reverse transcriptase inhibitors (NRTIs) as the backbone of an effective ART regimen with the addition of a drug from another class, either a non-nucleoside reverse transcriptase (NNRTI), a protease inhibitor (PI) or an integrase strand

transfer inhibitor (InSTI) (12). The 2019 guidelines stated that children could be switched to DTG containing regimens once they were stable on their current regimen and weighed more than 20 kg. Before reaching 35kg and ten years of age, children received ABC and 3TC as their NRTI backbone. Once they were more than 35 kg and ten years of age or older, with normal renal function, they could then be switched to a fixed dose combination that included TDF and 3TC which is also the current first line adult regimen. The weight cut-off for starting TDF has since been lowered to 30kg in the 2023 guidelines but did not affect our population of patients.

The transition to a DTG based regimen required a VL of <50 copies/ml six months prior to regimen switch (4), which indicates viral suppression on the current regimen or <1000 copies/ml on two occasions in the past year. VLs were done at six- and twelve-months post-switch and then annually unless clinical indication necessitated earlier repeat. Clinical Information is initially captured on paper and then transcribed electronically into a Research electronic data capture (REDCap) database hosted at the University of the Witwatersrand (13).

De-identified data were analysed 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. suppressed vs not suppressed based on VL at 6 months (3-9 months), 12 months (9-15 months), 24 months (16 – 27 months) and last VL. 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, VL and a cumulative total of VL>1000 copies/ml and VL>50 copies/ml since ART start categorised as <6 months, 6 to 12, 12 to 24 and >24 months respectively. The time of viraemia exposure was determined by assessing subsequent VL measures in patients and categorising the intervals as ≥1000 copies/ml consistently (whole period counted), moving from ≥1000 to <1000 (half the period counted) or <1000 consistently (not counted) towards a cumulative ≥1000 copies/ml viraemia time (similarly applied using the ≥50 copies/ml cut-off to determine a cumulative ≥50 viraemia time). Prior viraemia exposure was displayed by means of spaghetti plots with superimposed Loess spline curves. Follow-up dynamics were assessed by presence or absence of late visits (>90 days) post-DTG

switch and timing of VL test during the year (January-June vs. July-December). Univariate analysis was used to assess the effect of individual variables against the outcome of being virally suppressed (HIV VL < 50 copies/ml) and a multivariate logistic regression model was used to assess more complex interactions with all variables reaching a p-value of 0.2 or less included. In a more detailed assessment of viral outcomes, participants with a VL <50 copies/ml are further categorised into being undetectable (target not detected) and being detectable but not quantifiable (typically denoted as <50 copies/ml).

All parents/caregivers were invited to sign prospective data sharing consent and adolescents are re-consented when they reach the age of 18. Confidentiality was maintained at all times and patient data remained anonymous. This study was submitted for approval to the Human Research Ethics Committee at the University of Witwatersrand and falls as a sub-study (M210563) under an existing approved protocol (M220559).

Results

A total of 1222 patients were switched to DTG, which is 69% of 1783 patients who attended a visit during the study period between November 2019 to October 2022 and >80% of the active clinic population of 1325 at the end of the study period. Of these, 747 participants were included in the analysis (Figure 1). The switch to DTG occurred at a median age of 13.3 years (inter-quartile range [IQR]: 11.1-15.7; range: 4.8-19.8 years), a median weight of 39.2 kg (IQR: 29.2-49.0; range: 17.0-93.0); 617 (83%) were aged above 10 years and 379 (49%) were females (Table 1). The median duration on ART pre-DTG switch was 10.8 years (IQR: 7.8-13.1). The majority of participants started ART before the age of two years, at a median age of 1.6 years (IQR: 0.5-4.2). The median longest pre-DTG exposure was to any PI for 7.2 years (IQR: 4.5-9.3) and the longest NRTI exposure was to ABC for 6.8 years (IQR: 4.4-8.7).

A total of 239 (32%) participants switched to ABC/3TC/DTG and 508 (68%) switched to TDF/3TC/DTG. Of the 239 patients who switched to ABC/3TC/DTG initially, 86 (36%) went on to subsequently change to TDF/3TC/DTG. Of the 508 who switched

to TDF/3TC/DTG one patient later changed to ABC/3TC/DTG and one patient changed to TDF/3TC/EFV. The median follow-up was 25.2 months (IQR: 18.4-28.7) and did not differ significantly between 624 (90%) with last VL <50 copies/ml and 73 (10%) with last VL≥50 copies/ml.

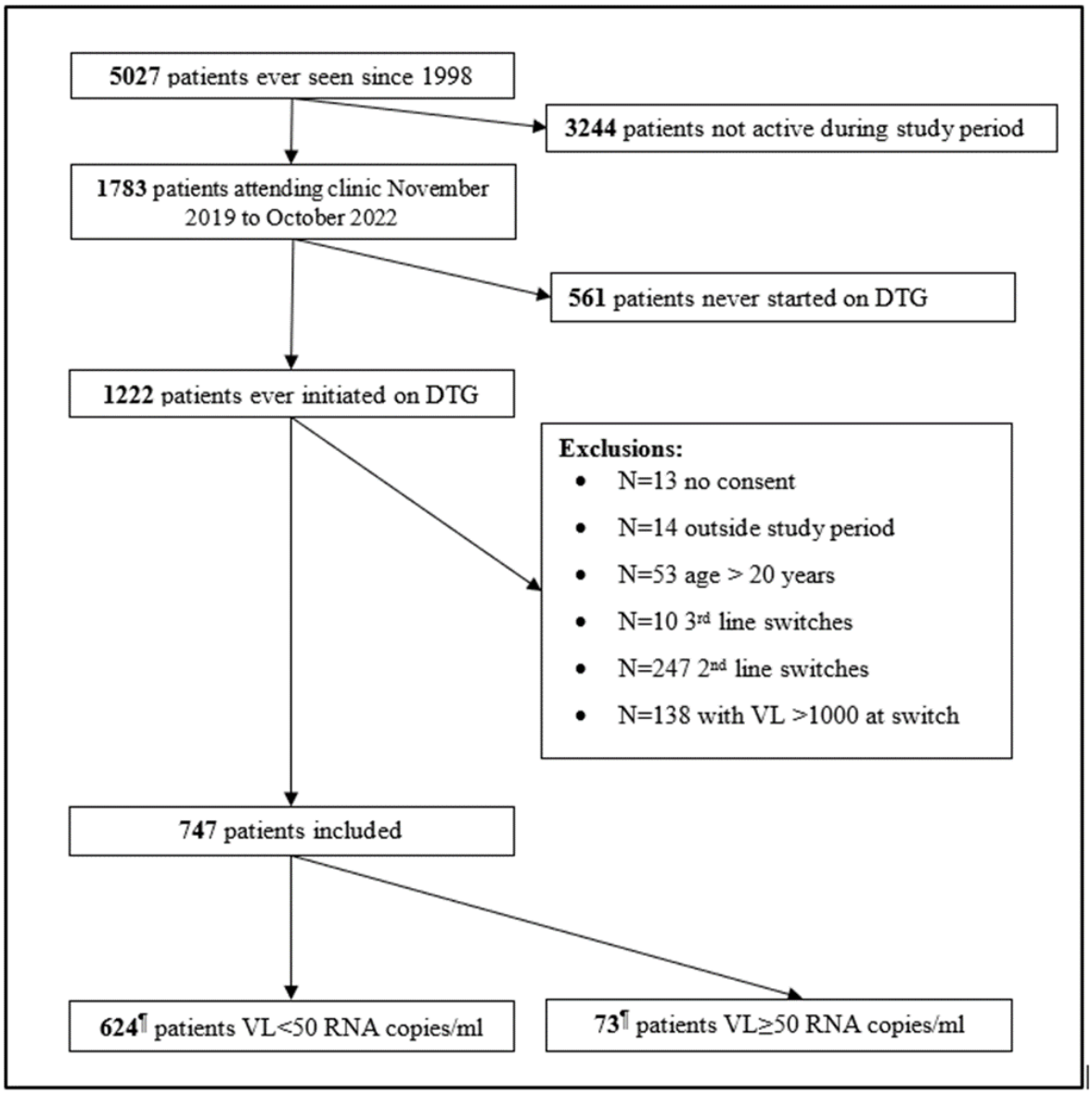

Figure 1: Study population with inclusion and exclusion criteria. VL= viral load; DTG= Dolutegravir; RNA= Ribonucleic Acid; TLD = Tenofivir/Lamivudine/Dolutegravir; ABC = Abacavir. ¶ This refers to the last VL available for patients by the end of the monitoring period; 50 patients did not have a final VL outcome and were excluded from the outcome analysis.

