



## **Dolutegravir (DTG) Based Fixed Dose Combination (FDC) of Tenofovir/Lamivudine/Dolutegravir (TLD) and Viral Load Suppression in Children in Port Harcourt, Nigeria**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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### **ABSTRACT**

**Background:** Currently, dolutegravir (DTG) based fixed dose combinations (FDC) of tenofovir/lamivudine/dolutegravir (TLD) and Abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) is now recommended by the World Health Organisation (WHO) as the preferred first-and second line antiretroviral drug necessitating transition of eligible children to TLD.

**Objective:** The objective of this study is to compare the HIV viral suppression rate at baseline and after 6 months of transition to TLD and to determine adverse drug reaction associated with the use of TLD if any.

**Methods:** This was a prospective cross-sectional study carried out among stable children who were on treatment and follow up for HIV disease at the Paediatric HIV clinic of the University of Port Harcourt Teaching Hospital (UPTH). All Children who were eligible for transition to TLD, whose care givers/parents gave a verbal consent and who gave consent or accent were recruited for the study. Information obtained included the sociodemographic characteristics, weight and height, ART regimen at initiation of treatment and when it was commenced, the baseline viral load

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and viral load 6 months after transition and any adverse drug reaction. Obtained data were analysed. Comparison of categorical variables was done using chi square and Fischer's exact test while A p-value of < 0.05 was set as statistically significant.

**Results:** A total 106 children aged 9 to 18 years with a mean age of 13.4±2.3 years were recruited for the study. Sixty (56.6%) were males, while 59 (55.5%) were from the lower socioeconomic class. The mean weight was 44.4±11.1 kg while the mean height was 151.3 ± 15.2 cm. At baseline, 48 (45.3%) were virally suppressed (viral load < 1000 copies/ml), however after 6 months, 97 (91.5%) became virally suppressed, the difference in viral suppression rate was statistically significant ( $X^2 = 53.77$ ,  $p = 0.0001$ ). Twenty-five (23.6%) had undetectable viral load (<20 copies/ml) at baseline while 61(57.5%) had undetectable viral load after transition. All those who were virally suppressed at baseline remained so 6 months after transition. Also, 80.6% (29/36) of those with treatment failure became virally suppressed. Only one child developed severe erythematous skin rashes. There was no statistically significant relationship between viral suppression and age, sex and social class ( $P > 0.05$ ).

**Conclusion:** This study has shown that DTG-based FDC is efficacious in the treatment of eligible children and adolescents with HIV/AIDS with significant viral load suppression in all age groups, gender and social class. Adverse drug reaction with the use of DTG-based ART is low. Transition to TLD is therefore advocated in eligible patients.

*Keywords: Dolutegravir (DTG); TLD; viral-load suppression; children.*

## 1. INTRODUCTION

Guideline on anti-retroviral (ARV) drug use in the management of Human Immunodeficiency virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS) has evolved since the onset of HIV pandemic. The 2016 World Health Organisation (WHO) consolidated guideline on the use of ARVs for prevention and treatment of HIV infection introduced the use of Tenofovir disoproxil fumarate (TDF) or abacavir (ABC) + Lamivudine (3TC) [or Emtricitabine (FTC)] + Dolutegravir (DTG) as an alternative first-line for adolescents who are DTG eligible [1]. This guideline acknowledged the clinical and programmatic advantages of DTG including: improved tolerability, lower potential for drug interactions, shorter median time to viral suppression and a higher genetic barrier to resistance [1].

In 2017, there was a technical update published by the WHO on the Transition to New Antiretroviral Drugs in HIV Programmes, providing advice on a phased approach to transitioning to new HIV treatment regimens and noted that DTG in particular is a strategically preferred choice for drug optimization in the longer term [2].

