HIV/AIDS - Research and Palliative Care

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ORIGINAL RESEARCH

Virological Non-Suppression, Non-Adherence and the Associated Factors Among People Living with HIV on Dolutegravir-Based Regimens: A Retrospective Cohort Study

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Background: HIV is one of the leading causes of morbidity and mortality, with 39.0 million people living with HIV worldwide, 25.6 million of whom reside in the African region. Highly active anti-retroviral therapy (HAART) has improved survival and quality of life, yet some patients develop viral non-suppression. Dolutegravir (DTG) has been recommended since 2018 as a first-line treatment option in low- and middle-income countries owing to its effectiveness, low cost, and tolerability, but some studies have reported virological non-suppression with its use. This study aims to explore the prevalence and factors associated with virological non-suppression in adults taking DTG-based regimens in Mbarara Regional Referral Hospital.

Methods: A retrospective cohort study was carried out among people living with HIV (PLWHIV) taking DTG-based HAART regimens by way of record review. SPSS was used for analysis, and both binary and multivariate logistic regression analyses were performed to test associated factors.

Results: Among the 422 participants' records reviewed, 62.8% were female (median age 40 years, IQR=13). The prevalence of virological non-suppression was 4.2%. Poor adherence to HAART was significantly associated with virological non-suppression, with 100.3 increased adjusted odds (95% CI: 28.90–348.12, $p<0.001$) compared to those with a record of good adherence. The reasons for poor adherence included alcohol use, stigma, forgetting to take medication, transport problems, and irregular timing of swallowing.

Conclusion: This study found poor adherence to be associated with a 4.2% prevalence of virological non-suppression among PLWHIV in a large public HIV care clinic. Despite the high suppression rates on DTG-based regimens, adherence counseling and viral load monitoring need to be emphasized at all HIV care centers to mark the trends of virological non-suppression.

Keywords: virological, non-suppression, dolutegravir, regimens

Background

Human immunodeficiency virus (HIV), with its associated opportunistic infections, is one of the world's leading causes of suffering and death. About 39.0 million people worldwide were living with HIV by 2022, with almost two-thirds of them (25.6 million, 66%) residing in the African region;[1] of these, 1.4 million were children aged 0–14 years. Cumulatively, 79.3 million people have been infected since the beginning of the HIV epidemic, with 40.4 million dying from AIDS-related illnesses.[1] Uganda, one of the 10 high-burden countries in Sub-Saharan Africa, had a nationwide HIV prevalence of 6.2% among 15–49-year-olds in 2018, with the South-Western region having the country's second highest HIV prevalence at 7.9%, with 7.6% among females and 4.7% among males.[2]

Highly active anti-retroviral therapy (HAART) is a medication regimen used to manage and treat HIV, and is made up of various anti-retroviral medicines.[3] There has been a significant increase in survival and quality of life among people living with HIV (PLHIV) around the globe since the introduction and expansion of HAART in 1995,[4] as well as a reduction in HIV

Received: 15 November 2023
Accepted: 13 March 2024
Published: 21 March 2024

infection rates in areas with high treatment coverage.[5] Different HAART drug combinations block HIV replication at various stages of its life cycle,[6] thereby suppressing viral replication, restoring the immune system, and improving quality of life.[7] However, over time, some individuals on HAART have developed failure on these regimens, necessitating gradual transitions from one line of treatment to the next.