Table 1: Baseline characteristics of study population stratified by virological outcome (N=747)

Characteristic	Total	Suppressed[§]	Unsuppressed	P-value
Regimen pre-DTG				
NNRTI	549 (73)	470 (75)	55 (75)	1.00
PI	198 (27)	154 (25)	18 (25)	
Age at ART start, median years (IQR)	1.6 (0.5-4.2)	1.6 (0.5-4.2)	2.0 (0.9-4.9)	0.19
Time on ART pre-DTG, median years (IQR)	10.8 (7.8-13.1)	10.9 (8.1-13.1)	11.6 (6.7-13.3)	0.46
Age at DTG start, median years (IQR)	13.3 (11.1-15.7)	13.4 (11.2-15.7)	13.7 (11.4-16)	0.83
ART exposure per drug, n (%), median years (IQR)[∂]				
NRTI pre-DTG				
d4T	4.9 (3.3-6.9)	4.8 (3.2-6.7)	5.5 (3.5-8.3)	0.14
AZT	3.2 (1.1-5.1)	3.3 (1.0-5.7)	2.1 (0.9-2.4)	0.21
ABC	6.8 (4.4-8.7)	7.1 (4.6-8.7)	5.8 (3.4-8.5)	0.04
TDF	0.5 (0-1.3)	0.5 (0-1.3)	0.0 (0-1.3)	0.99
NNRTI pre-DTG				
EFV	6.3 (4.1-9.7)	6.4 (4.3-9.6)	6.0 (3.2-9.8)	0.51
Any PI pre-DTG	7.2 (4.5-9.3)	7.3 (4.6-9.3)	7.0 (3.9-9.8)	0.44
VL pre-DTG switch [£]				
0-------<50	657 (89)	557 (90)	58 (81)	0.01
50------1000	81 (11)	60 (10)	14 (19)	
Viraemia time before switching to DTG, median years (IQR)				
VL above 50 copies/ml	3.4 (1.9-5.0)	3.4 (2.0-4.8)	3.8 (1.9-5.7)	0.11
VL above 1000 copies/ml	0.6 (0.1-1.4)	0.6 (0.1-1.3)	0.7 (0.2-1.7)	0.36

All data is presented as n (%) unless otherwise indicated. NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: Protease inhibitor, ART: antiretroviral treatment, IQR: interquartile range, D4T: Stavudine, AZT: Zidovudine, ABC: Abacavir, TDF: Tenofivir, EFV: Efavirenz, , DGT: Dolutegravir, VL: Viral load copies/ml.§ VL suppression defined as <50 RNA copies/ml at last assessment. ¶ N=50 patients did not have a final VL outcome available. £ 9 patients did not have a baseline VL within the six month window prior to switch but all patients had a VL within the last 12 months (666[89%] VL<50 and 81 [11%] VL 50-1000. ∂ N= number of years exposure per drug

All participants had a VL <1000 copies/ml before switching, 666 (89%) participants had a VL <50 copies/ml and 81 (11%) of participants had a VL between 50 and <1000 copies/ml. Despite this, there was a history of viraemia with median exposure time to VL ≥50 copies/ml estimated to be 3.4 years (IQR: 1.9-5.0), while the median exposure to VL ≥1000 copies/ml was estimated to be 0.6 years (IQR: 0.1-1.3). The past exposure to viraemia along the course of participants' VL trajectories is displayed in Figure 2. Using the overall spline summary of all VL results, we noted the appearance of a minor initial increase of VL post switch which however was not maintained (Figure 2 – Panel 5).

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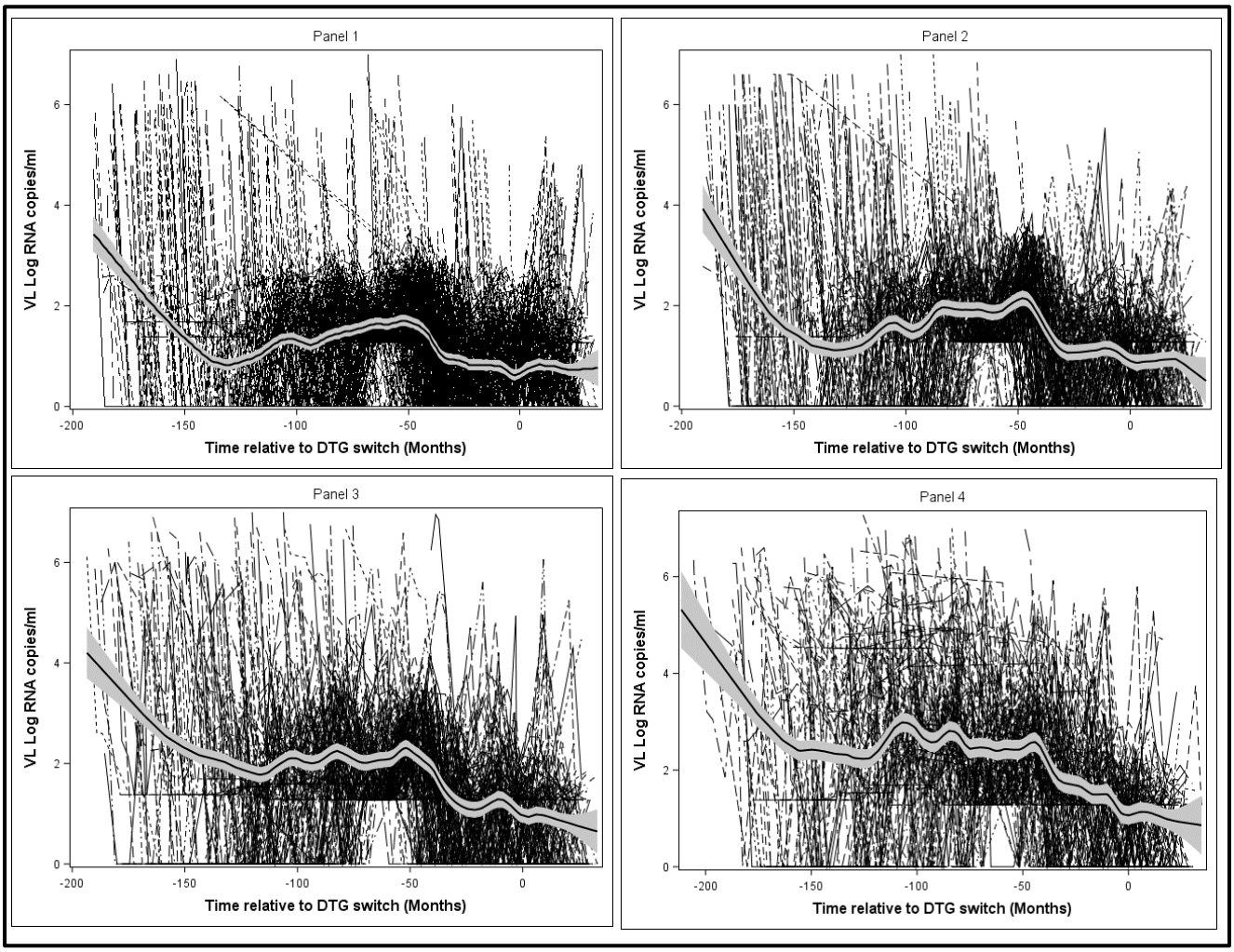