A year later in July 2018, the WHO released another updated interim guidance on first- and second-line ARV regimens including DTG-based regimens as a preferred first-line ARV for adults, adolescents and all infants and children with

approved DTG dosing [3]. However, given concern about the potential increased risk of birth defects, the WHO included a note of caution around the use of DTG during the periconception period, recommending that adolescent girls and women of childbearing potential who do not currently want to become pregnant use DTG together with reliable and consistent contraception [3].

Presently, DTG-containing regimens is now recommended as the preferred first-line antiretroviral therapy (ART) and the preferred second line ART for those with failing Zidovudine/Lamivudine/Nevirapine or efavirenz (AZT+3TC+NVP or EFV) FDC because it has been shown to have superior efficacy, tolerability and higher threshold for resistance compared to AZT and EFV-containing regimens. The fixed-dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD) is now available at a cost affordable to low- and middle-income countries and prices are expected to further decrease as generic manufacturers increase production.

Dolutegravir (DTG) has been demonstrated to be effective in several randomized control trials conducted among antiretroviral therapy (ART) naïve (SINGLE, SPRING, FLAMINGO) and experienced patients (STRIIVING) [4-7]. Among the treatment naïve patients, DTG is superior to both efavirenz (EFV) and ritonavir-boosted darunavir and non-inferior to raltegravir – a twice-daily dosed integrase inhibitor. Recent

systematic reviews and meta-analysis conducted by WHO have showed that DTG-based regimens are better tolerated and tend to be protective against treatment discontinuation due to adverse events (AEs), when compared with EFV 600 [8]. Among stable, virologically suppressed patients on non-nucleoside reverse transcription inhibitor (NNRTI) or protease inhibitor-based first-line antiretroviral (ARV) treatments, substitution with a DTG-containing regimen was also well-tolerated and non-inferior in maintaining viral suppression, with high rates of satisfaction compared to those remaining on their existing regimen. Furthermore, DTG is associated with a more rapid viral suppression and higher genetic resistance barrier, when compared with NNRTIs. It is also effective against HIV-2 (which is naturally resistant to NNRTIs) [9-11]. Pharmacokinetic studies showed that DTG is effective in subpopulations, including pregnant women and tuberculosis (TB)-coinfection, with a dose increase of DTG to overcome drug-drug interactions with rifampicin in the latter [12,13].

DTG has been shown to be a well tolerated drug, with lower overall incidence of adverse effects (AEs) (<5%) when compared with EFV [14]. The most common reported AEs associated with DTG are gastrointestinal symptoms (nausea, vomiting), hypersensitivity skin reactions, and central nervous system effects (insomnia, dizziness) which are most often mild and self-limited. Discontinuation rates observed in clinical trials and in programme data are low [14].

A few European cohorts have detected an increased occurrence of central nervous system side effects in people over 60 years of age, those using abacavir (ABC) and women [15-17]. However, channelling and other confounding factors are likely to be the reasons for these findings. An increased occurrence of immune reconstitution inflammatory syndrome (IRIS), cardiovascular events and suicidal ideation was initially suspected, but recent analysis has not detected significant differences when compared with other standard regimens [18].

Optimization of current antiretroviral drug regimens is a critical component to support country efforts to achieve the 90/90/90 treatment targets. Many low- and middle-income countries (LMICs) including Nigeria are including or planning to include dolutegravir (DTG) containing regimens in their national protocols, as the preferred first-line option, particularly the fixed dose combination (FDC) tenofovir/lamivudine/

dolutegravir (TLD). In line with international best practices, there was a need to transit all eligible children who were on follow up to TLD FDC. The objective of this study was to compare the HIV viral suppression rate at transition (baseline) to TLD and after 6months of transition and to determine adverse drug reaction associated with the use of TLD if any.

