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Clinical Effectiveness of Dolutegravir-based Antiretroviral Therapy and its Determinants in Persons Living with HIV at a Kenyan Referral Hospital

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Dolutegravir is widely used for HIV treatment as a first line drug. Though proven to be efficacious in other settings, its clinical effectiveness in resource-constrained settings is not yet confirmed. To determine the clinical effectiveness of dolutegravir regimens and associated factors in adults living with HIV at the Kenyatta National Hospital, a cross-sectional study was conducted at the HIV clinic using data abstracted from randomly sampled patient files. Descriptive and regression analysis were done using STATA version-13 at an α of ≤ 0.05. Most of the 154 participants enrolled were females (95, 61.7%). The mean age was 45.2 (SD ± 10.6) years. Viral load suppression was 92.6% and 95.5% at 6 and 12 months respectively. The TDF/3TC/DTG regimen (aOR = 21.607, 95% CI 1.118, 417.591) gave better odds of viral suppression at six months. Prevalence of opportunistic infections significantly decreased after dolutegravir initiation with bacterial pneumonia (6, 3.9%) being most common. Being treatment-experienced (aOR = 0.066, 95% CI 0.005, 0.886) resulted in lower odds of opportunistic infections after dolutegravir initiation. Adverse drug reactions to dolutegravir were infrequent though headache (11, 7.1%), weight-gain (3, 1.9%), and insomnia (2, 1.3%) were reported. Males (aOR = 0.222, 95% CI 0.061, 0.814) had lower odds of having adverse drug reactions. Dolutegravir-based regimens are clinically effective and well-tolerated with minimal adverse drug reactions.

Key words: Clinical effectiveness, dolutegravir-based antiretroviral therapy, persons living with HIV, Kenyatta National Hospital

INTRODUCTION

Nearly 39.9 million people were documented to be living with HIV globally at the close of 2023, of which 65% resided in sub Saharan Africa.[1] The prevalence of HIV among adults in Kenya was 4.9% in 2019, translating to approximately 1.3 million people.[2] The World Health Organization (WHO) recommends the use of dolutegravir (DTG) and a Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone when initiating individuals on Anti-retroviral Therapy (ART).[3] The Kenya Ministry of Health recommends TDF/3TC/DTG as the first line for adult patients with HIV [4], and as such it was rolled out in the country in 2017 and has become the most used regimen. DTG is known to be better tolerated, has high potency with a high genetic barrier to HIV drug resistance.

The effectiveness of an antiretroviral can be estimated by assessing its ability to lower the viral load to undetectable levels (< 50 viral copies/ml). Several factors can influence viral load suppression including, adherence, long- and short-term toxicities, pharmacogenomics, drug-drug and drug-food interactions, and drug product factors such as pill burden or availability.[5] Though the clinical effectiveness of DTG is well established in other populations, the same cannot be said of sub-Saharan Africa (SSA) where there exists a paucity of data. Most studies are done in high-income settings and findings generalized thereafter. The present study assessed the clinical effectiveness of dolutegravir-based ART among adult Persons Living with HIV (PLHIV) at the Kenyatta National Hospital (KNH) from January 2017 to December 2020.

METHODS

A hospital-based cross-sectional study was implemented, where data was obtained through a review of patient records covering January

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2017 - December 2020. Outcome variables included viral load suppression, opportunistic infections, adverse drug reactions, and DTG drug switches.

The study was conducted at the Comprehensive Care Clinic (CCC) of the KNH (KNH-CCC). The calculated sample size was 154 participants (based on the prevalence of viral suppression reported by Pujari *et al.*).[6] Patients were included in the study if they were above 18 years of age, had a documented HIV diagnosis, were enrolled at KNH-CCC for care, had been on a DTG based ART regimen for at least 6 months, had documented viral load results at 6 and 12 months within the study period, and gave consent to participate in the study. Patients were excluded from the study if they were declared lost to follow-up or were on antituberculosis medication at any point within the study period, and had no documented baseline viral load results during the switch to DTG-based ART regimen.