Dolutegravir (DTG) is an integrase strand transfer inhibitor approved for the treatment of HIV infection,[8,9] and was recommended by the WHO as a first-line treatment option in combination with other anti-retrovirals for HIV infections in low- and middle-income countries in 2018.[10] The national rollout of DTG-based regimens in Uganda began in early 2018, with access being first restricted to women of reproductive age, although this was later expanded to include all adults living with HIV.[11,12] The efficacy of DTG has been studied in several studies, whereby it was demonstrated that DTG is superior to both efarvirenz (EFV) and ritonavir-boosted darunavir, and non-inferior to raltegravir,[11,13] and it is expected to play a major role in sub-Saharan Africa owing to its barrier to resistance, high potency, good tolerability, and low cost.[14] However, although this treatment has generally been accepted and taken up for the treatment of HIV in most of the endemic areas, viral non-suppression by DTG-based regimens has been reported in some studies.[15–17]

Anti-retroviral therapy success can be diagnosed clinically, immunologically, or virologically, and HAART failure can be classified as virological, immunological, or clinical failure, with virological failure defined as an increase in viral RNA copies to 1000 or more per milliliter of blood, measured consecutively 3–6 months apart.[18,19] Virological non-suppression in patients on a DTG-based regimen has strong implications for virological failure, which calls for early detection so that measures can be instituted early enough to prevent possible virological failure,[20] along with its related higher second-line treatment costs as well as more adverse drug effects.[21,22] Thus, interventions that improve the management of virological non-suppression are urgently needed to maintain control of the global HIV epidemic and ensure attainment of the UNAIDS target of having 95% of patients on treatment virally suppressed.[23]

Since the introduction of the DTG-based HAART regimens in Uganda in 2018, published information has been scarce on virological non-suppression and associated factors in patients on this regimen in this country. As a result, addressing this information gap would aid healthcare practitioners, local administrators, public health planners, policymakers, and partners in developing and implementing effective intervention measures among HIV patients taking DTG-based regimens.

This study, therefore, attempted to identify the prevalence of virological non-suppression and to explore the factors associated with it among adults taking DTG-based regimens in the HIV Clinic of Mbarara Regional Referral Hospital (MRRH) to ensure better practices and achieve better clinical results from the use of DTG.

Methods

Aim, Design, and Setting of the Study

The aim of this study was to the determine the prevalence of and explore the factors associated with virological non-suppression among people on DTG-based HAART regimens at MRRH, in South-Western Uganda. We employed a retrospective cohort study among adult patients initiated on DTG-based HAART regimens from January 2018 to October 2021.

MRRH is the biggest referral hospital in South-Western Uganda, and is located about 280 km from the Ugandan capital, Kampala. Currently, the HIV clinic serves a total number of 11,218 active clients on anti-retroviral therapy, including 10,619 adults, of whom 9462 clients are on DTG-based regimens.

Study Population

The study population consisted of adults aged 18 years and older living with HIV who had been treated with DTG-based regimens for at least 6 months at the Immune Suppression Syndrome (ISS) clinic of MRRH.

Sample Size Determination

The sample size for this study was determined using Fisher's formula for the estimation of sample size (Fisher, 1998):

$$n = \frac{Z^2_{\propto/2} P(1-P)}{\delta^2}$$

where n is minimum sample size required, $Z^2_{\propto/2}$ is standard normal variation at the 95% confidence interval corresponding to 1.96, P is estimated prevalence of 50%, and δ is absolute error of 0.05. The addition of 10% to compensate for possible incompleteness of some data gave a total sample size of 422.

Sampling Procedures

The study utilized the pre-existing database to determine eligibility based on age, regimen used, viral load results, and duration on DTG since initiation. A systematic random sampling method was then applied to select the 422 client files for the study. Microsoft Excel version 16.0 was used to generate random numbers from the clients' numbers, which were then used to pick files for enrollment.

Data Collection Tools and Procedures

The study used a document review guide to extract relevant information from the participants' files. The document review guide was able to gather patient-related and drug-related data, as well as information on adherence to HAART. The data collection tool was pretested on 10 patient files to ensure its reliability. Research assistants were given a two-day training course on data collection and there was close supervision by the principal investigator (PI) throughout the data collection process. Virological non-suppression was established if the plasma viral load was greater than 1000 RNA copies/mL on any viral load assessment results at any time 6 months or longer after the initiation of the DTG-based regimen. Information on drug adherence and opportunistic information was directly obtained from the patient charts. Good adherence referred to taking ≥95% of the doses correctly, whereas fair and poor adherence referred to 80–94.9% and <80%, respectively. The study also reviewed case notes to ensure additional reliability.