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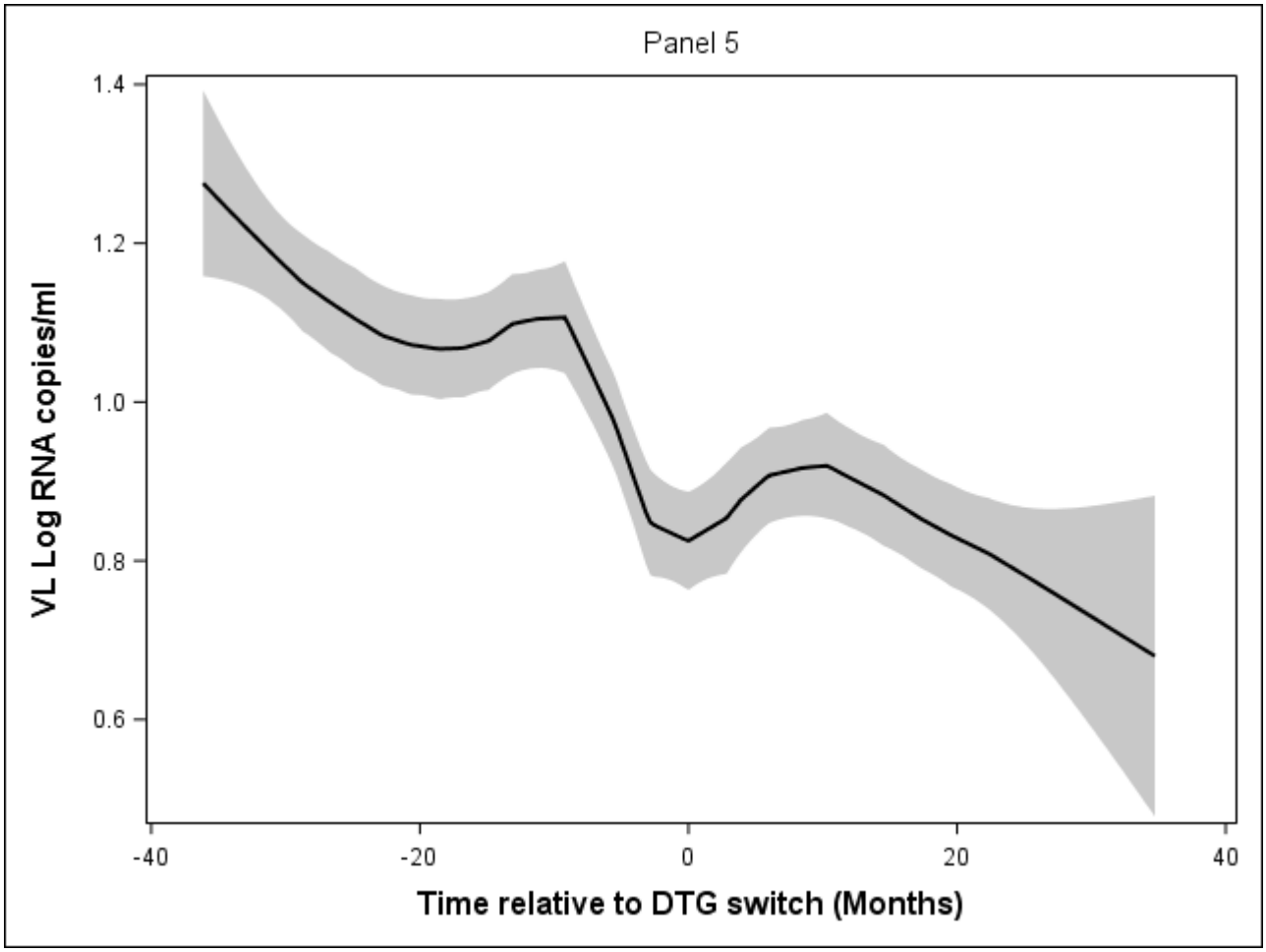

Figure 2: Viral load trajectories (spaghetti plots) with superimposed Loess spline summary (95% confidence limits) for participants with <6months (Panel 1), 6-12 months (Panel 2), 12-24 months (Panel 3), >24 months (Panel 4) of viraemia >1000 copies/ml prior to DTG switch and combined Loess Spline for all VL measures for the period 36 months before and after switch (Panel 5). DTG: dolutegravir, VL: viral load measured in RNA copies/ml

Of the 724 (97% of 747) who qualified for a VL at six months, 543 (73%) had a VL done and 450 (83%) were suppressed (Table 2). Of 680 (91%) qualifying at twelve months, 504 (74%) had a VL and 434 (86%) of these had reached suppression. At 24 months, 623 (83%) qualified for a VL, and 534 (86%) had one done of which 487 (91%) were suppressed. A VL ≥50 copies/ml post-switch was observed in 93 (17%) patients at six months, in 70 (14%) at 12 months and 47 (9%) at 24 months.

Table 2: Six, twelve, 24 month and last virological outcomes of patients after switching to DTG

Timing of VL	
6 Months	
Median days to VL (IQR)	180 (164-252)
Qualified for VL§, N (%)	724 (97)
VL done¶, N (%)	543 (75)
< 50 copies/ml	450 (83)
50-1000 copies/ml	85 (16)
>1000 copies/ml	8 (1)
Median VL (IQR)	19 (1-31)
Median VL log (IQR)	1.3 (0-1.5)
12 Months	
Median days to VL (IQR)	364 (342-427)
Qualified for VL§, N (%)	680 (91)
VL done¶, N (%)	504 (74)
< 50 copies/ml	434 (86)
50-1000 copies/ml	53 (11)
>1000 copies/ml	17 (3)
Median VL (IQR)	1 (1-22)
Median VL log (IQR)	0 (0-1.3)
24 Months	
Median days to VL (IQR)	665 (588-728)
Qualified for VL§, N (%)	623 (83)
VL done¶, N (%)	534 (86)
< 50 copies/ml	487 (91)
50-1000 copies/ml	31 (6)
>1000 copies/ml	16 (3)
Median VL (IQR)	1 (1-19)
Median VL log (IQR)	0 (0-1.3)
Last VL	
Median days to VL (IQR)	637 (490-777)
Qualified for VL§, N (%)	724 (97)
VL done¶, N (%)	697 (96)
< 50 copies/ml	624 (90)
50-1000 copies/ml	56 (8)
>1000 copies/ml	17 (2)
Median VL (IQR)	1 (1-19)
Median VL log (IQR)	0 (0-1.3)

DTG: dolutegravir, VL: viral load measured in RNA copies/ml, IQR: interquartile range. ¶ Using the above total as denominator. § Qualified for VL implies that the patient reached the window of VL assessment

In more detailed VL analysis, of 345 participants with an undetectable VL at switch, 217 (63%) maintained undetectable VL at their last measure, 103 (30%) moved from

undetectable to detectable VL but <50 copies/ml, and 25 (7%) moved from an undetectable to detectable VL that was >50 copies/ml at their last measure. On the other hand, of 74 participants with a detectable VL >50 copies/ml at switch, 30 (41%) reached an undetectable VL while 14 (20%) had a VL >50 copies/ml at their last measure (p<0.0001).

Using the outcome of VL>50 copies/ml at the last measurement a uni- and multivariate logistic regression analysis was done. This included 686 participants with complete data and 72 (11%) achieved a VL of >50 copies/ml at a median of 636 days (IQR: 490-777; range: 91-1057) post switch to DTG (Table 3). There were no independent associations between missing follow-up visits during the study period, having had viraemia ≥1000 copies/ml for more than two years, timing of blood taking (first vs. second half of the year), nor with the pre-switch VL (<50 vs 50-1000 copies/ml). There was however a statistically significant association between time on ART and viraemia ≥1000 copies/ml (p=0.0013) and hence the former was left out of the final model. The following factors were significantly associated with not achieving the desired outcome in multi-variate analysis (results are displayed as OR [odds ratios] and 95% CI [confidence intervals]): missing a follow-up visit by more than 90 days post-switch to DTG (OR: 3.2 [CI:1.5-6.8], p=0.003), switching to DTG with a VL of 50-1000 rather than <50 copies/ml (OR 2.0 [CI:1.1-3.9], p=0.04) having the blood test done during July-December (OR 2.0 [CI:1.2-3.4], p=0.011), and having had exposure to viraemia ≥1000 copies/ml for more than two years between first ART start and DTG switch remained associated but less significantly (OR: 1.9 [CI: 0.9-3.7], p=0.07). The power for the sample size was calculated to be 0.65 and estimated to reach 0.8 with a sample size of 963.