## 2. METHODOLOGY

This was a prospective cross-sectional study carried out over 12 months from January 2019 to December 2019 among children who were on treatment and follow up for HIV disease at the Paediatric HIV clinic of the University of Port Harcourt Teaching Hospital (UPTH). All Children who were eligible for transition to TLD, whose care givers/parents gave a verbal consent and who gave consent (those up to 18 years or emancipated minors) or consent were recruited for the study. Eligibility criteria for transition to TLD include; Children who weighed at least 30 kg or more, Children without HIV/TB coinfection (this is because TLD only existed as an FDC during the study period without single 50 mg pill of dolutegravir which is needed by these patients to be on DTG), those who were virally suppressed (viral load <1000copies/ml), those with virologic failure (virally unsuppressed and adherent to ART) and those who were virally unsuppressed but not adherent to their medications. However, for those who were not adherent to their medication, adherence was addressed before transition to TLD was made. This was done by giving them monthly follow up visits for 3 consecutive months, encouragement to use phone alarms as reminders to drug intake and use of weekly phone calls to remind them of their pills and their follow up days. In each visit, they were counselled and evaluated by enhanced adherence counsellors (EAC) who will note the number of pills missed in the past one month if any, reason for missing a pill and addressing the reason until adherence was ensured. For all recruited patients, the need for adherence to the new regimen was stressed before transition to TLD was made and reinforced on each follow up visit by the Paediatric care providers and the enhanced adherence counsellors (EAC). Information obtained from recruited patients included the sociodemographic characteristics, weight and height, the parental highest educational level and occupation, ART regimen at commencement of treatment and when it was commenced, the baseline viral load and CD4 count while the main outcome measure was CD4

count and viral load 6months after transition to TLD and any adverse drug reaction. Socioeconomic class was calculated using the model designed by Oyediji. [19] Due to faulty CD4 machine in the hospital during the study period, very few patients had CD4 count result so this was not included in the final analysis. Obtained data were analysed using SPSS version 22. Comparison of categorical variables was done using chi square and Fischer's exact test while a p-value of < 0.5 was set as statistically significant.

### 3. RESULTS

#### 3.1 Sociodemographic Information

A total of 106 children aged 9 to 18 years with a mean age of 13.4±2.3 years were recruited for the study. Forty-two (39.6%) were aged 13-15 years, 60 (56.6%) were males, while 59 (55.5%) were from the lower socioeconomic class Table 1. The mean weight was 44.4±11.1 kg while the mean height was 151.3 ± 15.2 cm

**Table 1. Sociodemographic information**

Variable	Frequency	Percent
<b>Age groups</b>		
<10 Years	2	1.9
10 - 12 years	38	35.8
13 - 15 years	42	39.6
16 - 18 years	24	22.6
<b>Sex</b>		
Female	46	43.4
Male	60	56.6
<b>Socio-economic class</b>		
Lower	59	55.7
Middle	35	33
Upper	12	11.3

**Table 2. Viral load levels in study subjects at baseline and 6 months after transition to TLD**

Viral load category copies/ml	Baseline viral load n (%)	6 months viral load n (%)	Chi square (P-value)
<20	25 (23.6)	61 (57.5)	53.77 (0.0001)
20-1000	23 (21.7)	36 (34.0)	
≥1000	58 (54.7)	9 (8.5)	
<b>Total</b>	<b>106 (100.0)</b>	<b>106 (100.0)</b>	

*There was a statistically significant difference between the baseline and 6 months viral load. (p = 0.0001)*

**Table 3. Category of Virally unsuppressed patients at baseline and 6 months later transition**

Category	Baseline No (%)	6 Months after transition	
		<1000 cells/ml	≥1000 cells/ml
Virologic failure	22 (37.9)	18 (81.8)	4 (18.2)
Adherence Issues	36 (62.1)	31 (86.1)	5 (13.9)
<b>Total</b>	<b>58 (100.0%)</b>	<b>49 (84.5%)</b>	<b>9 (15.5%)</b>

