Journal of the International Association of Providers of AIDS Care
Volume 21: 1-12

DOI: 10.1177/23259582221109613
journals.sagepub.com/home/jia
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Adherence, Effectiveness and Safety of Dolutegravir Based Antiretroviral Regimens among HIV Infected Children and Adolescents in Tanzania

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Abstract

Objectives: This study aimed at assessing adherence, effectiveness, and safety of DTG-based HAART regimens among HIV-infected children and adolescents in Tanzania. **Methods:** This was a single-center prospective cohort study, conducted at the pediatric HIV Clinic in Mbeya, Tanzania. A binary logistic regression model was used to determine predictors of undetectable viral load at week 24. The results were significant when P-value was <0.05. **Results:** A total of 200 patients were enrolled with the majority (85.5%) being treatment experienced. High adherence levels (71%) were observed using the pharmacy refill method. At week 24, the overall proportion of patients with undetectable viral load was 70.2%. The predictors of undetectable viral load were age, World Health Organization (WHO) clinical stage, baseline VL and adherence to pharmacy refill. **Conclusion:** The majority of patients attained undetectable viral load 6 months after using DTG based regimen. DTG-based regimens were generally safe with few ADEs reported.

Keywords

HIV/AIDs, Children, Adolescents, Effectiveness, Safety, Adherence, Dolutegravir

Date received: 2 May 2022; revised: 31 May 2022; accepted: 4 June 2022.

Introduction

Sub-Saharan Africa (SSA) accounts for approximately 89% and 88% of children and adolescents living with HIV worldwide.[1] The toll of mortality due to acquired immunodeficiency syndrome (AIDS) is also significant among children living with HIV (CLHIV). For instance, in 2018 children <20 years contributed 15% out of the estimated 770,000-1,500,000 AIDS-related deaths globally.[1] Tanzania mainland has an estimated prevalence of 4.7%, with 1.6 million people living with HIV (PLHIV).[2]

Tanzania has made good progress towards attaining the 90-90-90 global targets whereby so far, 60.6% of PLHIV are aware of their HIV-positive status, 93.6% of adults who are aware of their HIV positive status are on antiretroviral therapy (ART), and 87.0% of adults who are on highly active antiretroviral therapy (HAART) have suppressed viral load (VL).[3] Like other low- and middle-income countries (LMICs), Tanzania recently rolled out Dolutegravir (DTG) HAART-based regimen as per WHO recommendations.[4] DTG is a new third-generation integrase single strand inhibitor (INSTI) ARV drug which is replacing non-nucleoside reverse transcriptase inhibitors (NNRTIs) from the HAART combination.[5] Currently, DTG combined with two nucleoside/nucleotide reverse-transcriptase inhibitors (NRTI) backbone is recommended as the preferred first-line HAART regimen for PLHIV.[6]

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The change towards DTG-based HAART is based on several reasons: once-daily dose (to improve adherence), tolerability, non-inferior or slightly higher efficacy, few drug-drug interactions, and high barrier to resistance compared to existing NNRTIs based regimens.[7] However, several questions remain about the rollout of DTG in LMICs, especially in children and adolescents where the variations in pharmacogenetics, nutritional status, and other socio-demographic characteristics may significantly affect the effectiveness and safety of the regimen.[8] It was previously noted in one DTG study that the virological failure was high among patients born in SSA compared to those born in other countries.[9] Moreover, children and adolescents living with HIV have lower rates of viral suppression, and higher rates of mortality.[10,11] Therefore, this study aimed at determining the adherence, effectiveness, and safety of DTG based antiretroviral regimens in children and adolescents.

Method

Study Design

This was a prospective cohort study conducted from September 2020 – September 2021 whereby participants were followed up for 1 year.

Study Setting

The study site was the HIV Care and Treatment Clinic (CTC) operated by Baylor College of Medicine Children's Foundation at Mbeya region in Southern Tanzania. Baylor-Tanzania is a patient-centered, pediatric HIV prevention and treatment program currently providing direct care to more than 6224 children.[12]

Study Population

HIV-infected children and adolescents up to 19 years were enrolled.

Inclusion Criteria

The study recruited children and adolescents weighing ≥20kg and INSTI naïve.

Exclusion Criteria

Children and adolescents with co-morbidities like diabetes mellitus, tuberculosis (TB), liver disease, renal disease, and malaria were excluded. Patients taking medicines that are likely to interact with DTG, such as herbal supplements, antacids, and ferrous sulfate, were excluded.

Sample Size and Sampling Technique

The sample size was calculated based on the sample size calculation for the cohort study whereby p = proportion of patients (84%) who achieved viral load <50 copies/mL at week 24 from the previous study.[13] Therefore, 200 patients were enrolled.

Data Collection

The case report form (CRF) was used to record patients' socio-demographics, adherence, effectiveness, and safety data of DTG-based therapy. The developed CRF was pre-tested to ensure that the contents were relevant to the study objectives. Pre-testing involved 20 patients (children and adolescents) attending CTC at Mbeya Zonal Referral Hospital. The information was collected from the CTC patient database to reduce recall bias and through direct interviews with the patients or parents/ guardians.