Table 3: Multiple logistic regression model for the outcome of a last viral load >50 RNA copies/ml (N=686)

Characteristic	Total	Outcome - Last VL >50 RNA copies/ml	Unadjusted OR and 95% CI	p	Adjusted OR and 95% CI	P
Sex						
Female	334	37 (11)	0.9 (0.5-1.4)	0.62		
Male	352	35 (10)	REF			
Age (years)						
<10	105	13 (12)	REF			
10-<13	206	17 (8)	0.6 (0.3-1.4)	0.24		
13-<16	225	24 (11)	0.8 (0.4-1.7)	0.64		
16 and above	150	18 (12)	1.0 (0.5-2.1)	0.92		
Time on ART						
<5years	71	14 (20)	2.0 (1.0-3.9)	0.04§		
5-10 years	209	14 (7)	0.6 (0.3-1.1)	0.1		
>10 years	406	44 (11)	REF			
Viraemia time >1000 copies/ml pre-DTG						
<0.5 years	290	26 (9)	REF		REF	
0.5-1 year	157	15 (10)	1.1 (0.6-2.1)	0.83	1.1 (0.5-2.1)	0.84
1-2 years	136	14 (10)	1.2 (0.6-2.3)	0.66	1.3 (0.6-2.5)	0.53
>2 years	103	17 (17)	2.0 (1.0-3.9)	0.04	1.9 (0.9-3.7)	0.07
VL pre-DTG switch						
0-------<50	612	58 (9)	REF		REF	
50------1000	74	14 (19)	2.2 (1.2-4.2)	0.014	2.0 (1.1-3.9)	0.04
Late for visit during follow-up (>90 days)						
Yes	45	11 (23)	3.1 (1.5-6.4)	0.003	3.2 (1.5-6.8)	0.003
No	641	61 (10)	REF		REF	
pre-DTG exposure						
ABC	676	68 (10)	0.9 (0.8-1.0)	0.004	0.9 (0.8-1.0)	0.006
d4T	344	40 (10)	1.0 (1.0-1.1)	0.21		
AZT	45	4 (9)	0.8 (0.6-1.2)	0.30		
TDF	382	35 (9)	1.0 (0.8-1.2)	0.87		
EFV	549	60 (11)	1.0 (0.9-1.1)	0.99		
Any PI	434	42 (10)	1.0 (0.9-1.0)	0.29		
Regimen post-DTG		Continue after single drug code				
TDF/3TC/DTG	478	48 (10)	0.9 (0.5-1.4)	0.56		
ABC/3TC/DTG	208	24 (12)	REF			
Timing of VL test during the year						
January-June	328	24 (7)	REF		REF	
July-December	358	48 (13)	2.0 (1.2-3.3)	0.01	2.0 (1.2-3.4)	0.01

ART: antiretroviral treatment, PI: Protease inhibitor, D4T: Stavudine, AZT: Zidovudine, ABC: Abacavir, TDF: Tenofivir, EFV: Efavirenz, , DGT: Dolutegravir, VL: Viral load copies/ml.§ VL suppression defined as <50 RNA copies/ml at last assessment. ¶ N=50 patients did not have a final VL outcome available. § Time on ART was left out of the final model due to its interaction with viraemia time >1000 copies/ml

Discussion

Since 2019 more than 80% of all the children and adolescents currently in care at this large Johannesburg treatment site were switched to DTG. Most of the population switched were in the adolescent age group and the majority were on NNRTI based regimens at the time just before switching. On average, patients that were switched to DTG had more than 10 years ART experience. These patients had been exposed to different drugs pre-DTG, with the longest median exposures being to any PI, ABC and EFV, demonstrating the extensive treatment experience of this paediatric population. Despite this, 90% of patients achieved virological suppression at last VL. The study showed that age, gender, weight and ABC vs TDF in the first on-DTG regimen were not significant factors and had little to no effect on suppression rates. Variables that were significantly associated with poorer last VL outcome included evidence of missed visits, level of VL suppression at switch, period of prior viraemia ≥1000 copies/ml (weaker association) and, interestingly, time of year when blood was drawn.

The strengths of the study were that it was a relatively large cohort. The study period also ensured that patients were followed up for long enough to assess the viral response more effectively, at least over the first 24 months. Although the study occurred at a central academic centre, the cohort included a diverse study population which arguably is representative of the larger South African paediatric population on ART. The limitations and weaknesses were that CD4 count and clinical staging were not considered and this could have potentially been important in those that did not maintain suppression. Our cohort was a routine care cohort and not a research-based cohort which led to some missing outcomes and incomplete information on all the clinical factors assessed. We had limited measures of adherence. Children who had a VL> 1000 copies/ml at switch were not included in

this analysis, and it would be important to understand how these children do after switching. The new 2023 guidelines further extend the use of DTG in children >3kg and don't require a VL prior to switching to a DTG Regimen. This is important because our study showed that viraemia prior to switch had a significant effect on rates of virological suppression, and it would be important to follow up these much younger, less treatment experienced patients to assess if they had a similar risk of not attaining virological suppression (5). Reassuringly, Amuge et al., as part of the ODYSSEY trial, looked at the efficacy of DTG based regimens in children weighing between 3kg and 14kg and showed that DTG was superior when compared to standard regimens of care, with lower rates of virological failure (14).

Overall, our findings are reassuring in that the large majority of patients who switched to DTG when their VL was < 1000 copies/ml, remained virally suppressed as was seen in the clinical trials (ADVANCE and NAMSAL) that prompted the guideline changes (15). However, it must be noted that a switch to DTG did lead to a loss of viral suppression for a small minority of patients. It will be important to track the longer term VL trajectories in patients on DTG. Switching to DTG with a VL of 50-1000 copies/ml occurred in 11% of patients and was unfortunately associated with a higher chance of not reaching <50 copies/ml.

In showing all the past VL data of our patients in Figure 2, by calculating viraemia time and assessing time on past ART drugs we aimed to demonstrate how complex a paediatric population can be in terms of their prior treatment and VL suppression history. This makes application of strict guidelines of switching patients difficult and implies that children and adolescents with a long history of prior ART require close monitoring after switching. Our data show that caution is needed in children who have had prior viraemia, possibly irrespective of timing relative to the switch. Further studies are needed to assess the relevance of timing of prior viraemia and its implication for regimen choices and its relationship to possible underlying resistance mutations. The emergence of a temporary rise in VL in the first months of DTG (Figure 2 – Panel 5) was anecdotally reported by clinicians but cannot be easily explained. This minor blip post-switch was usually less than one log value and was not sustained, and its significance is uncertain. In a study by Frange et al., it was

also noted that VL failure was more common in patients with ART experience pre-DTG switch and this was also for short periods of time as was noted in our study (8).

Our only measure of adherence in this study was a proxy measure, namely visit frequency. Poor adherence is likely to have played an important role in poorer outcomes and our study shows that for our population, missed visits were the strongest predictor of poor virological suppression. With such a rough adherence measure, a lot of poor adherence may have been missed. The timing of VL testing was considered due to the nature of the South African school year (January-December) and the potential that the end of the year may be associated with higher stress levels and more pressure at school but we cannot confirm whether this was ultimately the reason for poorer VL outcomes if the VL was measured in the latter half of the year. The occurrence of missed visits and the timing of blood taking were not associated statistically.

In a paper published by a Nigerian team at the University of Port Harcourt, they saw similar results to our study. However, they found that adolescents had worse outcomes when compared to children < 10 years of age, whereas we saw similar outcomes in adolescents and younger children. The patients with longer ART history had better outcomes in their study (7). Similar to our study population, pre-DTG regimens included NNRTI's and PI'S. The authors also thought that poor virological suppression rates were most likely linked to poor adherence. Their study showed that DTG was efficacious in the treatment of eligible children and adolescents and showed good virological suppression rates (6, 16). This is important as the study setting and population of the Nigerian study are similar to ours, being a low- to middle-income country with similar resources and population dynamics.

In a systematic review by Townsend et al. that looked at various studies on the virologic response of patients, which included children and adolescents up to the age of 19, post-DTG switch, they found that at 12 months post switch >70% participants were virally suppressed compared to 85% of participants in our study (17).