Simple random sampling with replacement was used to attain the sample size. The KNH-CCC patient register provided a complete list of all adult PLHIV patients actively attending the clinic and their respective ART regimens. Once the eligible participants from the sampling frame had been serialized, Microsoft® Excel (Microsoft Inc, Redmont, WA, USA) was used to generate random numbers to create a simple random sample. Replacement by generation of the next random number was done if an eligible file was picked but found to miss a lot of data. Secondary data were abstracted from patient records covering the study period and entered into the data abstraction form. The secondary data sources used included patient and electronic databases (DHIS, Kenya-EMR, and Pharmacy Web-ADT).

Pre-testing of the research instruments was done on 10 eligible participant files which were later excluded during the actual study. The data collection form was also tested on secondary data sources thus capturing data for the selected 10 patients for piloting purposes. All reviews of patient files were done on-site at the KNH-CCC with no file translocation. All filled data collection forms were securely stored under lock and key. The study was approved for conduct by the KNH/UoN ERC (KNH-ERC/A/204)

Data analysis

Raw data was entered into a Microsoft® Excel worksheet to create the database. Data were cleaned and exported to the STATA version 13 software (StataCorp LLC, College Station, TX, USA) for analysis. Descriptive statistics were used to summarize clinical data such as regimen details, viral load suppression, adverse drug reactions, whereas logistic regression was performed to determine the relationship between various independent variables such as age, gender and the outcome variable. Logistic regression analysis was used to determine predictors of viral load suppression at 6 months and 12 months on a DTG based ART regimen. A p-value $\leq$ 0.05 was considered statistically significant.

RESULTS

A total of 154 participants were recruited into the study, most of whom were females (95, 61.7%) Participants were aged 45.2 (SD $\pm$ 10.6) years, with a range of 19 to 70 years. The mean duration living with HIV among the participants was 9.1 (SD $\pm$ 4.6) years (Table 1). Participants had been on treatment with a DTG based regimen for a mean duration of 21.3 (SD $\pm$ 6.5) months.

At 6 and 12 months on a DTG based ART regimen, a majority of the participants were virally suppressed (137, 92.6%) and (105, 95.5%), respectively. During these periods, viral load suppression was significantly associated with marital status ($p = 0.02$) and smoking status ($p = 0.045$), respectively (Table 2). Clinically, utilization of DTG based regimens was associated with viral load suppression at 6 months ($p = 0.017$) as shown in Table 3.

Cases of opportunistic infections (OIs) following initiation of a DTG based ART regimen were very few (<4%). The prevalence of OIs was higher before initiation on a DTG based therapy [before (mean = 0.221; SD $\pm$ 0.034) and after (mean = 0.078; SD $\pm$ 0.022); $t(153) = 3.612$, $p < 0.001$]. In addition, after initiation of a DTG based ART regimen, a majority (126, 81.8%) of the participants did not experience any adverse drug reaction (ADR). No switch from dolutegravir based regimens was observed for the entire duration of the study.

Table 1: Sociodemographic characteristics of the study population

	Variables	Total (N=154)	%
Sex; n (%)	Male	59	38.3
	Female	95	61.7
Age in years; mean (SD)	45.2 (10.6)		
Marital status; n (%)	Single	36	23.5
	Married	75	49.0
	Widowed	20	13.1
	Separated	20	13.1
	Divorced	2	1.3
Education; n (%)	Primary	18	12.2
	Secondary	69	47.0
	Tertiary	60	40.8
Employment; n (%)	Self employed	75	49.3
	Employed	36	23.7
	Unemployed	36	23.7
	Retired	5	3.3
Smoking status; n (%)	Yes	2	1.3
	No	152	98.7
Alcohol use; n (%)	Yes	3	2.0
	No	151	98.0
Duration LHIV in years; mean (SD)	9.1 (4.6)		

Following initiation of a DTG based ART regimen, the likelihood of a patient getting an OI was found to be associated with whether they were treatment-experienced or treatment naïve (p = 0.042). The occurrence of ADRs after initiation of DTG based ART was associated with the specific type of DTG regimen prescribed (p = 0.048) (Table 3).