Data Analysis

Data were checked for completeness by the PI, entered into Microsoft Excel version 16.0, cleaned, and exported to SPSS version 25 for analysis. For descriptive statistics, frequencies were used to describe the demographic characteristics of patients as well as for the prevalence of virological non-suppression, drug factors, patient factors, and disease factors. Bivariate logistic regression was carried out for all independent variables to indicate their ability to predict the outcome variable (virological non-suppression).

To identify candidate variables for multivariate logistic regression analysis, factors with $p<0.25$ on bivariate logistic regression analysis were included. Finally, independent variables that had a significant association with virological non-suppression were identified based on the adjusted odds ratio (AOR), 95% confidence interval (95% CI), and p-value <0.05.

Results

Demographic and Clinical Characteristics of the Participants

The majority of participants (62.8%) were female. Participants had a mean age of 41 years, and had attained mostly a secondary level of education (54.9%), mainly earning their living as peasant farmers (53.6%). Furthermore, many of the participants belonged to the Anglican religion (55.1%), and 59.2% were married, with only 7.8% not using any family planning method. About 23.5% had a record of alcohol use (Table 1).

Clinical Characteristics

About 90.6% of the participants had disclosed their serostatus, with 5.2% having a positive history of discordance. TDF/3TC/EFV (62.8%) was the most commonly used HAART regimen before DTG use. The overall duration of HAART for most clients was between 6 and 10 years (44.3%), and only 14% had used HAART for 5 years or less. About 56.2% of

Table 1 Sociodemographic Characteristics of People Living with HIV at Mbarara Regional Referral Hospital

Variable		Frequency	Percentage
Sex	Female	265	62.8
	Male	157	37.2
Age (years)	≤35	123	29.1
	36–45	168	39.8
	>45	131	31.0
Family planning used	Hormonal	104	25.2
	Non-hormonal	276	67.0
	None	32	7.8
Education status	Primary	49	14.6
	Secondary	184	54.9
	Tertiary	102	30.4
Occupation	Unemployed	67	17.4
	Employed	21	5.5
	Business	90	23.4
	Peasant	206	53.6
Marital status	Separated	115	27.8
	Single	54	13.0
	Married	245	59.2
Religion	Catholic	119	33.6
	Protestant	195	55.1
	Others	40	11.3
Alcohol use	No	323	76.5
	Yes	99	23.5

the participants had been on a DTG based regimen for more than 2 years, with the biggest number (99.3%) currently using DTG as the first-line regimen. All PLHIV in the sample had used and completed Isoniazid prophylaxis against tuberculosis infection and 2.4% had comorbidities, mostly hypertension and diabetes (Table 2).

Table 2 Clinical Characteristics of People Living with HIV at Mbarara Regional Referral Hospital

Variable		Frequency	Percentage
Discordance	No	364	86.3
	Yes	22	5.2
	Unknown	36	8.5

(*Continued*)

Table 2 (Continued).

Variable		Frequency	Percentage
Disclosure status	No	29	9.4
	Yes	281	90.6
Drug allergy	No	419	99.3
	Yes	3	0.7
Prior ART use	PMTCT	1	50.0
	PEP	1	50.0
Ever changed regimen	No	313	74.2
	Yes	109	25.8
Current regimen	ABC/3TC/DTG	2	0.47
	TDF/3TC/DTG	415	98.3
	TDF/3TC/DTG/DRV/r	2	0.47
	AZT/3TC/DTG	3	0.71
Regimen before DTG substitution	None	29	6.9
	TDF/3TC/EFV	265	62.8
	TDF/3TC/NVP	13	3.1
	AZT/3TC/NVP	67	15.9
	AZT/3TC/EFV	37	8.8
	Others [TDF/3TC/ATV/r, CBV/LPV/r, TDF/3TC LPV/r, ABC/3TC/EFV]	11	2.3
Duration on HAART (years)	≤5	59	14.0
	6–10	187	44.3
	>10	176	41.7
Duration on DTG-based regimen (years)	≤2	185	43.8
	>2	237	56.2
HAART line of treatment	1	412	97.6
	2	9	2.1
	3	1	0.2
Ever taken INH	No	0	0.0
	Yes	422	100.0
Opportunistic infections	None	419	99.3
	Genital ulcer disease	1	0.7
	Oral thrush	1	
	TB	1	

