

## Effectiveness of Dolutegravir (DTG), an HIV integrase inhibitor in improving viral load suppression among HIV infected treatment experienced patients in General Hospital Minna, Nigeria

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### Abstract

Despite the increasing access to antiretroviral medications several studies have demonstrated suboptimal levels of viral load suppression among different population groups especially in low resource settings. In order to achieve the 90-90-90 strategy of UNAIDS by 2020 and 95-95-95 by 2030 ensuring a sustained viral suppression in HIV patients on antiretroviral (ARVs) is critical. The viral load suppression level among people living with HIV on Highly Active Antiretroviral Therapy (HAART) in Nigeria in 2019 was as low as 44.5%. In Nigeria, the Dolutegravir (DTG) an HIV integrase inhibitor, fixed dose-based combination therapy was approved as the preferred first line ART in 2018 and implementation commenced in July 2019. Therefore, the objective of this study was to determine the effect of DTG based combination regimen Tenofovir/lamivudine/Dolutegravir (TDF/3TC/DTG) in suppressing viral load among HIV treatment experienced patients in Minna, Nigeria. Data analyzed was obtained from a prospective single arm trial to evaluate the effect of DTG fixed dose combination therapy (TDF/3TC/DTG) in suppressing viral load involving 418 randomly selected HIV treatment experienced patients. A questionnaire was administered to collect data from respondents. The outcome variable was viral load suppression pre and post intervention. The results of the study revealed that DTG based combination regimen elicited a statistically significant effect in suppressing viral load ( $Z = -11.134$ ,  $p = 0.001$ ). Overall, 398 (95.2%) of respondents had viral load suppressed ( $VL < 1000$  copies/ml) after 6 months of intervention compared to 302 (72.3%) of respondents who had viral load suppression ( $VL < 1000$  copies/ml) pre-intervention. We recommend that all eligible HIV treatment experienced patients in Nigeria, on other combinations should be transitioned to DTG based combination regimen to facilitate the attainment of UNAIDS 3<sup>rd</sup> 95 target of 95-95-95 by 2030.

**Key words:** Antiretroviral, Dolutegravir, HIV Patients, viral load, UNAIDS target

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### I. Introduction

The Human Immunodeficiency Virus (HIV) response in Nigeria has reached roughly 1 million patients with highly-active antiretroviral therapy (HAART) in about 1500 treatment sites [1]. Despite the increasing access to antiretroviral medications several studies have demonstrated suboptimal levels of viral load suppression among different population groups especially in low resource settings [2, 3]. In order to achieve the 90-90-90 strategy of UNAIDS by 2020 and 95-95-95 by 2030 ensuring a sustained viral suppression in HIV patients on ARVs is critical [1].

The 2016 guidelines developed by Nigeria for the prevention, treatment and care of HIV patients which was in line with the 2016 WHO consolidated guidelines on the use of ARV drugs recommended TDF/3TC/DTG as the preferred first line combination as against Zidovudine/lamivudine/Nevirapine (ZDT/3TC/NVP) or Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV) [4]. The integrase inhibitor Dolutegravir has shown evidence to play a major role in antiretroviral therapy (ART) regimens in sub-Saharan Africa because of its high potency and genetic barrier to resistance, good tolerability, and low cost [5].

The viral load suppression rate among people living with HIV on HAART in Nigeria in 2019 was as low as 44.5% [6]. There are ongoing challenges with antiretroviral therapy (ART) in Nigeria and indeed in sub-Saharan Africa despite the scale up which is seen as a major achievement. These challenges include increasing transmitted drug resistance, poor coverage of viral load monitoring, and low numbers of people who have fulfilled the criteria for failure of first-line ART switching to second-line regimens. Dolutegravir based regimens are associated with less need to switch to other antiretroviral drugs and there is a lower risk of development of major drug resistance mutations compared with efavirenz-based regimens (5). Besides, 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 has shown to be naturally resistant to NNRTIs (7).

There is paucity of research on the effect of DTG based combination in suppressing viral load among HIV patients in Nigeria. In Nigeria, the DTG fixed dose-based combination therapy was approved as the preferred first line ART on the 5<sup>th</sup> of October 2018. The implementation of its use started in July 2019 (4).