Assessment of Patient`s Adherence to DTG-Based Therapy

Adherence was assessed using self-reporting and pharmacy refill methods. Parents/guardians responded on behalf of children under 10 years, while those with 10 years or more responded directly under the parent/guardian supervision. Four questions were used for assessing self-reporting adherence; the answer was either yes or no. Grading was based on the number of questions answered as yes or no; when a participant responded no to all questions, it is marked as having high adherence, yes to 1 question as moderate adherence, yes to two or more as low adherence.[14] Pharmacy refill adherence was monitored by calculating refill adherence % = (number of days for the pills dispensed previously - delay in days for next pickup) / number days for the pills dispensed previously) * 100. The patient was considered to have good adherence if he/she had a refill ≥85% and poor adherence if he/she had a refill <85%.[15] The pharmacy refill records were collected at three months intervals for the period of one year. The overall % of adherence was obtained by calculating the average % from all the recorded visits.

Assessment of the Effectiveness of DTG-Based Therapy in Patients

The CD4 + cell counts and viral load data were obtained from the patients' laboratory data. The viral load was measured using the Abbott Real-Time HIV-1 (Abbott Molecular Diagnostics, Wiesbaden, Germany) with a minimum detection level of <50copies/ml. These data were collected at baseline, 6 months, and 1 year after initiation of the DTG-based HAART regimen.

Assessment of the Safety of DTG-Based Therapy in Patients

Safety was monitored based on the incidence and severity of adverse drug events (ADEs) and toxicity based on the abnormal range of laboratory tests and spontaneous reporting. The laboratory tests were the complete blood count (CBC), Alanine

aminotransferase (ALAT) for liver injury test, and serum creatinine for renal function test.

Data Analysis

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 23 (SPSS Inc, Chicago, IL) software. Continuous variables were log-transformed before analysis. Descriptive statistics was used to summarize all clinical and laboratory results. Continuous variables were summarized using mean and standard deviation (±SD) and categorical variables by frequencies and percentages. The primary outcome was the proportion of patients who achieved undetectable viral load <50copies/ml at week 24. Secondary outcomes were the proportion of patients who maintained undetectable viral load at week 48, the mean change in CD4 + cell counts, and viral load from baseline to week 24. Safety outcomes included the proportion of patients who reported ADEs after using DTG based HAART regimens and patients who had laboratory parameters out of range at week 24. The predictors of viral load <50copies/ml at week 24 were determined using a binary logistic regression model. The results were statistically significant when the p-value was <0.05. Patients with missing outcome variable were excluded in the multivariable analysis.

Ethical Consideration

This study was approved by the Muhimbili University of Health and Allied Sciences (MUHAS) Research Ethics Committee (MUHAS-REC) (Approval Ref. No: MUHAS-REC-2-2020-095). Also, the ethical clearance was obtained from Mbeya Medical Research and Ethics review committee (Approval Ref. No: SZEC-2439/R.A/V.1/82) where the study was conducted. All eligible children and their parents/guardians attending the HIV CTC at the study site were informed about the aim of the study. A written consent was obtained from the parents, and assent was requested from the children prior to interviews, enrolment in the study and data collection. . The consent included the brief description of the study, use of the information to be collected, benefits and risks of participation, data privacy/ confidentially and handling of the collected information. To ensure confidentiality, identification numbers were used during data collection in the CRFs and analysis.

Results

The mean age of patients was 13 years, with 103 (51.5%) of having 10–15 years. The majority (82.5%) had normal BMI during the initiation of the DTG-based regimen. Most (75%) of them had been perinatally infected with HIV. Only 57 (28.5%) patients were known to have had been exposed to the prevention of HIV from mother to child through the prevention of mother-to-child transmission (PMTCT) program. The majority (85.5%) of patients were ART-experienced, with more than half (69.5%) on ART for more than 5 years. Most (60.5%) of enrolled patients had siblings who were HIV positive, with more than 90% having 2 or more HIV positive siblings. The baseline characteristics of enrolled patients are as shown in Table 1.

Assessment of Adherence Levels to DTG Regimen among Enrolled Patients

Adherence levels through self-report were high (48%), moderate (40.5%), and low (11.5%) among the assessed 200 patients (Figure 1). Self-reported adherence was higher among ART naïve (69%) than in treatment-experienced (44.4%) patients ($p = 0.015$).

Using the pharmacy refill, it was found that 71% of patients were highly adherent to the DTG-based HAART regimens (Figure 1). High levels of adherence were also observed among ART naïve (82.8%) compared to treatment-experienced (69%) patients ($p = 0.131$). Out of 142 patients who had high adherence based on pharmacy refill, only 51.4% had high levels of adherence based on self-reporting assessment.