Another study showing similar results, was a monocentric retrospective study done in the French pediatric Necker Hospital that included paediatric patients who were

divided into three groups according to age at the time of DTG initiation: 5-11, 12-17 and 18-25 years old. These patients were switched to DTG between 2014 and 2020 and this study found lack of VL suppression in 32.1% of participants that was linked to prior ART experience. Despite prior VL suppression, some participants had periods of loss of suppression with subsequent recovery that was due to successfully addressing adherence issues. In this study, VL failure was more common in patients who had a baseline VL ≥50 (18). This is similar to what was found in our study, with the vast majority (79.8%) of patients in all the categories (87.9%, 72,4% and 84.0% respectively) of their study showing good suppression.

Poor adherence can contribute to lack of virological suppression and the timing of the study coincided with the COVID pandemic when the country was under hard lockdown and where patients missed some of their visits and didn't always have access to health care, medication and lab facilities to have VL done. Dorward et al. conducted an interrupted time series study in KZN primary health care centres and found that despite the hard lockdown due to the COVID pandemic, patients still managed to receive treatment despite issues that arose such as suboptimal HIV testing, monitoring and initiation of treatment (19).

Conclusion:

It is encouraging that this study showed that DTG allowed for the maintenance of suppression in our ART-experienced children and adolescents and our results are generally in line with prior clinical trials. Age, gender, and weight had no bearing on virological suppression and neither did the switch regimen (ABC or TDF containing). It is important that the effects of a switch to a DTG-based regimen be monitored closely in the paediatric population as these are individuals who have a lifetime of ART ahead of them. Further research is needed to understand the implications on long term outcomes of prior regimens and exposure to viraemia in children and adolescents and how to best design guidelines to take these aspects into account. Our study has also only looked at first line switches, and outcomes on patients undergoing second- or third-line switches are equally important.

Competing interests

There were no competing interests

Author's contributions

TM was involved in all phases of the study and drafted the manuscript, KT assisted with data collection, data analysis and revision of the manuscript was conducted by TM, KT, GS, NV, TF. All the author's approved the final version of the paper.

Acknowledgements

We appreciate the assistance of the data team at the study site. The study would not have been possible without the dedicated families, children and adolescents of the clinic. We gratefully acknowledge the National and Gauteng Provincial Department of Health for their support and funding of HIV treatment. 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).

Data availability statement

Complete data for this study cannot be made available publicly but the corresponding author may be contacted with reasonable requests to be processed on a case by case basis.

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481 **Ethics clearance**

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr T Mafora

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210563

NAME: (Principal Investigator)	Dr T Mafora
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*Virological response in children and adolescents switching to Dolutegravir-based regimens in Johannesburg, South Africa - a longitudinal cohort study*
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M170778
SUPERVISOR:	Professor K-G Technau
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/06/03

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **May** and therefore reports and re-certification will be due in the month of **May** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

24/06/2021
Date

482 **Plagiarism Certificate**

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ORIGINALITY REPORT

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*These authors have contributed equally to the work.

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JS: author1@email.com
MC : author2@email.com
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Keywords:

Word count:
Abstract: xx/350
Main text: xx/3500

Abstract

Introduction: Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso carinae ad supremos usque carbasos aedificet onerariam navem.

Methods: Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso carinae ad supremos usque carbasos aedificet onerariam navem omnibusque armamentis instructam mari committat.

Results: Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso carinae ad supremos usque carbasos aedificet onerariam navem omnibusque armamentis instructam mari committat.

Conclusions: Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso.

Clinical Trial Number: xxxx

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Introduction

Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis [1]. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso carinae ad supremos usque carbasos aedificet onerariam navem omnibusque armamentis instructam mari committat [2].

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Methods

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Subheading

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Subheading

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Results

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Table 1. Title of Table

Variable	Number
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Characteristic 2	10
Characteristic 3	100

Characteristic 4	1000

Legend of table: *explanation here

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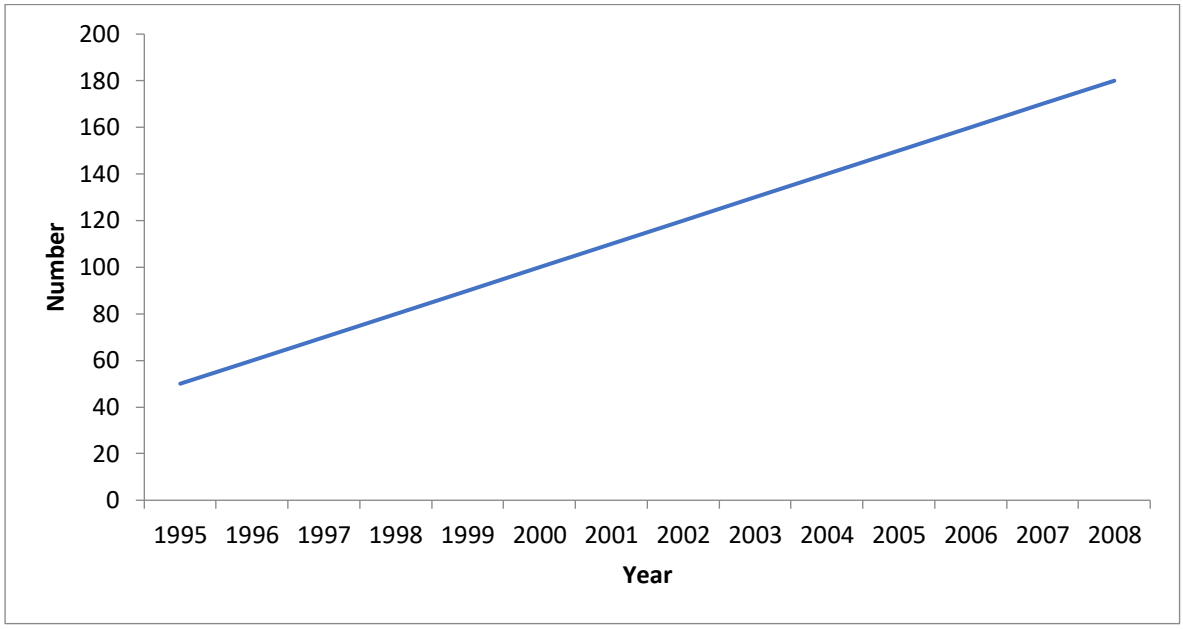

Figure 1. Title of Figure. Brief description of figure here.

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Discussion

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Conclusions

Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso.

Word limit: 3500 words

Competing interests [Mandatory]

Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso.

Authors' contributions [Mandatory]

Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso.

Author information [Optional]

Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso.

Acknowledgements [Mandatory]

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Funding [Optional]:

Disclaimer [Optional]

Data Availability Statement [Mandatory]

Supporting Information [Optional]

Supporting Information file 1: Title of Supporting Information file
Information on file format. Brief description of file content.

List of abbreviations [Optional]

Cyprum itidem insulam procul a continenti discretam et portuosam inter municipia crebra urbes duae faciunt claram Salamis et Paphus, altera Iovis delubris altera Veneris templo insignis. tanta autem tamque multiplici fertilitate abundat rerum omnium eadem Cyprus ut nullius externi indigens adminiculi indigenis viribus a fundamento ipso.

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Appendix: Research protocol

Title:

Virological response in children and adolescents switching to dolutegravir based regimens in Johannesburg, South Africa – A Longitudinal Cohort Study

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Abstract (Summary)

Dolutegravir (DTG) is a new drug that has been rolled out as part of the antiretroviral treatment (ART) regimens in most countries, South Africa being no exception, introducing the drug into first- and second-line options in November 2019. The Department of Health has encouraged widespread roll-out, although in phases, facilities have had to report compliance with increasing their numbers of patients on DTG. Not only is it part of adult regimens but also paediatric regimens. Some clinicians have noted patients post DTG roll-out to have increases/blips in their viral loads. There is not much information published on (DTG) since large-scale switching in South African paediatric or adolescent populations. This study aims to investigate the viral loads of patients post switching to or starting DTG-based regimens to assess the effects and implications the switch has had. We intend on looking at the population that has switched to DTG in the 15 months post implementation of the 2019 ART guidelines, to determine the viral load responses in these patients by looking at their viral loads at 6- and 12-months post switching and also identifying underlying factors in those patients that have not achieved viral load suppression. Data will be extracted and analysed from an existing prospective database collected at Empilweni clinic.