(*Continued*)

Table 2 (Continued).

Variable		Frequency	Percentage
Comorbidity	No	412	97.6
	Yes	10	2.4
Current HAART adherence	Good	390	95.8
	Fair	2	0.5
	Poor	15	3.7
DTG-baseline adherence	Good	376	99.5
	Fair	1	0.3
	Poor	1	0.3

Abbreviations: ABC, abacavir; ART, anti-retroviral therapy; ATV/r, atazanavir/ritonavir; AZT, azidothymidine; CBV, carbovir; DRV, darunavir; DTG, dolutegravir; DTG/r, dolutegravir/ritonavir; EFV, efavirenz; HAART, highly active anti-retroviral therapy; INH, isoniazid; LPV, lopinavir; LPV/r, lopinavir/ritonavir; NVP, nevirapine; PEP, post-exposure prophylaxis; PMTCT, prevention of mother-to-child transmission; TB, tuberculosis; 3TC, lamivudine; TDF, tenofovir.

Prevalence of Virological Non-Suppression Among PLHIV on DTG-Based HAART Regimens

Out of 422 patients included, 18 participants had a viral load value greater than 1000 copies/mL, giving an overall prevalence of virological non-suppression of 4.3% (Figure 1).

Three participants had virological non-suppression 6 months after initiation of the DTG-based regimen, 10 after 12 months, 17 after 24 months, and 18 after 36 months (Figure 2).

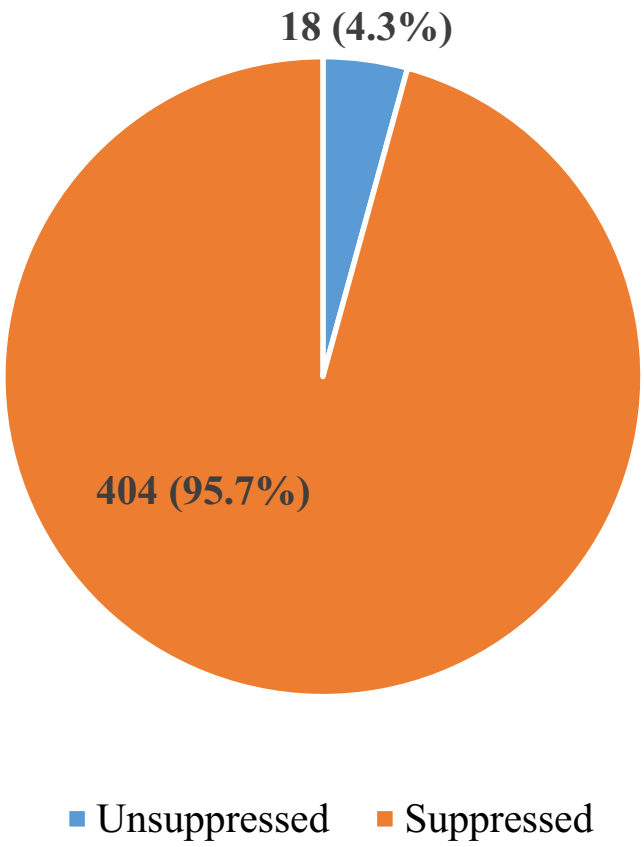

Figure 1 Prevalence of virological non-suppression among people living with HIV on dolutegravir-based highly active anti-retroviral therapy regimens.