#### 3.2 Viral Load Levels in Study Subjects at Baseline and 6 Months after Transition to TLD

Table 2 shows that at baseline, 48 (45.3%) were virally suppressed while 58 (54.7) were virally unsuppressed (viral load ≥ 1000copies/ml), however 6 months after transition to TLD, 97 (91.5%) became virally suppressed. This is a 100% increase in viral suppression rate. Twenty-five (23.6%) had undetectable viral load (<20copies/ml) before transition while 61(57.5%) had undetectable viral load after transition. Of the nine patients who remained virally unsuppressed after six months on TLD, 7 (77.8%) had reductions in their viral load levels but levels were still >1000 copies/ml. Of note was the fact that all those who were virally suppressed (<1000 copies/ml) remained suppressed with some of them having undetectable viral levels (<20 copies/ml) and those who had undetectable viral load levels (<20 copies/ml) remained so 6 months after transition. Only one child developed severe erythematous skin rashes within 72 hours of commencement of TLD and DTG was discontinued and medications changed to EFV.

#### 3.3 Category of Virally Unsuppressed Patients at Baseline and 6 Months after Transition

Among the 58 (54.7%) who were virally unsuppressed at baseline, 22 (37.9%) were due to virologic failure and 36 (62.1%) due to adherence issues. Of the forty-nine who achieved viral load suppression (<1000 cells/ml) 6 months later, 18 (36.7%) had virologic failure at baseline. This constitutes 81.8% (18/22) viral suppression rate among those who had virologic failure at baseline Table 3.

### 3.4 First Line ART and Baseline Viral Load at Commencement of Treatment

The first line ART for most of the patients were AZT based FDC, 101 (95.3%) were on Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP) combination Table 4. Fig. 1 shows that 48 (45%) of the patients have been on ART for more than 10years.

### 3.5 Sociodemographic Data and Viral Load (VL) at Baseline and at 6 Months

The proportion of children who were virally unsuppressed (VL >1000) at baseline was higher among older children aged 16-18 years when compared with the others, but this difference was not statistically significant (p>0.05), however, this proportion of virally unsuppressed children was near equal among the sex and social class. Table 5a, Table 5b shows that at 6 months there was near representation of those who were virally unsuppressed among the age groups and the gender, however, 25% of patients in upper social class were virally unsuppressed compared to less than 10% in the other social classes, but there was no statistically significant relationship between viral suppression and age, sex and social status.

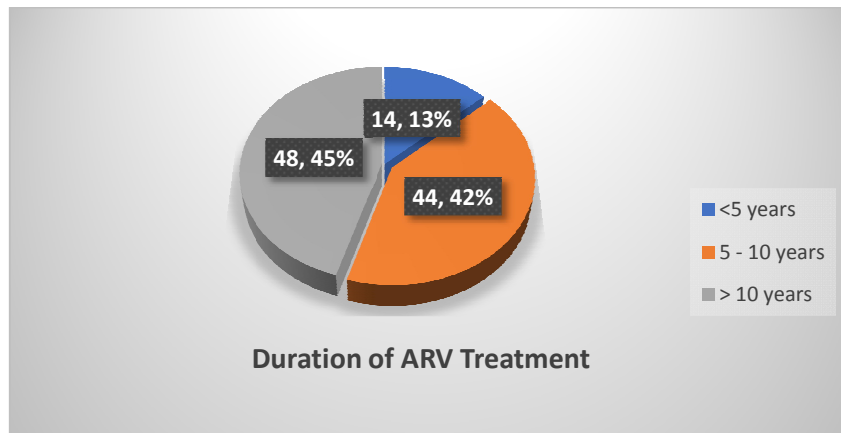
### 4. DISCUSSION

This study showed a statistically significant improvement in the viral load suppression in patients transitioned to TLD, a DTG based FDC. There was a 100% increase in the rate of viral suppression after transition to TLD. This suppression in viral load occurred among all categories of patients – those with virologic failure, those who were previously virally unsuppressed due to non-adherence to treatment, while those who were virally suppressed maintained their suppressed status. This finding confirms previous study that showed the efficacy and superiority of DTG-based FDC to zidovudine (AZT) based FDC as most of our patients were on AZT based regimen prior to transition and indirectly also show the efficacy of DTG containing FDCs in the treatment of patient with HIV in terms of viral suppression as was observed in this study. At baseline, more of the older adolescents were virally unsuppressed and poor adherence is a common finding among this group of patients. Therefore, it is possible that addressing the issue of adherence before transition to TLD contributed to viral load suppression however the fact that a significant proportion of those with virologic failure achieved viral suppression lends strong support to the efficacy of DTG-based FDC regimen.