Immunological and Virological Outcomes among Patients Using DTG Based Regimen

At baseline, the mean CD4 + cell counts for the whole cohort was 595 cells/mm3. The CD4 + cell counts were less than 200 cells/mm3 in 13% of all patients. Also, 6 months after initiation of DTG-based HAART regimens, the mean CD4 + cell counts was 567.5 cells/mm3, with only 6% of patients having CD4 + count less than 200 cells /mm3. All patients with CD4 + cell counts less than 200 cells /mm3 after starting a DTG-based regimen had low baseline CD4 + cell counts. The mean difference of CD4 + cell counts from baseline to 6 months after using DTG-based regimen was 0.63 (95% CI 0.48-0.82) cells/mm3, ($p = 0.001$). Figure 2 shows the results of immunological outcomes before and 6 months after using the DTG-based regimen.

In addition, 6 months after initiation of DTG-based HAART regimens, the overall proportion of participants who had undetectable viral load was 70.2%, as shown in Figure 3A. The proportion of patients who achieved undetectable viral load was higher in ART-naïve (88.5%) than treatment-experienced patients (67.3%) ($p = 0.036$), as shown in Figure 3B.

Out of 171 treatment experienced patients, 63.2% had viral load < 50 copies/ml before the switch to DTG regimens. Proportion of patients who attained undetectable viral load among treatment experienced patients was higher for patients who had viral load < 50 copies/ml before initiation of DTG-based regimens than those with viral load > 50 copies/ml (81.7% vs 49.2%, respectively; $p < 0.01$). Out of 52 treatment experienced patients who did not have undetectable viral load at 6 months, 33 (63.5%) had viral load > 50 copies/ml at baseline. The virological mean difference among treatment experienced patients was 4.04 (95% CI 1.19-13.69) copies/ml ($p = 0.026$).

On one-year follow-up, 66.7% of patients had viral load < 50 copies/ml of which 64.5% had sustained suppression from 6 months ($p = 0.023$). Virological suppression after one-year

Table 1. Baseline Characteristics of Enrolled Patients (N = 200).

Variable	Mean (± SD)	Frequency	Proportion (%)
Patients characteristics			
Age (years)	13.1 (± 1.3)		
< 10		28	14.0
10–15		103	51.5
> 15		69	34.5
Sex			
Male		100	50.0
Female		100	50.0
BMI			
Normal		165	82.5
Underweight		19	9.5
Overweight		13	6.5
Obese		3	1.5
Perinatal infection			
Yes		150	75.0
No		5	2.5
I don't know		45	22.5
Child exposed to PMTCT			
Yes		57	28.5
No		84	42.0
I don't know		54	27.0
Not applicable		5	2.5
ART Naïve			
Yes		29	14.5
No		171	85.5
ART duration (years)	6.8 (± 1.5)		
≤ 5		27	13.5
> 5		139	69.5
Unknown		5	2.5
Not applicable		29	14.5
WHO clinical stage at DTG initiation			
1		28	14.0
2		34	17.0
3		57	28.5
4		81	40.5
Baseline viral load (copies/ml)	887.1 (± 28.8)		
<50		109	54.5
50–999		30	15.0
1000–100,000		28	14.0
> 100,000		8	4.0
Not available		25	12.5
Baseline CD4 count (counts/mm^3)	595.4 (± 2.8)		
< 200		25	12.5
> 200		167	83.5
Not available		8	4.0
Child aware of HIV status			
Yes		95	47.5
No		105	52.5
Current DTG based regimen			
AZT/3TC/DTG		3	1.5
ABC/3TC/DTG		49	24.5
TDF/3TC/DTG		148	74.0
Family members characteristics			
Parents status			
Both alive		74	37.0
Only mother alive		50	24.0
Only father alive		29	14.5
Both are dead		47	23.5

(continued)

Table 1. (continued).

Variable	Mean (±SD)	Frequency	Proportion (%)
Current caretaker			
Father and mother		60	30.0
Mother only		54	27.0
Father only		22	11.0
Others		64	32.0
Parent status			
Positive		122	61.0
Negative		14	7.0
Unknown		64	32.0
Family size	5 (±1.7)		
1–5		122	61.0
6–12		73	36.5
>12		5	2.5
Sibling HIV status			
Positive		121	60.5
Negative		18	9.0
Unknown		53	26.5
No sibling		8	4.0
Number of siblings infected	2 (+1.4)		
1		9	4.5
2		58	29.0
3		33	16.5
> 3		18	9.0