This study was aimed at determining the effect of DTG based combination in suppressing viral load among HIV treatment experienced patients in Nigeria. It will also contribute to the body of knowledge by generating valuable information, which will serve as baseline for future research in Nigeria.

## **II. Methods and Materials**

### **Study setting and population**

Nigeria is located in sub-Saharan Africa with a population of over 140 million people and occupying a landmass of 923,768 square kilometers. Niger state is located in the North central geopolitical zone of Nigeria with a population of 3,950,249 people according to the 2006 national population commission census [8]. The projected population of Niger state for 2016 was 5,556,247 [9]. The state HIV prevalence currently stands at 0.7% [1]. The study population are registered HIV treatment experienced patients enrolled into care and treatment at the General Hospital, Minna, Nigeria.

### **Study design and sample size estimation**

A prospective single arm trial to evaluate the effect of DTG fixed dose combination (TDF/3TC/DTG) in suppressing viral load among HIV treatment experienced patients in general Hospital, Minna. The formula for calculating sample size for one proportion  $n = Z^2 P(1-P)/d^2$  [10] was used to estimate the sample size and was based on a viral load suppression prevalence of 44.5% among people living with HIV in Nigeria [6]. A total sample size of 380 participants is estimated for the study. Considering an attrition rate of 10%, 38 participants were added, making the final sample size of 418 participants

### **Sampling Method**

Simple random sampling method was used for the study. The random sample was selected using a computer-based random number generator (<http://www.randomizer.org>) used by earlier researchers [11]. The sample frame comprised of a list of 630 HIV patients who were transitioned from Zidovudine (ZVD/3TC/NVP) or Efavirenz based combination regimen (TDF/3TC/EFV) to DTG based combination regimen (TDF/3TC/DTG) receiving treatment and care at the study center. The inclusion criteria for this study were adult's HIV treatment experienced patients receiving treatment at the study center and those that did not consent were excluded.

### **Study duration**

The study was conducted from July to December 2019

### **Intervention activities**

Patients on either ZVD/3TC/NVP or TDF/3TC/EFV were transitioned to TDF/3TC/DTG combination as recommended by WHO [4]. A staff was trained to collect data from all participants. Demographic Characteristics of participants, pre-intervention viral load and viral load 6 months after transition were the information collected from respondents.

### **Data collection**

A questionnaire was administered to respondents to collect information on demographic characteristics at baseline, baseline viral load at the time of recruitment and 6 months' viral load from their medical records. Data was collected from participants in July 2019 and December 2019.

### **Operational definition of terms**

- Effectiveness refers to the degree in which DTG based combination was successful in producing the desired effect in suppressing viral load among respondents.
- HIV treatment experienced patients are HIV patients receiving treatment for HIV with either ZDV/3TC/NVP or TDF/3TC/EFV combination for at least 6 months.
- Viral load suppression is when a patient viral load reduces to less 1000cp/ml after 6 months of ARV medication commencement.

**Declaration**

We, the author(s) declared no conflicts of interest with respect to the research, authorship and publication of this paper.

**Ethical consideration**

Ethical clearance to conduct the study was obtained from General hospital Minna, Ethics Committee for Research Involving Human Subjects. Informed consent was sought from each participant before the conduct of the study.

**Data analysis**

Data analysis was carried out using Statistical package for social sciences (SPSS) version 22 (IBM 2014). Data collected was carefully checked, cleaned and successfully entered into SPSS. Exploratory data analysis was conducted in SPSS purposely to clean and make sure that there was no mistake in data entry, identify outliers and missing data. Normality tests was conducted for all continuous variables using graphical methods (histogram, normal Q-Q plots, stem and leaf plots, box plots) and other statistical methods (skewness and kurtosis ratio). However, the data of the outcome variable (viral load) at pre-intervention was not normally distributed. Therefore, Non-parametric test (Wilcoxon signed-rank test) was conducted to test the effect of DTG based combination regimen on suppressing viral load. Chi Square ( $\chi^2$ ) was conducted to analyze categorical variables. Frequency & percentages were done to analyzed demographic variables and percentage of participants that had viral suppression at baseline and at the end of the study. The p-values of the results of the analysis was compared to an alpha ( $\alpha$ ) level of significance of 0.05 and the power of 80% to detect the impact of the intervention.