**Table 4. Baseline viral load and first line ART at commencement of treatment**

Initial ART	<20 n (%)	20 – 1000 n (%)	≥1000 n (%)	Total N (%)	Fischer's exact
ABC/3TC/EFV	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.9)	(0.9505)
AZT/3TC/EFV	1 (4.0)	1 (4.4)	1 (1.7)	3 (2.9)	
AZT/3TC/NVP	23 (92.0)	22 (95.6)	56 (96.6)	101 (95.3)	
TDF/3TC/EFV	1 (4.0)	0 (0.0)	0 (0.0)	1 (0.9)	
<b>Total</b>	<b>25 (100.0)</b>	<b>23 (100.0)</b>	<b>58 (100.0)</b>	<b>106 (100.0)</b>	

Note: AZT-Zidovudine, 3TC-Lamivudine, ABC-Abacavir, EFV-Efavirenz, NVP-Nevirapine, TDF- Tenofovir disoproxil fumarate



**Fig. 1. Duration of ART**

**Table 5a. Sociodemographic data and baseline viral load (VL)**

Variables	Category of baseline VL (Copies/ml)			Total	Fischer's exact
	<20	20 -< 1000	≥1000		
<b>Age Groups</b>					
< 10	1 (50.0)	1 (50.0)	0 (0.0)	<b>2 (100.0)</b>	<b>0.198</b>
10 – 12	13 (34.2)	8 (21.1)	17 (44.7)	<b>38 (100.0)</b>	
13 – 15	9 (21.4)	9 (21.4)	24 (57.1)	<b>42 (100.0)</b>	
16 – 18	2 (8.3)	5 (20.8)	17 (70.8)	<b>24 (100.0)</b>	
<b>Gender</b>					
Female	13 (28.3)	8 (17.4)	25 (54.3)	<b>46 (100.0)</b>	<b>0.484</b>
Male	12 (20.0)	15 (25.0)	33 (55.0)	<b>60 (100.0)</b>	
<b>Socio-economic class</b>					
Lower	11 (18.6)	14 (23.7)	34 (57.6)	<b>59 (100.0)</b>	<b>0.741</b>
Middle	10 (28.6)	7 (20.0)	18 (51.4)	<b>35 (100.0)</b>	
Upper	4 (33.3)	2 (16.7)	6 (50.0)	<b>12 (100.0)</b>	

**Table 5b. Demographic data and 6-month viral load (VL)**

Variables	Category of 6-month VL (Copies/ml)			Total	Fischer's exact
	<20	20 -<1000	≥1000		
<b>Age Groups</b>			0 (0.0)	<b>2 (100.0)</b>	
< 10	2 (100.0)	0 (0.0)			<b>0.871</b>
10 – 12	23 (60.5)	12 (31.6)	3 (7.9)	<b>38 (100.0)</b>	
13 – 15	23 (54.8)	16 (38.1)	3 (7.1)	<b>42 (100.0)</b>	
16 – 18	13 (54.2)	8 (33.3)	3 (12.5)	<b>24 (100.0)</b>	
<b>Gender</b>					
Female	24 (52.2)	17 (37.0)	5 (10.9)	<b>46 (100.0)</b>	<b>0.559</b>
Male	37 (61.7)	19 (31.7)	4 (6.7)	<b>60 (100.0)</b>	
<b>Socio-economic class</b>					
Lower	32 (54.2)	24 (40.7)	3 (5.1)	<b>59 (100.0)</b>	<b>0.741</b>
Middle	22 (52.9)	10 (28.6)	3 (8.6)	<b>35 (100.0)</b>	
Upper	7 (58.3)	2 (16.7)	3 (25.0)	<b>12 (100.0)</b>	