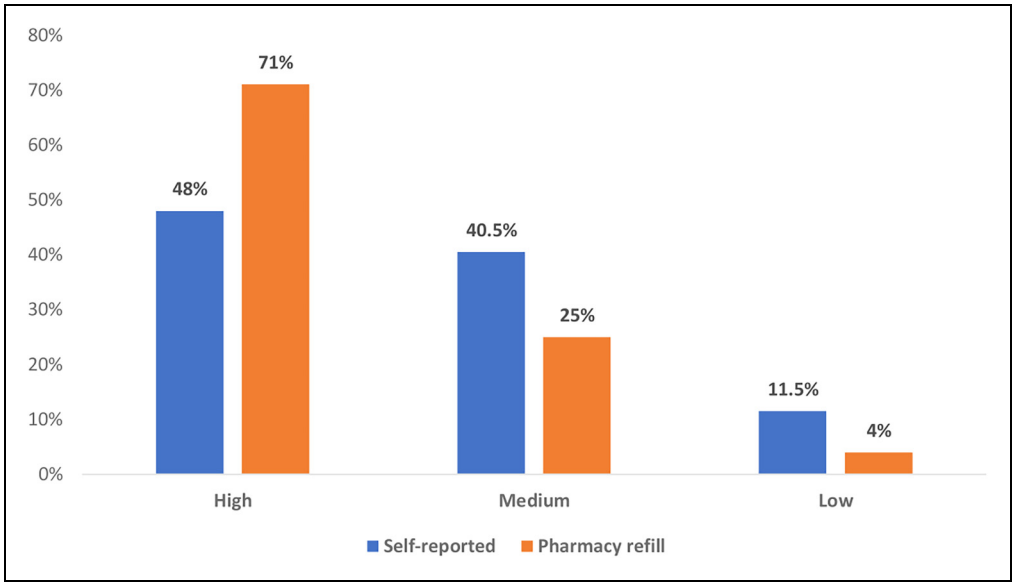

Figure 1. Estimation of adherence levels by self-reporting and pharmacy refill methods.

follow up was significantly associated with baseline (p = 0.008) and 6 months (p = 0.023) viral load count. Out of 38 patients who did not attain virological suppression after one-year, 60.6% and 57.9% had viral load > 50 copies/ml at baseline and at 6-month follow-up, respectively. Virological failure (viral load > 1000 copies/ml) was 16.2% and 16.5% after 6- and 1-year follow-up period, respectively as shown in Figure 3A.

Determinants of Virological Suppression 6-Months After Using DTG Based Regimen in Children and Adolescents

After adjustment of covariates, older patients had higher odds of unsuppressed viral load (>50 copies/ml) than younger patients, an increase in age per year was associated with 31% higher odds of viral load > 50 copies/ml (p = 0.035). The increase in the WHO clinical stage at baseline was also associated with 3

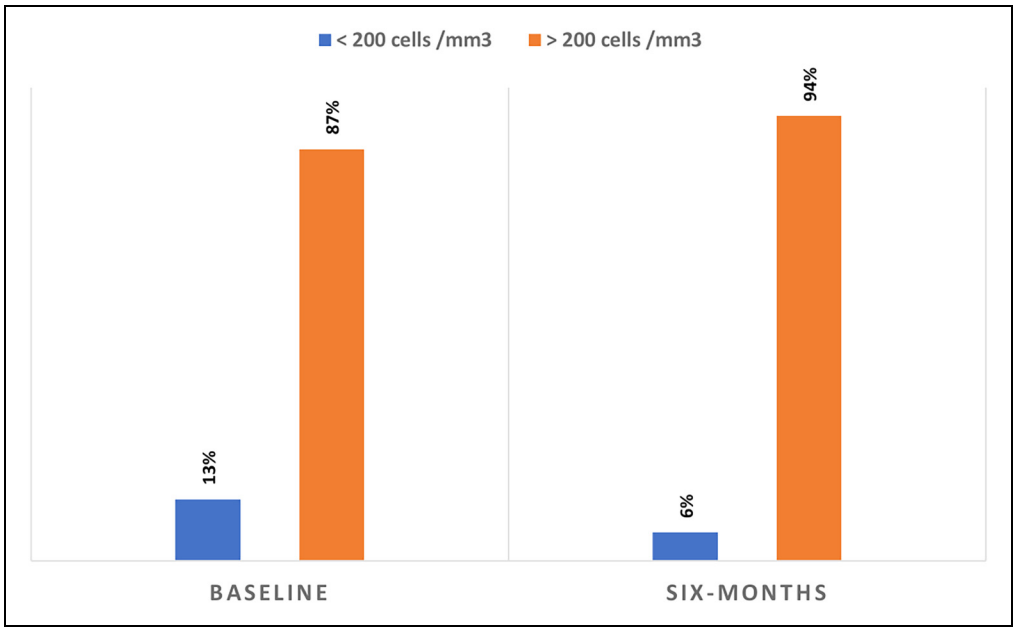

Figure 2. Immunological outcomes at baseline and 6-months after using DTG-based regimen.

times higher odds of viral load > 50 copies/ml (p = 0.035). Also, higher baseline viral load was associated with an increase in odds of viral load > 50 copies/ml by 92%. Adherence levels predicted through pharmacy refill were also associated with virological suppression. Patients graded as highly adherent had 14% lower odds of unsuppressed viral load (VL > 50 copies/ml) than those graded as low or medium adherent patients. Other baseline characteristics were not significantly associated with virological suppression in HIV patients (Table 2).