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1. Introduction

HIV has become a significant problem in Southern Africa. The World Health Organization (WHO) has estimated that there are approximately 7.7 million people currently living with HIV in South Africa making up 20.2% of the people living with HIV globally (1). The paediatric population is no exception with South Africa being home to about 340 000 children (18.8%) of children living with HIV globally (1).

The use of antiretroviral treatment (ART) has decreased the progression of HIV in those infected by inhibiting viral replication and reconstituting the immune system of patients, therefore decreasing morbidity and mortality. South Africa currently has the largest ART programme in the world since its large-scale public introduction in 2004, with an estimated 3.1 million people receiving ART. Even with the largest ART programme there are still a number of people not on treatmentestimated at 2 269 000 people in 2019 .

The treatment of HIV is in itself challenging, more so in the paediatric population. There have been major gains made in the treatment of HIV in children allowing for a decline in the number of new HIV infections and deaths associated with HIV. Despite the gains made there are still a number of challenges, these include social and clinical factors which in turn affect children's adherence to treatment. The challenges faced in treating the paediatric population become barriers that prevent the achievement of adherence. These include: stigma, lack of paediatric friendly formulations, palatability of available formulations, pill burden, complex regimens and psychosocial factors (2).

Guidelines for the treatment of HIV continue to list two nucleoside reverse transcriptase inhibitors (NRTIs) as the backbone of an effective antiretroviral regimen with the addition of a drug from another class, either a non-nucleoside reverse transcriptase, a protease inhibitor or now, since the introduction of dolutegravir (DTG), an integrase inhibitor(3). With advances in medicine and the acquisition of resistance by the virus, new drugs have had to be used. DTG is one such drug that has since 2019 been approved for use in the South African population and is now part of the WHO and South African guidelines. On 12 June 2019 the US Food and Drug administration (FDA) approved DTG tablets and oral suspension for use in infants and children. Its use is approved for first, second- and third-line regimens. Before 2019, DTG was used only in third line regimens within the public sector.

DTG is a relatively new drug now used at large scale and there is therefore a paucity in the amount of data available, particularly from large routine cohorts. Not much research is available especially in paediatric populations where there are smaller numbers and research is often neglected. It is therefore imperative to analyse the post-marketing/post-roll-out outcome and ramification of DTG use in South Africa(SA) both as a new first line agent and post switching.

2. Literature review

2.1 Dolutegravir General studies

DTG is a second-generation integrase strand transfer inhibitor (INSTI) which acts by inhibiting the HIV-1 integrase enzyme, a very important enzyme for HIV that transfers HIV DNA material into the human host chromosomes (4). Therefore, DTG prevents the virus from replicating. DTG has shown advantageous pharmacokinetic and

pharmacodynamic properties making it an excellent drug to use, even better than the first-generation INSTI, raltegravir (5) (3). These factors include: good genetic barrier to resistance, minimal side effects and drug-to-drug interactions. It is also an efficacious drug as evidenced by the SAILING and ADVANCE trials.

The use of DTG has been approved in children more than 10 years old and/or weighing more than 20kg. In the SAILING trial DTG was shown to be efficacious when used as part of the second line regimen, no resistance mutations against INSTIs were found (3, 6). In the ADVANCE trial DTG was compared with efavirenz, and it was shown to be just as effective as efavirenz in suppressing HIV, it was cheaper and had fewer side effects (3).

2.2 Paediatric studies

Treatment of HIV infection in children and adolescents is challenging due to the long duration of therapy and risk of more difficult adherence(2). Recently DTG has been approved for the use in adolescents with HIV, but evidence in clinical practice is limited. The IMPAACT P1093 study is a phase 1/2 open-label dose-finding study that is evaluating DTG (7). Previously reported DTG dosing met the target concentrations required in children aged 4 weeks to <6 months but was noted to need dose modification in children 6 months to <6 years. The IMPAACT P1093 team showed that the use of DTG achieved a result indicating safety and efficacy of higher dosing of DTG for children in the older age group mentioned above. In a retrospective study done in France safety and efficacy of DTG was found to be good in children and adolescents between the ages of five and 18 and amongst those 18 years and older (7) (8). In the above study, data from 109 participants was analysed, participants started DTG-based ART between January 2014 and December 2017.The endpoint

was the relative number of participants with viral load <50 copies/mL at <3 months after starting DTG, and the number of those with detectable viral load, and the proportion of all participants of those who remained suppressed i.e. low viral load, until the last follow-up visit (6). In another study published in the Lancet HIV , paediatric patients from Uganda and Zimbabwe were noted to have adequate viral load suppression and efficacy, on the adult dosages of DTG (8). The results from the abovementioned literature points to an effective drug and are also important for informing clinicians on making recommendations.

The South African guidelines state that for preterm neonates and neonates with birth weight < 2.5 kg, or neonates with comorbidities such as severe anaemia, further advice needs to be sort from an expert and for infants ≥ 4 weeks of age, ≥ 42 weeks gestational age, but weighing less than 3 kg, an expert should be consulted as above to determine the most appropriate regimen as this can be difficult due to the physiology of a neonate(9). For children not falling into the above categories the standard paediatric regimens can be used. Current paediatric regimens include the regimens listed below:

- Abacavir(ABC)/Lamivudine(3TC)/Lopinavir/ritonavir(LPV/r)
- ABC/3TC/Efavirenz)EFV
- Zidovudine(AZT)/3TC/Nevirapine(NVP)

2.3 Switching guidelines

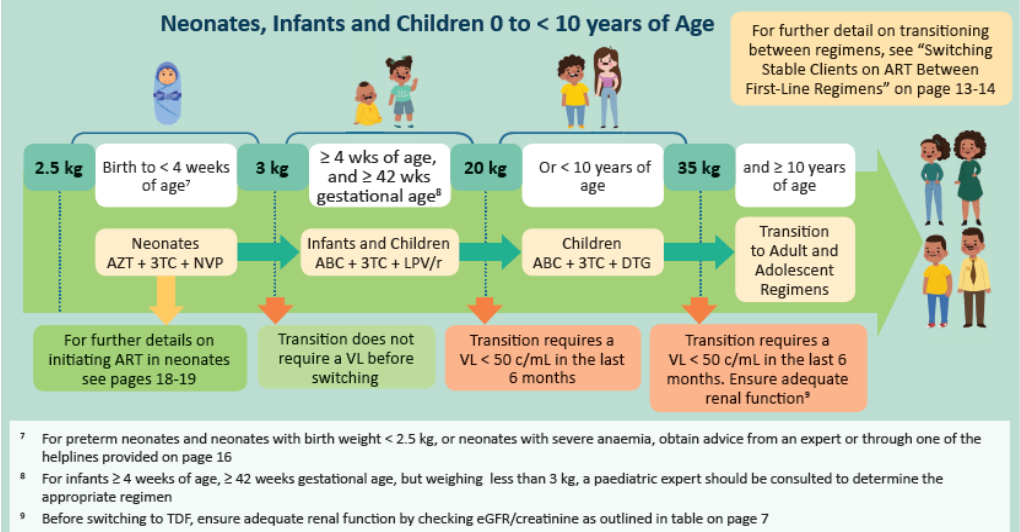

Figure 1: Paediatric antiretroviral treatment (ART) guidelines(9)

Children can be switched to DTG containing regimens once they are stable on their current regimen and weighing more than 20kg. Once they are more than 35kg and ten years of age or older, with normal renal function, they can then be switched to a fixed dose combination that includes TDF, which is also the current adult first line regimen (9). The transition to a DTG based regimen requires a viral load of <50 six months prior to the switch, which indicates viral suppression on the current regimen. According to the guidelines, only within first-line regimens should there be a switch from LPV/r to DTG. This is important because both ABC and 3TC may have limited activity in a second-line regimen consisting of ABC, 3TC and LPV/r (9). DTG should not be used without at least one active NRTI. When failing first line regimen and DTG is considered as second line, expert advice should be sought to ensure that there is active NRTI.