Among the 9 (8.5%) who remained virally unsuppressed after 24 weeks of TLD, 7 (77.8%) had reductions in their viral load levels but the levels still exceeded the benchmark for the definition of viral suppression. It is possible that some of these patients were not 100% adherent to their medications - though transition to TLD, a once daily dosing regimen, made it easier to maintain adherence among these adolescents, or are "slow responders" to TLD or with the remaining two may have developed genetic cross resistance to tenofovir and lamivudine leaving only dolutegravir as the only active ART. Dolutegravir-based regimens have however, demonstrated superiority over both efavirenz (EFV) and protease inhibitor (PI) based regimens with better tolerability and fewer discontinuations, rapid suppression of viral load (VL), and a high genetic barrier to resistance. [6] It is presently difficult to assign these virally unsuppressed patients as cases of DTG resistance as TLD has been found to be a more durable regimen and patients not responding to TLD are more likely to

have adherence challenges than resistance compared to those failing on Non-nucleoside reverse transcriptase inhibitor (NNRTI) - containing regimen. Walmsley et al. [4] in their study found that none of the participants on DTG based regimen had detectable antiviral resistance. Walmsley et al. [4] also in their study on Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection reported viral suppression at the end of 48 weeks, therefore it is possible that those who had lowered viral load levels ("slow responders") in this study may achieved viral suppression by the end of 48weeks if adherence issues are addressed and patients continued on TLD.

Only one child, a 16-year-old male developed an adverse skin reaction, severe erythematous skin rashes which necessitated discontinuation of DTG to EFV. Though this patient was not included in the final analysis of this study, a similarly low rate of 2% of participants who discontinued therapy due to adverse drug

reaction was reported in DTG group than in EFV group by Walmsley et al. [4].

Current evidence demonstrates the effectiveness of TLD as a second-line regimen after failure on an AZT-containing first-line or with the use of genotyping that can allow for the selection of at least one active NRTI. The use of TLD as a second-line drug will reduce the need for expensive protease inhibitors (PIs). Additionally, as was found in this study, available evidence demonstrates that non-adherence is a significant contributor to poor rates of viral suppression in patients on AZT based first line drugs and protease inhibitor (PI) -based second-line regimen [20] and substitution of a more convenient and better-tolerated regimen like TLD may increase rates of second-line treatment success as was also shown in this study where over 80% of those with virologic failure and adherence issues achieved viral suppression .

The observed viral load suppression was observed across the age groups, gender and social class. Therefore, irrespective of the age group, sex and socioeconomic class especially among patients with virologic failure, it is safe to transit to TLD among eligible adolescents and children. The WHO call for the use of TLD as both a first line and 2<sup>nd</sup> line ART is a worthy one and may help to achieve the 90/90/90 goal of HIV detection, ART treatment and viral load suppression as was found in this study.

## 5. CONCLUSION

In conclusion, this study has shown that TLD, a DTG-based FDC is efficacious in the treatment of children and adolescents with HIV/AIDS with optimal viral load suppression in all ages, both gender and all social class. Adverse drug reaction with the use of TLD, a DTG-based ART is low. Due to the fact that it is efficacious, with very low adverse drug reaction risk, single daily dosing regimen and cheap, transition to its use among eligible persons in centres yet to do so is encouraged once adequate clinical and logistics preparation have been done.

## 6. LIMITATION OF THE STUDY

Inability to conduct drug resistance testing and antiretroviral drug level testing due to lack of facilities. This would have helped to determine the contributions of resistance before the switch to TLD to risk of treatment failure especially among those who were virally unsuppressed.

## CONSENT AND ETHICAL APPROVAL

All Children who were eligible for transition to TLD, whose care givers/parents gave a verbal consent and who gave consent (those up to 18 years or emancipated minors) or accent were recruited for the study. Ethical approval for the study was obtained from the Research and Ethics committee of the UPTH.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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