Assessment of Safety of DTG Regimens among Enrolled Patients

The proportion of patients who reported ADEs following the DTG-based regimen was 16.5%. The majority (75.6%) of patients reported one ADE, 6 (18.1%) patients reported two ADEs, and 2 (6.1%) reported more than two ADEs. Of the 33 patients who reported ADEs, dizziness (30.3%), insomnia (18.2%), and nausea (15.2%) were mainly reported (Figure 4). All reported ADEs were categorized as grade I (mild) and II (moderate) and resolved within a few days without medical intervention.

The CBC results of the 200 participants revealed high ranges of erythrocytes count (13.5%), ALAT (8%), lymphocytes (6%), eosinophils (4.5%), monocytes (4.5%), creatinine clearance (4%) and platelet count (2.5%). Low ranges were also observed in leucocytes (28%) and hemoglobin (10%) The mean and range are provided in table 3.

Discussion

This is among the few studies in Africa that assessed the adherence, effectiveness, and safety of DTG-based HAART regimens among HIV-infected children and adolescents. Children and adolescents are among the age groups reported to have a high HIV-related mortality rate.[16] Previous studies conducted in Tanzania have reported that HIV-infected children and adolescents have poor treatment outcomes mainly because of poor adherence to ART.[17–20] Since DTG (50mg dose/day) was recommended for children weighing ≥20kg, most patients (86%) enrolled were adolescents (age range 10-15 years).

The majority (75%) of the study participants were known to be HIV perinatally infected similar to previous findings that reported that almost 90% of HIV-infected children were perinatally infected.[21] Despite the high number of perinatally infected children, only 28.5% of study participants were known to have received PMTCT services. Of the study participants, a few (14.5%) were ART-naïve patients, which could be one of the outcomes of the improved PMTCT services, which has resulted in 47% reduction in new HIV cases.[22] Most patients had advanced HIV disease as observed by the number of patients at baseline with WHO stage 3 (28.5%) and stage 4 (40.5%) and CD4 + cell counts <200 counts/mm3 (12.5%). Advanced HIV disease has been associated with poor treatment outcomes in HIV patients, including high mortality rates and loss to follow-up.[23–25]

Most enrolled patients had siblings who were HIV positive, and more than 90% had 2 or more HIV positive siblings. Here, a " sibling " is defined as a child from the same biological parents as the index patient. Although PMTCT programs are generally successful when implemented, there is a need to strengthen strategies for scaling up the services' coverage and increasing early infant diagnosis after birth and during breastfeeding. A family-centered approach for HIV care programs to reduce the risk of HIV infection at the family level, especially in HIV endemic areas, must be emphasized.