Marital status was found to be a predictor of viral load suppression at 6 months of therapy on bivariable analysis (cOR = 9.682; 95% CI 1.194, 78.511; p = 0.034) (Table 4). Married individuals were 9.682 times more likely to be virally suppressed at 6 months on a DTG based ART regimen compared to the unmarried. However, the effect was lost on multivariable analysis.

At 6 months on DTG regimens, participants who were on TDF/3TC/DTG therapy were 21 times more likely to be virally suppressed compared to those who were on other DTG regimens (aOR = 21.607; 95% CI 1.118, 417.591; p = 0.042). No predictors of VL suppression among patients on DTG based regimens were identified at 12 months of therapy on the bi- and multi-variable models (Table 4).

The ART status of the patient (i.e. whether treatment-experienced or treatment naïve at the point of initiation to DTG) was found to be associated with an 82–93% lowered risk of acquiring an opportunistic infection at bivariable and multivariable logistic regression analysis respectively (Table 5). No risk factors for ADRs following initiation of a DTG based ART regimen were identified at bivariable logistic regression. However, males had 22% lower odds of experiencing an ADR compared to female participants after DTG initiation (aOR = 0.222; 95% CI 0.061, 0.814; p = 0.023). Participants on TDF/3TC/DTG regimen had a lower risk of experiencing an ADR after DTG initiation compared to participants initiated on other DTG regimens (aOR = 0.090; 95% CI 0.012, 0.690; p = 0.021).

Table 2: Association between viral load (VL) suppression, sociodemographic and medical characteristics

	VL suppression at 6 months (n=148)			VL suppression at 12 months (n=110)		
Variable	**Suppressed n (%)**	**Not suppressed n (%)**	**p value**	**Suppressed n (%)**	**Not suppressed n (%)**	**p value**
Age (years)						
< 45	63 (92.6)	5 (7.4)	0.973	45 (97.8)	1 (2.2)	0.301
≥ 45	74 (92.5)	6 (7.5)		60 (93.7)	4 (6.3)	
Sex Male	52 (91.2)	5 (8.8)	0.623	58 (95.1)	3 (4.9)	0.603
Female	85 (93.4)	6 (6.6)		47 (95.9)	2 (4.1)	
Marital status:						
Single	31 (91.2)	3 (8.8)	**0.02**	19 (95.0)	1 (5.0)	0.372
Married	71 (98.6)	1 (1.4)		57 (96.6)	2 (3.4)	
Widowed	15 (78.9)	4 (21.1)		12 (85.7)	2 (14.3)	
Separated	18 (90.0)	2 (10.0)		14 (100.0)	0 (0.0)	
Divorced	2 (100.0)	0 (0.0)		2 (100.0)	0 (0.0)	
Alcohol use:						
Yes	2 (66.7)	1 (33.3)	0.208	1 (50.0)	1 (50.0)	0.089
No	135 (93.1)	10 (6.9)		104 (96.3)	4 (3.7)	
Smoking status:						
Yes	1 (50.0)	1 (50.0)	0.144	0 (0.0)	1 (100.0)	**0.045**
No	136 (93.1)	10 (6.9)		105 (96.3)	4 (3.7)	
Duration LHIV (years)						
< 9	65 (94.2)	4 (5.8)	0.349	54 (98.2)	1 (1.8)	0.182
≥ 9	72 (91.1)	7 (8.9)		51 (92.7)	4 (7.3)	
Employment						
Self employed	67 (93.1)	5 (6.9)	0.391	51 (96.2)	2 (3.8)	0.869
Employed	32 (91.4)	3 (8.6)		24 (92.3)	2 (7.7)	
Unemployed	33 (97.1)	1 (2.9)		23 (95.8)	1 (4.2)	
Retired	4 (80.0)	1 (20.0)		5 (100.0)	0 (0.0)	
Education:						
Primary	15 (88.2)	2 (11.8)	0.53	9 (90.0)	1 (10.0)	0.38
Secondary	62 (92.5)	5 (7.5)		49 (94.2)	3 (5.8)	
Tertiary	54 (94.7)	3 (5.3)		41 (97.6)	1 (2.4)	
Chronic condition						
Present	65 (95.6)	3 (4.4)	0.165	48 (96.0)	2 (4.0)	0.586
Absent	72 (90.0)	8 (10.0)		57 (95.0)	3 (5.0)	
ART status on DTG initiation						
Treatment sensitive	126 (92.0)	11 (8.0)	0.414	97 (95.1)	5 (4.9)	0.681
Treatment naïve	11 (100.0)	0 (0.0)		8 (100.0)	0 (0.0)	
Duration on DTG based regimen in months						
< 20	63 (92.6)	5 (7.4)	0.973	32 (94.1)	2 (5.9)	0.493
≥ 20	74 (92.5)	6 (7.5)		73 (96.1)	3 (3.9)	
DTG-based regimen						
TDF/3TC/DTG	133 (93.7)	9 (6.3)	**0.017**	104 (95.4)	5 (4.6)	0.955
AZT/3TC/DTG	2 (100.0)	0 (0.0)				
ABC/3TC/DTG	2 (100.0)	0 (0.0)				
TDF/3TC/DTG (2nd Line)	0 (0.0)	2 (100.0)		1 (100.0)	0 (0.0)	