**III. Results**

Table 1 shows that the mean age of respondents for this study was 40 years and majority were between 40 to 49 years. Out of the 418 respondents, 253 (60.3%) were females. Majority 321 (76.8%) resided in urban areas, 259 (62%) were Muslims and 159 (38%) were Christians. Majority 358 (85.6%) of the respondents were married. The results also showed that 177 (42.3%) of the respondents had no formal education and the remaining had either primary, secondary or tertiary education. The main occupations of respondents were trading 137 (32.8%), civil servants 100 (23.9%) and 94(22.5%) were housewives. Majority of the participants 304 (72.7%) were in WHO clinical stage 1. There was no statistically significant relationship between the sociodemographic characteristics of the respondents and viral load suppression level pre-intervention.

**Table 1: sociodemographic characteristics of the respondents (n = 418) and their relationship with viral load suppression pre-intervention**

Variables	Frequency (n)	Percentage (%)	Viral load of HIV infected treatment experienced patients pre-intervention		Test statistics
			VL < 1000 copies/ml	VL ≥ 1000 copies/ml	
<b>Age (years)</b>					
< 30	54	12.9	37	17	$\chi^2 = 4.184$ p = 0.382
30 – 39	137	32.8	93	44	
40 – 49	147	35.2	108	39	
50 – 59	60	14.4	48	12	
≥ 60	20	4.8	16	4	
<b>Gender</b>					
Male	166	39.7	122	180	$\chi^2 = 0.213$ p = 0.644
Female	253	60.3	44	72	
<b>WHO clinical stage</b>					
Stage 1	304	72.7	215	89	Fisher’s exact test = 1.409 P = 0.708
Stage 2	60	14.4	46	14	
Stage 3	52	12.4	39	13	
Stage 4	2	0.5	2	0	
<b>Occupation</b>					
Farmer	37	8.9	26	12	Fisher’s exact test = 6.755
Civil servants	100	23.9	77	23	

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Traders/businessmen	137	32.8	97	40	P = 0.237
Students	30	7.2	17	13	
Housewife	94	22.5	69	25	
Others	20	4.8	17	3	
<b>Educational level</b>					$\chi^2 = 2.403$ p = 0.493
No formal education	177	42.3	122	55	
Primary	68	16.3	52	16	
Secondary	115	27.5	83	32	
Tertiary	58	13.9	45	13	
<b>Marital status</b>					Fisher's exact test $\chi^2 = 3.064$ P = 0.369
Married	358	85.6	262	96	
Single	27	6.5	16	11	
Divorced/separated	11	2.6	9	2	
Widowed	22	5.3	15	7	

Table 2 shows the result of Wilcoxon signed-rank test which indicates that the median post intervention score of 25.35 was statistically significantly lower than the median pre-intervention score of 174.0 after transition of HIV treatment experienced patients to DTG based combination regimen. The DTG based combination regimen elicited a statistically significant effect in suppressing viral load in respondents with unsuppressed viral load ( $Z = -11.134, p = 0.001$ ).