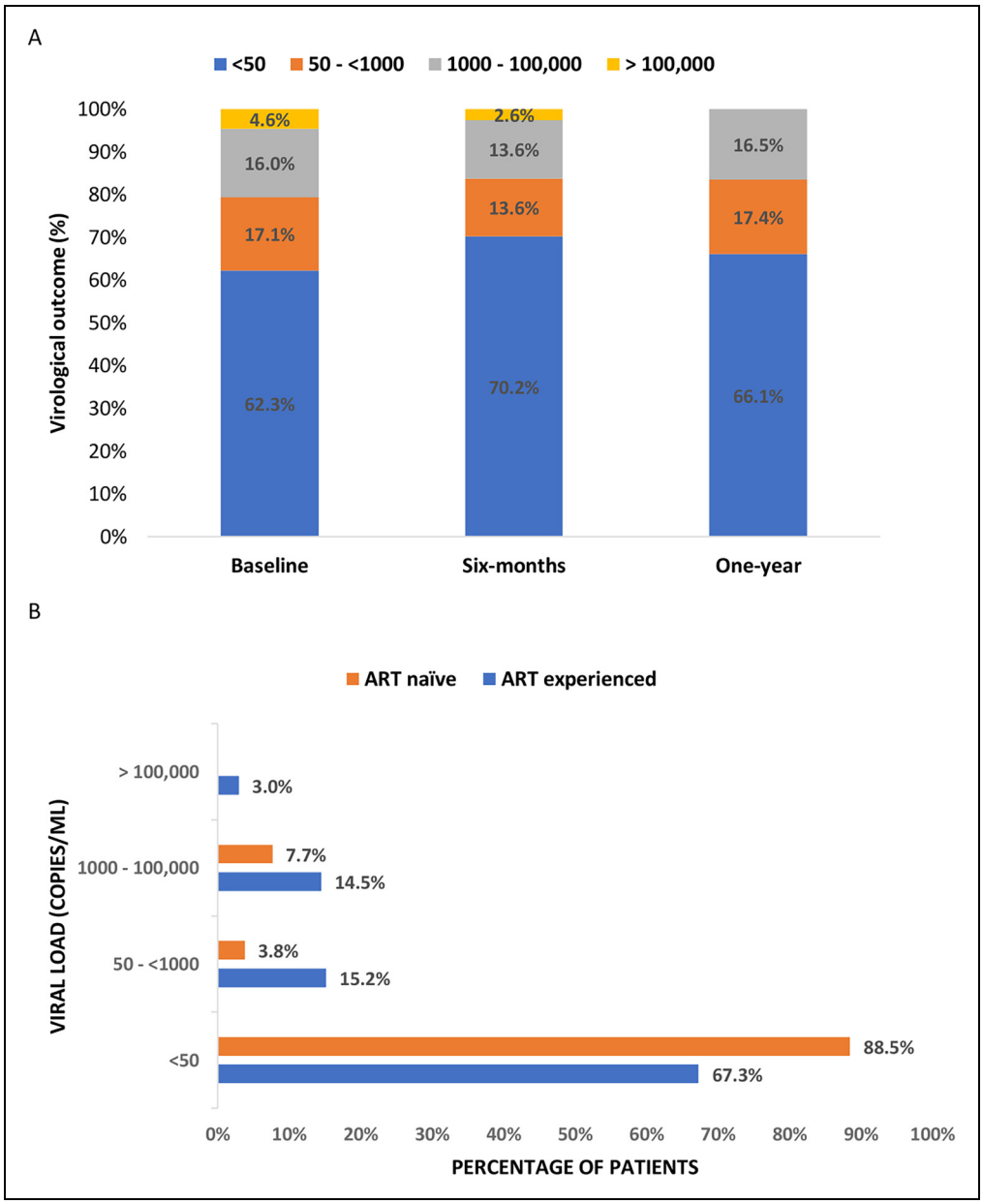

Figure 3 (A) Virological outcomes at baseline, 6-months and 1-year after using DTG based regimen. (B) Virological outcomes among treatment naïve and experienced patients 6-months after using DTG-based regimen.

In this study, two adherence assessment methods were used to allow triangulation to overcome the respective limitations of each data. Self-reported adherence was relatively lower than pharmacy refill adherence (48% vs 71%). Similar adherence measurements have been reported in other studies conducted in East Africa.[17,20,26–28] Nevertheless, adherence was higher among ART naïve than treatment experienced patients in both methods. This is contrary to previous studies conducted in adult populations where ART naïve patients were non-adherent compared to treatment-experienced patients. Reasons for this were that patients must come to terms with their HIV status-associated stigma and try to fit the drug regimen into their daily schedules.[29,30] These factors are uncommon in children because they are not aware of their HIV status during diagnosis, as are under the parent/guardian care but as they age and become independent and aware about their HIV status their level of adherence decrease due to difficultness of coming into terms with stigma associated with the condition.

In terms of effectiveness after 6 months of follow-up, 70.2% of all patients showed viral suppression below <50 copies/ml. The proportion of viral suppression reported in this study is less than the 84% reported in the CHIPS study, whereby one of the inclusion criteria was treatment-experienced children with suppressed viral load (viral load < 50copies/ml) before the switch to DTG based regimen. Another reason can be the study design as the current study was an observational cohort

Table 2. A Binary Logistic Regression Model Showing Factors Associated with Viral Load > 50copies/ml 6-Months After Using DTG-Based Regimen among Patients (n = 191).