Table 3: Association between opportunistic infections, adverse drug reactions and medical characteristics

	OIs after DTG			ADR after DTG		
Variable	**Present; n (%)**	**Absent; n (%)**	**p value**	**Present; n (%)**	**Absent; n (%)**	**p value**
Chronic Condition						
Present	4 (5.6)	68 (94.4)	0.254	11 (15.3)	61 (84.7)	0.381
Absent	8 (9.8)	74 (90.2)		17 (20.7)	65 (79.3)	
ART Status on DTG Initiation						
Treatment Experienced	9 (6.3)	134 (93.7)	**0.042**	25 (17.5)	118 (82.5)	0.32
Treatment naïve	3 (27.3)	8 (72.7)		3 (27.3)	8 (72.7)	
Duration on DTG based regimen in months						
< 20	5 (6.9)	68 (93.2)	0.679	16 (21.9)	57 (78.1)	0.254
≥ 20	7 (8.6)	74 (91.4)		12 (14.8)	69 (85.2)	
DTG-based regimen of participants						
TDF/3TC/DTG	11 (7.4)	137 (92.6)	0.391	25 (16.9)	123 (83.1)	**0.048**
AZT/3TC/DTG	0 (0.0)	2 (100.0)		0 (0.0)	2 (100.0)	
ABC/3TC/DTG	0 (0.0)	2 (100.0)		2 (100.0)	0 (0.0)	
TDF/3TC/DTG (2nd Line)	1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)	

DISCUSSION

In this hospital-based cross-sectional study examining the clinical effectiveness of DTG based ART regimens among PLHIV on follow up, a large number of participants with adequately suppressed viral loads, low prevalence of opportunistic infections, and good tolerability of the drugs were encountered. The prevalence of VL suppression among the participants was high, which was in agreement with reports by Mehari *et al*. and Nabitaka *et al*. showing 92% and 94% VL suppression among patients on TDF/3TC/DTG at 12 months and 6 months respectively.[7,8] This finding correlates with those published in the Kenya Population-based HIV Impact Assessment 2018 preliminary report.[2]