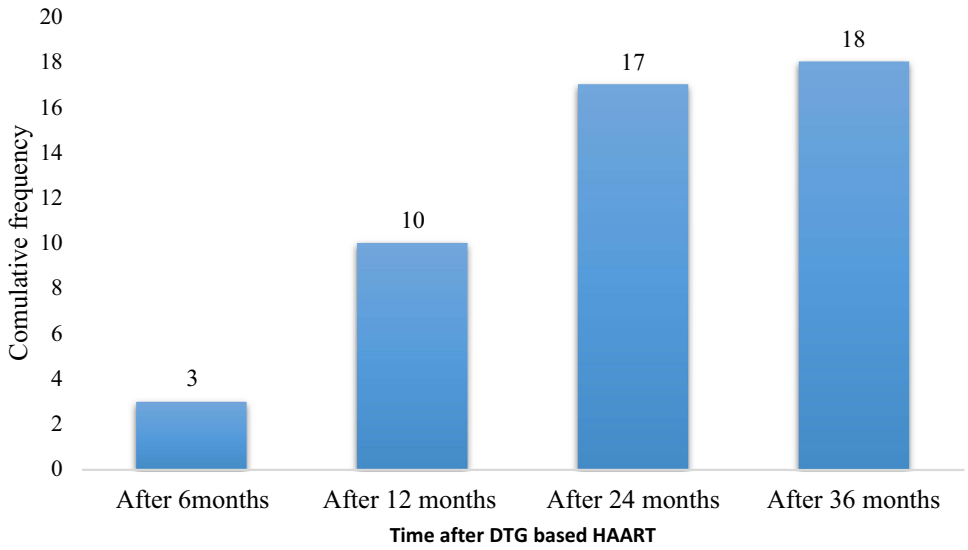

Figure 2 Time taken for non-suppression of viral load from the start of the DTG-based regimen.
Abbreviations: DTG, dolutegravir; HAART, highly active anti-retroviral therapy.

Reasons for Non-Adherence

Out of the 422-sample population, 95.8% had a recorded good adherence in their files, while 4.2% were poorly adherent to the HAART medicines. Stigma (46.7%) was the major reason for poor adherence in the study population, followed by travel problems at 33.3% and alcohol use at 20.0% (Figure 3).

Factors Associated with Virological Non-Suppression

A total of 18 variables were considered at univariate level and only four had a *p*-value <0.25: alcohol use (crude odds ratio [COR] =2.75, 95% CI: 1.06–7.18, *p*=0.038), ever changed regimen (COR=2.88, 95% CI: 0.65–12.74, *p*=0.163), greater than 2 years of taking DTG-based regimen (COR=2.84, 95% CI: 0.92–8.78, *p*=0.07), and poor current adherence (COR=100.31, 95%