Variable	Proportion	Univariate	p-value	Multivariable	p-value
Age (years)	57/191 (29.8%)	1.17 (1.06-1.30)	0.014	1.31 (1.02-1.67)	0.035
Sex				*	
Male	31/97 (32%)	1.23 (0.66-2.29)	0.517		
Female	26/94 (27.7%)	Reference			
BMI				*	
Low	5/18 (27.8%)	0.87 (0.29-2.59)	0.807		
High	4/16 (25%)	0.76 (0.23-2.47)	0.644		
Normal	48/157 (30.6%)	Reference			
Perinatal infection				**	
Yes	42/142 (29.6%)	0.28 (0.05-1.74)	0.172		
No	3/5 (60%)	Reference			
Child exposed to PMTCT					
Yes	15/56 (26.8%)	0.71 (0.33-1.49)	0.360	*	
No	28/82 (34.1%)	Reference			
ART Naïve				**	
Yes	3/26 (11.5%)	0.55 (0.29-1.04)	0.065		
No	54/165 (32.7%)	Reference			
ART duration (years)		0.94 (0.17-5.31)	0.944	*	
≤ 5	7/26 (26.9%)	0.73 (0.29-1.86)	0.508		
> 5	46/137 (33.6%)	Reference			
WHO clinical stage baseline	51/191 (29.8%)	1.42 (1.03-1.97)	0.034	3.91 (1.06-14.34)	0.041
Baseline viral load (copies/ml)	51/191 (29.8%)	1.42 (1.06-1.92)	0.020	1.92 (1.02-3.63)	0.044
Baseline CD4 count (counts/mm^3)	51/191 (29.8%)	0.55 (0.28-1.07)	0.079	**	
Child aware of HIV status				**	
Yes	32/91 (35.2%)	1.63 (0.87-3.04)	0.127		
No	25/100 (25%)	Reference			
Current DTG based regimen				*	
TDF/3TC/DTG	44/141 (31.2%)	1.29 (0.63-2.67)	0.490		
Other DTG regimens	13/50 (26%)	Reference			
Parents status				*	
Atleast one alive	43/146 (29.5%)	0.92 (0.45-1.19)	0.832		
Both are dead	14/45 (31.1%)	Reference			
Current caretaker				*	
Parent(s)	40/130 (30.8%)	1.15 (0.59-2.25)	0.683		
Others	17/61 (27.9%)	Reference			
Caregiver status					
Positive	34/114 (29.8%)	0.77 (0.24-2.45)	0.652	*	
Negative	5/14 (35.7%)	Reference			
Family size		0.55 (0.13-2.29)	0.410	*	
≤ 5	38/119 (31.9%)	1.31 (0.68-2.51)	0.418		
> 5	19/72 (26.4%)	Reference			
Sibling HIV status					
Positive	34/113 (30.1%)	0.86 (0.29-2.48)	0.781	*	
Negative	6/18 (33.3%)	Reference			
Number of siblings infected					
1–2	16/64 (25%)	0.57 (0.25-1.29)	0.179	**	
> 2	17/46 (37%)	Reference			
Adherence - Self Report					
High	21/90 (23.3%)	0.55 (0.29 −1.04)	0.065	**	
Moderate & Low	36/101 (35.6%)	Reference			
Adherence – Pharmacy refill					
High	34/135 (25.2%)	0.48 (0.25-0.93)	0.030	0.14 (0.03-0.67)	0.014
Moderate & Low	23/56 (41.1%)	Reference		Reference	

* = variables not used in the final model and ** = variables >0.05 in multivariable analysis.

study while the other was a controlled clinical trial where patients are usually closely monitored.[13] In agreement, a similar proportion of patients (74.5%) were reported to have had attained viral load < 50copies/ml at 48 weeks follow-up in a study conducted in Cameroon.[31] The similarity in the findings between the later research and ours could be because both

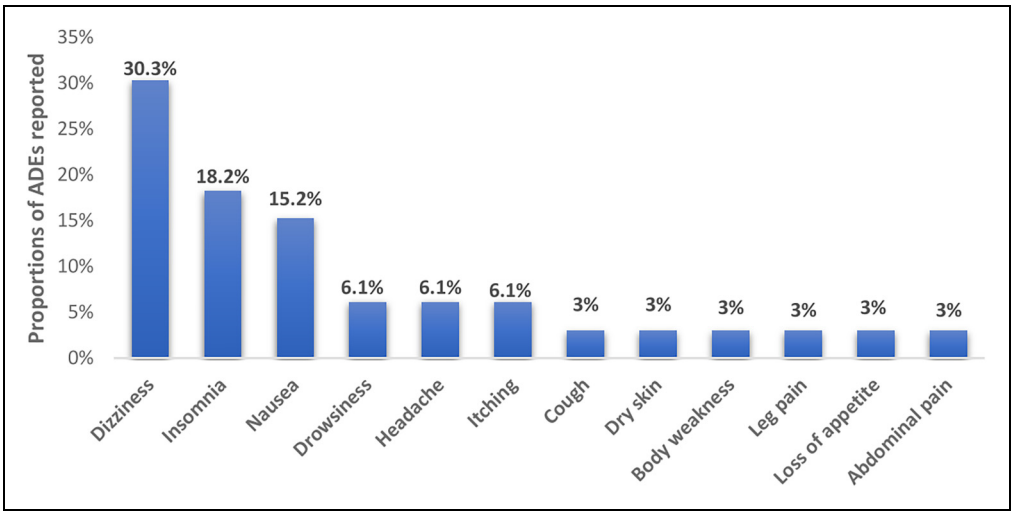

Figure 4. Adverse drug events reported among patients on DTG regimen (n = 33).

Table 3. Laboratory Parameters 6-Months Post DTG Regimen use among Patients.

Parameter	Mean (SD)	Min - Max
Creatinine(μmol/L)	51.7 (15.1)	10.97–90.00
ALAT (U/l)	21.4 (11.1)	8.14–84 .42
Hemoglobin (g/dl)	13.1 (1.5)	7.8–15.9
Leucocyte count ($x10^9$/l)	4.3 (1.2)	1.64–9.38
Erythrocyte count (10^6/l)	4.9 (0.5)	3.98–6.28
Platelet count (10^3/mm^3)	293.1 (67.3)	171–531
Neutrophils ($x10^9$/l)	1.8 (0.8)	0.55–4.10
Lymphocytes($x10^9$/l)	2.0 (0.7)	0.87–4.43
Monocytes ($x10^9$/l)	0.4 (0.2)	0.13–1.04
Eosinophils ($x10^9$/l)	0.2 (0.3)	0.01–1.74
Basophils ($x10^9$/l)	0.01 (0.01)	0.01–0.04

studies allowed the inclusion of patients who had high baseline viral loads during the switch to a DTG-based regimen.