Several studies have shown that marital status can have a significant influence on VL suppression, directly or indirectly by acting through aspects such as disclosure, adherence, a stable sexual partner, and social support system.[9–11] This study however did not align with such reports. On the contrary, the findings were in agreement with other reports averring that marital status was not an independent predictor of VL suppression.[12–14] However, a study by Meshesha *et al*. found that the divorced/separated individuals had threefold higher odds of virological failure than married individuals.[15]

Table 4: Independent predictors of viral load suppression at 6 & 12 months of dolutegravir therapy

	6 months				12 months			
	Bivariable analysis		Multivariable analysis		Bivariable analysis		Multivariable analysis	
Variable	cOR (95% CI)	p value	aOR (95% CI)	p value	cOR (95% CI)	p value	aOR (95% CI)	p value
Age in years	1.006 (0.949, 1.066)	0.852	1.025 (0.941, 1.116)	0.571	1.023 (0.937, 1.117)	0.606	1.081 (0.934, 1.251)	0.296
Sex	0.734 (0.213, 2.527)	0.624	4.667 (0.392, 55.561)	0.223	1.216 (0.195, 7.578)	0.834	2.013 (0.155, 26.133)	0.593
Marital status	9.682 (1.194, 78.511)	**0.034**	6.234 (0.670, 58.028)	0.108	1.819 (0.292, 11.345)	0.522	0.644 (0.052, 8.033)	0.733
Alcohol use	0.148 (0.012, 1.778)	0.132	0.019 (<0.001, 1.349)	0.068	-		-	
Duration LHIV in years	0.903 (0.785, 1.038)	0.150	0.882 (0.733, 1.063)	0.187	0.921 (0.751, 1.130)	0.431	0.765 (0.535, 1.095)	0.144
Employment	0.669 (0.136, 3.296)	0.621	0.476 (0.069, 3.287)	0.451	0.670 (0.072, 6.252)	0.725	0.182 (0.006, 5.426)	0.325
Education	1.933 (0.375, 9.968)	0.431	0.810 (0.044, 15.011)	0.888	2.500 (0.252, 24.834)	0.434	24.116 (0.528, 1101.636)	0.103
Chronic condition	2.407 (0.613, 9.461)	0.208	3.834 (0.539, 27.292)	0.180	1.263 (0.203, 7.874)	0.802	0.640 (0.052, 7.812)	0.727
Duration on DTG therapy (months)	0.987 (0.900, 1.082)	0.775	0.913 (0.787, 1.060)	0.232	1.048 (0.885, 1.240)	0.588	1.077 (0.835, 1.388)	0.568
DTG based regimen	7.389 (1.189, 45.909)	**0.032**	21.607 (1.118, 417.591)	**0.042**	-		-	

Table 5: Independent predictors of opportunistic infections and adverse drug reactions after DTG initiation