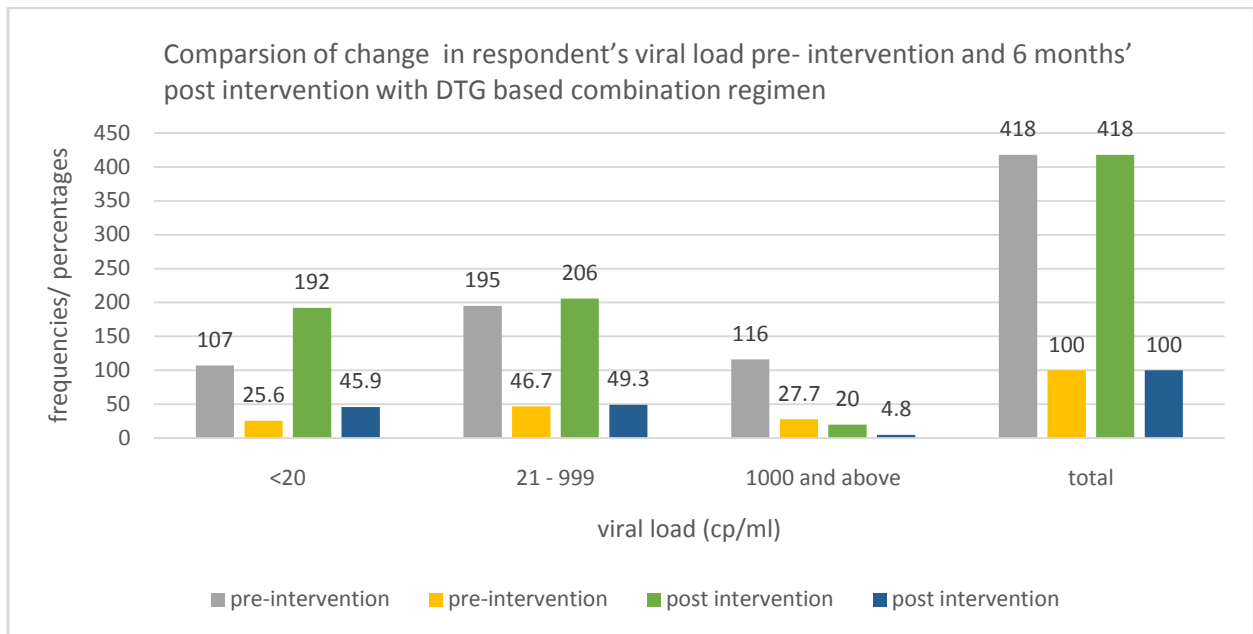
**Table 2: Change in Medianviral load among HIV treatment experienced patients from pre-intervention to 6 months' post intervention (Wilcoxon signed-rank test)**

Measured variable (viral load)	N	Percentiles	Range		Z score	p-value
		50 <sup>th</sup> (Median)	Minimum	maximum		
Viral load pre-intervention	418	174.00	19	1150000	- 11.134	0.001
Viral load post intervention	418	25.35	19	1510000		

Table 3 shows the comparison in change of the respondent's viral load from pre-intervention and 6 months' post intervention. 302 (72.3%) of respondents' pre-intervention had a viral load of less 1000 copies/ml (suppressed viral load). 398 (95.2%) after 6 months' post intervention had viral load of less than 1000 copies/ml. 107 (25.6%) of respondents' pre-intervention compared to 192 (45.9%) of respondent's post intervention had viral load less than 20copies /ml. 116 (27.7%) of respondents per-intervention compared to 20 (4.8%) of respondents post intervention had viral load of 1000 copies/ml and above.

**Table 3: Comparison of change in respondent's viral load pre- intervention and 6 months' post intervention with DTG based combination regimen**

S.no.	Outcome variable (viral load copies/ml)	Pre-intervention		Post intervention	
		Frequency(n)	Percentage (%)	Frequency (n)	Percentage (%)
1	<20 copies/ml	107	25.6	192	45.9
2	21 – 999copies/ml	195	46.7	206	49.3
3	1000 copies/ml	116	27.7	20	4.8
	Total	418	100.0	418	100.0



**Figure 1.** Graph showing the change in viral load of respondents at pre and post intervention of 107 (25.6%) and 192 (45.9%) respectively had Viral load less than 20 copies/ml. Also, 195 (46.7%) pre-intervention and 206 (49.3%) post intervention had Viral load between 21 – 999copies /ml. While 116 (27.7%) respondent's pre-intervention and 20 (4.8%) post intervention had` viral load of 1000 copies/ml and above.