Higher rates of viral suppression were observed in ART-naive patients compared to treatment-experienced patients (88.5% vs 67.3%) which could also be due to the observed decrease in level of adherence to later group. It was observed that virological suppression in the treatment-experienced patients was higher for patients who had baseline viral load < 50 copies/ml before the switch to DTG based regimen than those with viral load > 50 copies/ml (81.7% vs 49.2%, respectively). These findings are consistent with those reported in a study from Cameroon, which reported decreased DTG efficacy in patients with high viral load.[31] Patients with high baseline viral load (≥1000 copies/mL) were reported to be less likely to achieve virological suppression with INSTI-based ART.[32]

A recent study in Tanzania showed DTG-based regimens are still effective among treatment-experienced patients who had high viral load when using NNRTI regimens in Tanzania.[33] On 48 weeks follow-up, 5.7% of patients had rebound viremia. This observation has also been reported among patients using DTG regimens in previous studies[32,34] and requires further investigation to determine factors associated with rebound viremia.

Apart from baseline viral load, other predictors of undetectable viral load in this study were the age of the patients. Older patients were more likely to have viral load >50copies/ml than younger patients in this study. The effect of age has also been reported in a previous study where children and young adolescents aged <13 years were more likely to achieve virological suppression following INSTI initiation than adolescents and young adults.[32] HIV-infected adolescents and young adults experience multiple barriers to adherence, including developmental, physical, economic, emotional, behavioral, and social dynamic changes.[35–38] On the other hand, a previous study conducted in Tanzania reported that children of younger ages (≤ 5 years) were more prone to develop virologic failure than older ones.[39] Our study could not ascertain the effectiveness of DTG-based regimen in children <5years since most of them were not using a DTG-based regimen.

The increase in WHO clinical stage at baseline was also associated with 3 times higher odds of viral suppression. Patients with WHO clinical stages 3 and 4 have advanced HIV disease and hence have poor treatment outcomes. Besides the disease stage, adherence to ART regimen has been a strong predictor of treatment outcome whereby poor adherence has been associated with high viral load and can ultimately lead to the development of ART drug resistance. In this study, adherence levels predicted through pharmacy refill were strongly associated with virological suppression. Highly adherent patients had 14% lower odds of unsuppressed viral load than those with low or medium adherence levels.

In this study, ADEs were reported in 16.5% of the patients. The frequency of ADEs reported in our study is low compared to the 42.2% reported in the previous study in which all enrolled patients were using DTG/ABC/3TC regimen. Compared to the

previous trials conducted in children and adolescents, the proportion of ADEs reported in this study is lower than that reported in the IMPAACT and CHIPS studies.[13,40] The observed differences between our findings and those of the later studies could be based on the nature of the study designs, including strict inclusion criteria and active follow-up of patients in clinical trials compared to observational studies. Therefore, fewer ADEs are expected to be reported when ART is used in real-life settings, as spontaneous reporting is usually low. Like other studies, the commonest ADEs reported were dizziness, insomnia, and nausea.[41–43] Contrary to the findings from other studies,[44,45] there were no alarming changes in weight reported among the study participants. All the ADEs reported in this study were mild and did not cause any change or interruption of treatment.

Not much has been documented regarding the effect of DTG on hematological parameters. Some studies have reported increased creatinine among patients using DTG-based ART.[43,46,47] The increase in serum creatinine during DTG treatment is due to inhibition of the renal organic cation transporter (OCT) 2 which reduces the tubular secretion of creatinine.[46] Only a small proportion of DTG dose (< 1%) is excreted unchanged in the urine; therefore, currently, no dosage adjustments are recommended for DTG in patients with renal impairment.[48] In our study, the mean creatinine level of patients was in a normal range.

Dolutegravir is extensively metabolized in the liver by UGT1A1, and the raised ALAT/ aspartate transferase levels have been documented as one of the ADEs reported in patients using DTG-based therapy. Therefore, the regular liver function of patients on DTG-based therapy is recommended. In this study, few patients had raised ALAT levels and were graded as mild, which did not require any changes in the treatment regimen.

The main limitation of this study is its observational nature, which is prone to bias because of unmeasured confounders. But this might have been reduced by the relatively large sample size of the study participants. The use of two methods for measuring medication adherence may have enhanced the reported findings, especially the pharmacy-refill method.

Conclusion

This study revealed that the use of DTG-based ART in children and adolescents is safe with minor ADEs and changes in laboratory parameters which were well tolerated. In addition, the DTG regimen is effective in this population, even in treatment-experienced children who had high viral load before switching to DTG-based therapy. On the other hand, adherence to DTG regimens was good among children and adolescents.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the MUHAS-SIDA seed grant for junior faculty, (grant number 2019/2020).

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