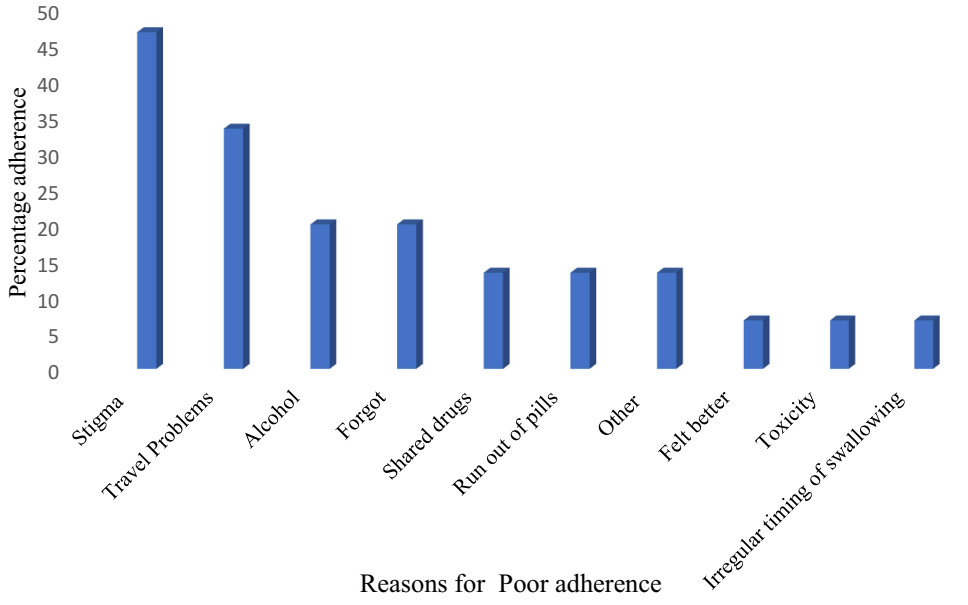

Figure 3 Bar chart showing reasons for poor adherence among people living with HIV using dolutegravir-based regimens at Mbarara Regional Referral Hospital.

CI: 28.90–348.12, $p<0.001$). These were subjected to multivariate analysis and only one variable retained statistical significance, which was poor adherence (AOR=100.30, 95% CI: 28.90–348.12, $p<0.001$) compared to those with good adherence. Patients with poor adherence had 100.3 higher odds of virological non-suppression compared to those with good adherence (Table 3).

Table 3 Univariate and Multivariate Logistic Regression of the Factors Associated with Virological Non-Suppression Among People Living with HIV on DTG-Based Regimens at Mbarara Regional Referral Hospital

Variable	Category	Virological Non-Suppression, n (%)		COR (95% CI)	*p* Value	AOR (95% CI)	*p* Value
		No	Yes				
Gender	Female	254 (95.8)	11 (4.2)	0.93 (0.35–2.45)	0.880		
	Male	15 (95.5)	7 (4.5)	1			
Age category (years)	≤35	120 (97.6)	3 (2.4)	0.63 (0.15–2.69)	0.533		
	36–45	158 (94.0)	10 (6.0)	1.60 (0.53–4.79)	0.405		
	>45	126 (96.2)	5 (3.8)	1			
Education level	Primary	49 (100)	0	–	0.997		
	Secondary	176 (95.7)	8 (4.3)	1.11 (0.33–3.79)	0.863		
	Tertiary	98 (96.1)	4 (3.9)	1			
Marital status	Separated	111 (96.5)	4 (3.5)	0.85 (0.26–2.76)	0.783		
	Single	52 (96.3)	2 (3.7)	0.90 (0.19–4.25)	0.898		
	Married	235 (95.9)	10 (4.1)	1			
Discordance	No	348 (95.6)	16 (4.4)	1			
	Yes	21 (95.5)	1 (4.5)	1.04 (0.131–8.19)	0.973		
	Unknown	35 (97.2)	1 (2.8)	0.62 (0.08–4.83)	0.649		
Occupation	Unemployed	65 (97.0)	2 (3.0)	0.55 (0.118–2.525)	0.438		
	Employed	20 (95.2)	1 (4.8)	0.89 (0.109–7.225)	0.910		
	Business	87 (96.7)	3 (3.3)	0.61 (0.166–0.246)	0.459		
	Peasant	195 (94.7)	11 (5.3)	1			
Disclosure status	No	29 (100)	0	–	–		
	Yes	269 (95.7)	12 (4.3)	1			
Alcohol use	No	313 (96.9)	10 (3.1)	1		1	
	Yes	91 (91.9)	8 (8.1)	2.75 (1.06–7.18)	0.038	2.05 (0.57–7.32)	0.271
Ever changed regimen	No	297 (94.9)	16 (5.1)	2.88 (0.65–12.74)	0.163	3.04 (0.51–18.21)	0.224
	Yes	107 (98.2)	2 (1.8)	1		1	
Duration on DTG (years)	≤2	181 (97.8)	4 (2.2)	1		1	
	>2	223 (94.1)	14 (5.9)	2.84 (0.92–8.78)	0.070	2.60 (0.66–10.32)	0.174
Duration on HAART (years)	≤10	237 (96.3)	9 (3.7)	0.71 (0.27–1.81)	0.468		
	>10	167 (94.9)	9 (5.1)	1			

(*Continued*)

Table 3 (Continued).