WHO recommends the use of DTG with a NRTI for all patients living with HIV, initiating ART or already on a non-DTG regimen that is failing i.e. one not resulting in a suppressed viral load (10) . According to the WHO guidelines DTG is approved for

use in children older than 6years and weighing more than 15kg. The current available formulation in South Africa is available for children weighing more than 20kg who can take the 50mg tablet.

It is clear from Figure 1 that children and adolescents in South Africa may have had a range of regimen exposures by the time they are switched to DTG. Over the past two decades there have been multiple guideline changes. Some resistances may be masked and while a person is on first line treatment and virally suppressed, they may yet have underlying resistance. The Earnest trial compared the efficacy and safety of three second line regimens (11), this was important as patients changing to second line regimens may have resistant mutations that can affect multiple drugs in the same class, which will in turn affect the backbone of future regimens as there might not be an active drug to use. The regimens in the study included Protease inhibitors (PI) with NRTI's, PI's and Raltegravir an INSTI like DTG, and PI monotherapy. It was found that PI's and NRTI were as effective as PI's and Raltegravir despite patients being on previous regimens they managed to achieve viral suppression (11). Therefore, a switch to DTG may occur after numerous past ART exposures, even if they were all first-line. Proving that these past exposures and possible masked resistance will still enable successful suppression after the switch is not well known.

2.4 Monitoring guidelines

The end goal in the use of ART is to improve immune function and thereby decrease the risk of opportunistic infections. ART achieves this by decreasing the viral replication rate and thus causing viral suppression. Successful treatment would be

evidenced by an increase in the number of CD4 T cells and a viral load that is on a downward trend, ideally supressed to less than 50 copies per ml. Also of significance is an improvement in the general wellbeing of the patient.

To ensure that ART being administered is effective, patients require monitoring. HIV viral load (VL) is a useful tool in the initiation and monitoring of ART treatment. The HIV VL is the amount of virus in an infected individual's blood, it is the number of viral particles in each millilitre of blood (12), the quantity of the viral genetic material (RNA) in the blood. It is an effective tool for the detection of virological failure as well as appropriate treatment response. VL testing is the gold standard for HIV treatment monitoring (12). Regularly timed VL tests are the most accurate way of establishing whether antiretroviral therapy is working to suppress replication of the virus. The cVL tests/assays currently in use in our laboratories are the Roche Cobas 8800 - main platform, Roche Cobas Ampliprep/Taqman – low volume samples which require more amplification, Abbott M2000 – backup platform, rarely used for routine work. These assays detect viral material (RNA) and measure how many copies are present in a millilitre of blood at a certain time. WHO recommends VL monitoring six and 12 months after initiating antiretroviral therapy and annually thereafter for people who are stable with a suppressed VL (13). The CD4+ T cell count also remains an important parameter in monitoring ART in HIV-infected individuals. A decreasing CD4+ T cell count is an important predictor of disease progression.

HIV Clinicians Society 2017 Adult ART guidelines recommend the following: VL monitoring should be done at baseline, at 3 months, at 6 months, and then 6 monthly (14). The initial VL test is the baseline and the test following indicate how a patient is

responding to treatment. The HIV VL provides a good indication of how well ART is working and it indicates what the immune and clinical response will be. If the VL is undetectable for >12 months, then monitoring frequency can be adjusted to annual (14). Adherence counselling should start if a VL is greater than 50 ml/copies and one should repeat the VL two to three months later. The National Department of Health (NDoH) 2019 ART guidelines recommend: VL monitoring at 6 months, and then annually. If the VL is undetectable at 12 months, then annual checks are sufficient. A viral load of more than 1000 calls for urgent assessment of the cause of an elevated VL (9) (14) (15).

3 Aims and Objectives

Problem Statement:

The treatment of HIV in the paediatric population is a challenge with regard to both the unique paediatric related adherence challenges as well as the unique ART regimens children are exposed to during their disease course. With new medications and improved formulations some headway has been made. Unlike in adult patients, there is a relative lack of published data on how efficacious these formulations/regimens are at suppressing viral load. Changes to first line ART have implications on thousands of children and adolescents in SA and changes in national guidelines require carefully monitoring post introduction. This study aims to contribute to this purpose.

Aim

To analyse the virologic response in patients, either starting DTG based ART or previously suppressed and switching to a DTG based regimen, in order to assess

the post-roll-out effectiveness of DTG-based regimens in a South African paediatric and adolescent population.

Objective 1

To describe the population that has switched to DTG-based regimens in the first 15 months of implementation of the 2019 ART guidelines in terms of

a) pre-switch characteristics: gender, age at ART start, age at DTG switch, time on ART, characteristics at ART start (anthropometric, immunological [CD4 count category] and clinical stage) and past virological history (episodes of non-suppression i.e. viral load>50 and their duration)

b) switch characteristics: numbers switched overall and numbers stratified by regimen pre-switch, age and weight bands at switch (20-35kg; 10 years and >35kg) and compliance with virological switching requirements (VL<50 copies/ml).

Objective 2

To determine viral response in patients that have switched to DTG by describing

a) proportion of switched patients with available VL result at six- and twelve-months post-switching or initiating

b) proportion of VL results at six- and twelve-months post-switch or initiation stratified by result (<50; 50-1000; >1000 copies/ml)

Objective 3

To investigate the associations between inadequate response to DTG switch (loss of suppression <50copies/ml by six or twelve months) and underlying factors described in Objective 1.

4. Methods

4.1 Study design

The study is a secondary data analysis of an existing prospective observational longitudinal cohort.

4.2 Setting and population

The study population will be drawn from patients living with HIV seen at the Empilweni Clinic at Rahima Moosa Mother and Child Hospital in Johannesburg. Rahima Moosa Mother and Child Hospital is a regional hospital that offers services ranging from primary to tertiary level care, the Empilweni Clinic which has been in operation since the late 1990's currently serves approximately 1500 active patients.

Participants and Inclusion/Exclusion Criteria

Inclusion criteria: Paediatric patients living with HIV attending Empilweni clinic who have started on or switched to DTG as part of first line treatment after November 2019. At the time of writing there are approximately 220 children who switched to ABC/3TC/DTG and at least 250 adolescents who have switched to TLD, the above information is from the clinics' monthly DTG report (February 2021).

Exclusion criteria: Patients or caregivers who have refused data sharing consent.

4.3 Study Procedures

When patients are seen, information is captured on paper (Appendix 1). From there it is captured electronically. Data is routinely captured into a REDCap database hosted at the University of the Witwatersrand (16). Data will be de-identified and extracted from the database at Empilweni Clinic, the data will be reviewed and analysed with emphasis on the viral loads done on the patients post switching to DTG based regimens at six months primarily and at twelve months.

Table 1: List of variables, derived values and proposed categorisations

Variable:	Derived values	Categorisations
Date of birth	Age	
Gender		Male/Female
Date of ART start	Duration on ART, Age at ART start	
Date of initiation on/switching to DTG	Duration on ART at time of DTG start, Age at DTG start	<10/10years and older at DTG start Age <10 or older than 10
Previous drug start and stop dates	Past ART regimens	PI/NNRTI based first line regimens
VL dates since ART start	Time on ART at VL, time on DTG at VL	
VL values for each date above		<50/50-1000/>1000
CD4 dates pre-ART and post ART	Time on ART at CD4, time on DTG at CD4	
CD4 values for each date above		<200/200-350/351-500/>500 (if Age at test > 5years) <15%/15-25%/25-35%/>35% (if age at test < 5years)
Weight at ART start and at DTG start		<20/20-35kg/>35kgs at ART start

DTG: dolutegravir; ART: anti-retroviral therapy

4.4 Data collection and management

The collected data will be stored on an external hard drive, that will be password protected, in a separate folder belonging and only available to the investigator. The

data will be analysed for the necessary inclusion criteria and any noted discrepancies or uncertainties will be correlated to a hardcopy of the patient's file. A final locked dataset will be created once the data has been cleaned and checked.

4.5 Statistical analysis

Objective 1:

Data will be described using descriptive statistics: frequencies and proportions for categorical data, means and standard deviations for normally distributed continuous variables that are not normally distributed.