#### IV. Discussion

A report from WHO indicated that viral load Suppression was found to be faster among those on DTG-based regimens compared to EFV-based regimens [7]. It stated that 81% of patients who started with a DTG-based regimen presented a suppressed viral load after 3 months of treatment, compared to 61% for those on an EFV-based regimen [7]. This was consistent with the finding of our study which revealed that 95.2% of patients achieved a viral load suppression with DTG based combination therapy within 6 months compared to 72.3% while on either EFV or ZDV combination therapy. Though our study was done on adults, nevertheless a comparative study conducted in university of Port Harcourt teaching hospital among children on the effect of TLD, revealed a statistically significant effect on suppressing viral load over a 6 months' period ( $X^2 = 53.77$ ,  $p = 0.0001$ ) [12] which is consistent with the findings of our study ( $Z = -11.134$ ,  $p = 0.001$ ). The same study reported that 91.5% of respondents achieved a viral suppression at the end of 6 months [12] consistent with the findings of our study which showed that 95.2% of respondents had viral load suppression ( $< 1000$  copies/ml). Likewise, a study to assess the effect of DTG on HIV infected treatment naïve patients in a hospital in Ireland reported that 88.57% of the patients had viral load suppression at the end of 48 weeks [13] compared to 95.2% of respondents in our study, even though it was on HIV infected treatment experienced patients. At the end of our study (6 months) only 45.9% of the patients had undetectable viral load ( $< 20$  copies/ml) compared to a study which reported 63.9% of patients had undetectable viral load ( $< 50$  copies/ml) at 3 months and 83.57% at 12 months [13]. An undetectable viral load is the limit below which the machine cannot detect the virus. This varies in different machines ( $< 400, 200, 100, 50, 20$ ) [14]. The cut-off point for the viral load in the two studies could explain the difference in the percentage of patients with undetectable viral load. Another study conducted in the United Kingdom on the effect of DTG revealed a rapid and sustained antiviral response with 82% of patients attaining viral load suppression of 50 copies/ml within 96 weeks of treatment [15]. Though our study was for a period of 6 months (24 weeks), 45.9% of our participants achieved an undetectable viral load suppression of  $< 20$  copies/ml which is comparable to the aforementioned report considering the time period of the study. This clearly shows that with a longer treatment period of over a year or more, 100% undetectable viral RNA (20 copies/ml) with a DTG based combination regimen is achievable. Several other studies have demonstrated the superiority of DTG based combination regimen over other combinations with 95.2% of patients in our study having suppressed viral load at 6 months (24 weeks) compared to other studies such as SPRING -2 with 88% at 48 weeks, SINGLE study 88% and the FLAMINGO study of 90% at 48 weeks [16]. The DTG based combination therapy is promising in actualizing treatment as prevention towards achieving UNAIDS target of 95-95-95 by the year 2030 [17] which is aimed at ending the HIV pandemic. It is therefore recommended that all HIV infected treatment experienced patients on other combinations to be transitioned to DTG based combination therapy if eligible based on its proven effectiveness in suppressing viral load. Eventually, this will

lead to undetectable viral load and reduction in the transmission of HIV. An individual with a viral load of less than 200cp/ml has been shown not to be able to transmit the virus via unprotected sexual intercourse [18]. In 2016, the Prevention Access Campaign, a health equity initiative with the goal of ending the HIV/AIDS pandemic as well as HIV-related stigma, launched the Undetectable = Untransmittable (U = U) initiative. U = U signifies that individuals with HIV who receive antiretroviral therapy (ART) and have achieved and maintained an undetectable viral load cannot sexually transmit the virus to others. This concept, based on strong scientific evidence, has broad implications for treatment of HIV infection from a scientific and public health standpoint, for the self-esteem of individuals by reducing the stigma associated with HIV, and for certain legal aspects of HIV criminalization [18]. The public health benefits of attaining an undetectable viral load is enormous. The concept of treatment as prevention (TasP) can only be actualized if the viral load is suppressed and this can be achieved through the use of potent antiretroviral like DTG based combinations. In our study, a viral load of less than 20cp/ml was used as undetectable which is the lowest attainable viral load the machine can detect. One major way of achieving the global target of ending the AIDS epidemic by the year 2030 and achieving the 3<sup>rd</sup> 95 is by ensuring access to potent ARVs and DTG based combination regimen has proven to be effective in accelerating this process.

## V. Conclusion

In conclusion, our study has shown that Tenofovir/lamivudine/dolutegravir (TLD), a DTG based fixed dose combination regimen is effective in suppressing viral load among HIV treatment experienced patients with suboptimal viral suppression on other combinations. We recommend that all eligible HIV treatment experienced patients in Nigeria, on other combinations should be transitioned to DTG based combination regimen to facilitate the attainment of UNAIDS 3<sup>rd</sup> 95 target by 2030 and ending the AIDS pandemic.

## LIMITATION OF THE STUDY

The center did not have the capacity to conduct resistance testing. This would have assisted in determining the possibility of resistance to DTG based combination on those that were virally unsuppressed at the end of the study despite good adherence.

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