Variable	Category	Virological Non-Suppression, n (%)		COR (95% CI)	*p* Value	AOR (95% CI)	*p* Value
		No	Yes				
Adherence	Good	383 (98.2)	7 (1.8)	1		1	
	Poor	6 (35.3)	11 (64.7)	100.31 (28.90–348.12)	<0.001	100.30 (28.90–348.12)	<0.001
Family planning	Hormonal	99 (95.2)	5 (4.8)	1.11 (0.38–3.24)	0.847		
	Non-hormonal	264 (95.7)	12 (4.3)	1			
Baseline CD4 count	<500	199 (95.7)	9 (4.3)	0.85 (0.33–2.19)	0.735		
	≥500	169 (94.9)	9 (5.1)	1			
Stage at start of DTG	I	347 (95.3)	17 (4.7)	2.79 (0.37–21.39)	0.323		
	II–IV	57 (98.3)	1 (1.7)	1			
Number of regimens ever changed	1	75 (96.2)	3 (3.8)	1.56 (0.25–9.80)	0.634		
	2–5	32 (94.1)	2 (5.9)	1			
Baseline regimen	Others	48 (98.0)	1 (2.0)	1			
	TDF/3TC/EFV	188 (95.4)	9 (4.6)	2.30 (0.28–18.58)	0.435		
	AZT/3TC/EFV or [NVP]	140 (95.2)	7 (4.8)	2.40 (0.29–20.01)	0.418		

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; DTG, dolutegravir; EFV, efavirenz; NVP, nevirapine; 3TC, lamivudine; TDF, tenofovir.

Discussion

The prevalence of virological non-suppression of 4.2% found in the current study is much lower than the assumed prevalence of 50% in our sample size calculation. Thus, our current sample size has achieved a better precision with a two-sided marginal error of 2.5% instead of the initial 5%. The current prevalence of 4.2% is comparable to other previous studies: 3.55% in Cameroon[20] and 6% in central Uganda.[22] However, our prevalence was lower than the prevalences reported in previous studies: 26.53% in Taiwan,[24] 21% in a clinical trial conducted in Cameroon,[25] and 16% in a clinical trial in South Africa.[26] The difference in prevalence can be explained by the high reported tolerability and low toxicity profile of the DTG-based regimen compared to others, which may improve compliance and subsequently lead to better outcomes.[27] This could also be due to improvements in the general HIV care service delivery in our setting, which includes intensive adherence counseling, which has been found in previous studies to be associated with enhanced viral load suppression among HIV patients who were previously non-suppressed.[28–30] The adoption of the use of viral load monitoring instead of CD4 cell count and clinical monitoring enables early high viremia among patients,[31] thereby allowing early intervention to be instituted.

On multivariate logistic regression analysis, the adherence status of the patients was the only independent risk factor associated with virological non-suppression. Patients who had poor adherence to HAART were at about 100.3 times higher odds of having virological non-suppression compared to those with good adherence. This was comparable to other studies.[32–35] Poor adherence to HAART has been highly linked to the development of drug resistance among PLHIV,[36–39] and this drug resistance leads to virological non-suppression as HIV replication is not well suppressed, which, in turn, leads to an increase in the viral load.[40–42] This shows the importance of continuous adherence monitoring and counseling among PLHIV.

Other factors were not found to be significantly associated with virological non-suppression, although they were significant in some previous studies, such as age[24,43,44] and duration of DTG regimen.[45] This shows that virological non-suppression can be associated with different factors in different populations; therefore, more studies are required.