The following tests will be used: Chi-square or Fisher exact (smaller numbers) for comparing groups of categorical variables and Anova (more than 2 groups) or Student's t-test (for two groups).

Objective 2:

Analysing the descriptive stats and defining VL testing windows in order to group patients based on their six and 12 month VL, either as maintaining suppression i.e., VL<50 or failing to maintain suppression if VL is >50. The six month viral load will be used as the primary endpoint for statistical analysis. VL testing windows will be defined as:

Within 4-8 months after DTG switch = six months VL

Within 9-15 months after DTG switch = 12 months VL

If more than one VL value is available in the window, we would then choose the one closest to 6 months and 12 months.

Objective 3

Create groups based outcome: at 6 months (12 months): suppressed/not suppressed (defined as <50 maintained vs not in line with the current NDoH guidelines)

1) Univariate analysis: individual variables vs the outcome variable
2) Multivariate – logistic regression model for confounding variables,

The endpoint of this study is to determine the effect of the switch to DTG based regimen in the paediatric population, whether there is a correlation between the viral load blips, which is a transient increase in the VL above 50 copies/ml for a short period and then returns to VL suppression, and the change to a Dolutegravir, can this be extrapolated further as a marker of possible virologic failure? A statistics application such as Statistica will we be used to consolidate and analyse all the collected data.

4.6 Ethical considerations

All parents/caregivers are invited to sign prospective data sharing consent (Appendix 2) and they can then make the decision to opt out. Adolescents are re-consented when they are 18. Confidentiality will be maintained at all times and patient data will be anonymous. No additional risk for patients is anticipated as de-identified data will be used. This protocol will be submitted for approval to the Human Research Ethics Committee at the University of Witwatersrand and will fall as sub-study under an existing approved protocol (M170778 – Appendix 3, with permission from the Principal Investigator – Appendix 4). Permission to conduct the study will be requested from the head of Empilweni HIV clinic and from the CEO of Rahima Moosa Mother and Child Hospital as well as from the electronic gatekeeper.

The purpose of the study and intention with outputs include: MMed degree completion, publication in a relevant journal (e.g. Pediatric Infectious Diseases Journal), presentation of data and results at conferences

4.7 Limitations

- There may be missing data as some patients may not have all the information because the data needs to be captured by someone and there may be some errors in the process.
- Due to the nature of the disease, multiple individual factors, and since it is not a prospective trial, not all the VLs will have be done at the required time intervals.
- To mitigate these, we can check the individual files to check what the reason behind the viral load being done earlier or later is and make sure it is within a certain range instead of a fixed time, and exclude those that are not eligible for the study. The team at Empilweni can also be contacted if there are any queries regarding discrepancies in the data.
- Patients may have adherence issues, i.e. other reasons for VL to not be suppressed. There are no simple adherence measures, a potential proxy measure would be the frequency of visits to clinic.

4.8 Budget

This will be a self-funded project, costs that will be incurred include those of printing, traveling costs for meetings with the supervisor as well as time dedicated to analysis

and data cleaning. An estimated amount of R1500.00 will be required for the above costs

4.9 Timeline

	July 2020	Aug	Sept	Oct	Nov	Dec	Jan 2021	Feb
Literature Review								
Preparing protocol								
Protocol writeup/assessment								
	Mar 2021	Apr	May	Jun	Jul	Aug	Sep	Oct
Ethics approval								
Data collection								
Data analysis								
Write up								

5 REFERENCES

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Appendix 1

RMMCH General Empilweni Clinic - Flow Chart Version March 2019

Name:_____ **Hosp No:**_____

Date								
Age								
Weight (kg)								
Height (cm)								
BMI ≥5years								
MUAC (cm) <5years								
Head Circ <2 years								
BP								
Urine Dipstix								
Co-Trimoxazole								
MVTs								
INH								
TB Meds:								
HAART:								
Other:								
Bloods: CD4 count								
CD4 %								
POC Viral Load								
Viral Load								
WBC								
Hb								
MCV								
PLTs								
RDW								
Neutrophils (Abs)								
Creatinine								
TB investigations								
Cholesterol / Trigs								
Other								
Lab stickers (Barcodes)								
TCB								

Appendix 2:

RMMCH General Empilweni Clinic - Flow Chart Version March 2019

Name:_____ **Hosp No:**_____

Date								
Age								
Weight (kg)								
Height (cm)								
BMI ≥5years								
MUAC (cm) <5years								
Head Circ <2 years								
BP								
Urine Dipstix								
Co-Trimoxazole								
MVTs								
INH								
TB Meds:								
HAART:								
Other:								
Bloods: CD4 count								
CD4 %								
POC Viral Load								
Viral Load								
WBC								
Hb								
MCV								
PLTs								
RDW								
Neutrophils (Abs)								
Creatinine								
TB investigations								
Cholesterol / Trigs								
Other								
Lab stickers (Barcodes)								
TCB								

Appendix 3:

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

16/07/2020

Professor K-G Technau
School of Clinical Medicine
Department of Paediatrics and Child Health
Empilweni Services and Research Unit
Rahima Moosa Mother and Child Hospital

Sent by e-mail to: Karl-Gunther.Technau@wits.ac.za

Dear Professor Technau

Re: **Protocol Ref No:** M170778
Grant Number: U01AI069924
Protocol Title: *Cohort study of HIV-infected and exposed children receiving care at Rahima Moosa Mother and Child Hospital, supported by Empilweni Services and Research Unit (IeDEA-SA)*
Principal Investigator: Professor K-G Technau (Overall PI's Professors Egger and Davies)

Thank you for your letter of 27/06/2020.

I confirm that the annual progress report provided in your letter is satisfactory and therefore that Clearance Certificate No. M170778 remains valid until 4 September 2022, subject to continued satisfactory progress.

Thank you for keeping us informed.

Yours Sincerely

.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

.....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Appendix 4:

Empilweni Services and Research Unit
Rahima Moosa Mother and Child Hospital, JHB

South Africa (Private Bag X20 Newclare 2112) • Tel: +27(0)11 470 9421 Cell: +27 (0)82 687 3633 Fax: +27(0)86 553 5046 •
E-mail:karltechnau@gmail.com

16th February 2021

Dear Dr Mafora

Re: Proposed MMed Project titled:

Virological response in children and adolescents switching to dolutegravir based regimens at Rahima Moosa Hospital – A Longitudinal Cohort Study.

As PI of the study: "Cohort Study of HIV-infected and exposed Children receiving care at Rahima Moosa Mother and Child Hospital supported by the Empilweni Services and Research Unit and participation in the International epidemiological Databases to Evaluate AIDS (IeDEA) Collaboration" (M170778) I have no objection for you to use de-identified data gathered during the project to answer your protocol objectives and am happy to support you in that venture and make the required data available.

Yours sincerely

Karl Technau, MBBCh, Dip HIV Man, DCH, MSc (Med), PhD
Associate Professor, Deputy Director Empilweni Services and Research Unit (ESRU)
Department of Paediatrics and Child Health, University of The Witwatersrand (Wits)
Rahima Moosa Mother and Child Hospital

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GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries : Karen Marshall
Tel : 011 470 9284
Email : Karen.Marshall@wits.ac.za

TITLE OF RESEARCH PROJECT:
"VIROLOGICAL RESPONSE IN CHILDREN AND ADOLESCENTS SWITCHING TO DOLUTEGRAVIR BASED REGIMENS IN JOHANNESBURG, SOUTH AFRICA – A LONGITUDINAL COHORT STUDY

NAME OF SUPERVISOR:
Professor Karl-Gunter Technau

NAME OF RESEARCHER:
Dr Tshiamo Mafora
Department of Paediatrics and Child Health
University of the Witwatersrand

NHRD REF NO: GP_202105_044

Dear Dr Mafora,

Permission is granted for you to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail.

Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

You are strongly advised to keep a signed copy of the declaration form to ensure that the terms of this agreement are always complied with.

Yours sincerely,

DR FREW BENSON
SENIOR CLINICAL EXECUTIVE
2021:06:10

ADDRESS: Cnr FUEL & OUDSTHOORN STREET CORONATIONVILLE 2093 / PRIVATE BAG X20 NEWCLARE 2112 JHB