	Opportunistic infections				Adverse drug reactions			
	Bivariable analysis		Multivariable analysis		Bivariable analysis		Multivariable analysis	
Variable	cOR (95% CI)	p value	aOR (95% CI)	p value	cOR (95% CI)	p value	aOR (95% CI)	p value
Age in years	1,019 (0.962, 1.079)	0.524	1.021 (0.958, 1.088)	0.527	1.026 (0.987, 1.066)	0.196	0.984 (0.941, 1.030)	0.496
Sex	1.679 (0.515, 5.474)	0.390	1.091 (0.193, 6.170)	0.922	0.588 (0.241, 1.438)	0.245	0.222 (0.061, 0.814)	**0.023**
Marital status	0.724 (0.219, 2.391)	0.597	0.395 (0.086, 1.810)	0.232	0.881 (0.387, 2.002)	0.762	1.249 (0.498, 3.134)	0.635
Alcohol use	6.364 (0.534, 75.813)	0.143	-		2.296 (0.201, 26.248)	0.504	8.741 (0.395, 193.323)	0.170
Smoking status	-		-		4.630 (0.281, 76.349)	0.284	-	
Duration LHIV in years	1.017 (0.894, 1.156)	0.798	1.116 (0.932, 1.335)	0.232	1.013 (0.927, 1.108)	0.769	1.068 (0.953, 1.198)	0.259
Employment	1.118 (0.287, 4.349)	0.873	1.111 (0.238, 5.177)	0.893	0.493 (0.208, 1.169)	0.108	0.563 (0.217, 1.464)	0.239
Education	0.529 (0.103, 2.713)	0.445	0.303 (0.046, 1.990)	0.214	0.564 (0.183, 1.739)	0.319	0.384 (0.104, 1.410)	0.149
Chronic condition	0.544 (0.157, 1.889)	0.338	0.498 (0.104, 2.379)	0.382	0.689 (0.299, 1.589)	0.383	0.505 (0.184, 1.383)	0.184
ART status on DTG initiation	0.179 (0.040, 0.794)	**0.024**	0.066 (0.005, 0.886)	**0.040**	0.565 (0.140, 2.280)	0.423	0.268 (0.039, 1.832)	0.180
Duration on DTG therapy (months)	1.024 (0.939, 1.117)	0.588	1.054 (0.934, 1.190)	0.391	0.988 (0.926, 1.053)	0.708	1.092 (0.999, 1.194)	0.054
DTG based regimen	0.401 (0.043, 3.745)	0.423	0.395 (0.021, 7.344)	0.533	0.203 (0.039, 1.066)	0.059	0.090 (0.012, 0.690)	0.021

In this study, there was a significant difference in VL suppression at 6 months among participants on different DTG based ART regimens. Other studies have demonstrated no significant difference in VL suppression when combining DTG with ABC/3TC compared to a combination with TDF/3TC.[16–18] Participants on second line TDF/3TC/DTG had been switched to this from a previous ritonavir boosted protease inhibitor (PI/r) based second-line regimen. Their odds of having VL suppression may be different from those on first line TDF/3TC/DTG as implied by this study. However, Gatell *et al*. found that switching from a PI/r-based ART regimen to a DTG based regimen did not result in virological failure.[19]

The burden of OIs among the study participants reduced following the initiation of DTG based ART, implying that that treatment was effective at preventing deterioration of the immune system and thus improving the individual's quality of life. The most prevalent OI before and after initiation of a DTG based ART regimen was bacterial pneumonia, corroborated by other studies.[20,21]

A systematic review conducted by Low *et al*. concluded that ART reduced the risk for most OIs especially in the first year of treatment [22], affirming the finding that treatment experience predicted OIs. Prompt initiation of ART is meant to prevent unchecked damage to the immune system by suppressing the rate of viral replication as early as possible. Therefore, an individual who is not on ART is more likely to develop and/or manifest OIs.

Hoffman *et al*. found that neuropsychiatric adverse events resulting from a switch to DTG occurred more frequently in women [23] which tallied with this report. This may be attributed to them having "a lower lean body mass, a reduced hepatic clearance, differences in the activity of cytochrome P450 enzymes and metabolize drugs at different rates compared to men", as well as hormonal and immunological differences.[24]

Boer *et al*. concluded that DTG was switched more frequently due to ADRs if the regimen contained Abacavir [25], mirroring the findings in the current report. In this study, none of the participants recorded any instances of switch of DTG due to ADRs or any other reason, a testament to the fact that DTG based ART regimens are well tolerated.

Notable limitations in the present study includes the small number of participants who were on other DTG based ART regimens apart from TDF/3TC/DTG. Despite this, consistent follow up of the available patients through the study period to obtain the required information was conducted. Furthermore, the extent of viral load suppression using DTG based ART regimens and the most prevalent ADRs associated with the regimen, were described.

CONCLUSION

DTG based regimens are clinically effective in VL suppression among the HIV infected individuals. The study demonstrates that married participants who are experienced on TDF/3TC/DTG regimens are likely to experience greater viral suppression, have fewer opportunistic infections as well as adverse drug reactions which is relevant clinical practice. More efforts should be made to continue monitoring and optimizing DTG based regimen according to the patients' characteristics.

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