The reasons for poor adherence identified included alcohol use, stigma, sharing pills, feeling better, forgetting to take medications, the toxicity of HAART, travel problems, running out of pills, and irregular timing of swallowing. These factors were comparable to those found in previous studies. Alcohol use[46–50] may reduce adherence because alcohol consumption lowers the concentration and reasoning capacity of the consumer, causing them to miss doses, especially on drinking days.[46] Stigma was another reason, as identified in previous studies;[51–53] this because it causes a diminished desire to take medication, self-rejection, and depression, leading to poor adherence. Another reason for poor adherence was forgetting to take medication, which was similar to findings in previous studies.[54–56] Adherence interventions that focus on assisting PLWHIV to remember their medications should be adopted. Patients who did not adhere properly were also reported to have had issues with transport to the hospital, which led to their missing doses. This problem was also identified in previous studies.[57–59] Travel problems were worsened during the COVID-19 pandemic, when there were travel restrictions. Satellite clinics could help to reduce this burden. Other reasons, such as sharing of pills, feeling better after the initial doses, the toxicity of DTG, running out of pills, and irregular timing of swallowing, although identified in a few patients in our study, were reported to significantly affect adherence in previous studies.[60–62] This shows that the reasons for poor adherence among PLHIV are diverse, and attention should be drawn to this issue. Similar studies should be conducted in other HIV care centers to provide a more comprehensive understanding of the challenges faced by PLHIV in different settings and inform the development of tailored interventions.

We faced some limitations during this study. Access to all the desired sample records was challenging since the files are not kept in one place, so files in use could only be accessed on another day. The study was conducted in a specific geographic location, and the results may not be generalizable to other populations with different characteristics or HIV care settings.

Conclusion

This study established that the prevalence of virological non-suppression among PLHIV in our setting is comparable to the level that was previously reported. Despite the efforts of the Ugandan government and the global community to control the HIV epidemic using DTG-based regimens for PLHIV, virological non-suppression remains a concern in this population. Failure to address this promptly could result in the emergence of virological resistance, underscoring the importance of broadening and enhancing surveillance through national HIV drug resistance surveys. Poor adherence to HAART remains the most significant independent risk factor for virological non-suppression. Numerous factors contribute to poor adherence, and we suggest implementing technology-based interventions that focus on reminding PLHIV daily to take their medications and addressing the underlying reasons for poor adherence.

We recommend that hospitals explore the possibility of establishing satellite clinics closer to the clients to make it easier for them to access HAART services. This could help to improve adherence and ensure better health outcomes for PLHIV who experience travel problems.

Abbreviations

AE, adverse event; ART, anti-retroviral therapy; DTG, dolutegravir; EFV, efavirenz; FDA, Food and Drug Administration; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; ISS, immune suppression syndrome; MRRH, Mbarara Regional Referral Hospital; MUST, Mbarara University of Science and Technology; PI, principal investigator; PLHIV, people living with HIV; UNAIDS, Joint United Nations Programme on HIV/AIDS; WHO, World Health Organization.

Data Sharing Statement

The data set and data collection tools used in this study are available upon reasonable request from the corresponding author.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Research and Ethics Committee (REC) of Mbarara University of Science and Technology (MUST); a waiver of informed consent was requested from REC.

Confidentiality was ensured by making sure that patients' names and any information that could identify them were not included in the data collection tool or were removed from the extracted data. The PI, health professionals on duty, research assistants, patients, and caregivers were protected from any harm, embarrassment, or exposure, especially to COVID-19, through adherence to the standard operating procedures, including social distancing, and the use of face masks, sanitizer, and hand washing. The clinical routines were not interrupted by the study.

Acknowledgments

We would like to thank the staff of Mbarara Regional Referral Hospital who collaborated with us during data collection. We would also like to extend our thanks to the research assistants for their unreserved support.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors report no competing interests in the research, authorship, and publication of this article.

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