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Dolutegravir-Associated Hyperglycemia in People Living with Human Immune-Deficiency Virus: A Cross Sectional Study

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Abstract

Introduction: Diabetes mellitus is being related with developing communicable and non-communicable diseases. Patients on highly active anti-retroviral therapy are at increased risk of developing diabetes mellitus than those who are treatment Naïve. Hyperglycemia has been mentioned as the side effect of some ART regimens. We assessed the incidence of hyperglycemia among patients taking Dolutegravir-based regimen in ACSH.

Method: A hospital-based prospective cross sectional study was conducted. The total sample size was 423. A simple random sampling technique was employed using excel function to select study participants. Four categories of data were collected, namely socio-economic, clinical and immunological, regimen type and outcome variables.

Results: A total of 421 HIV patients were included in the study. More than one-third (36.1%) of the subjects had an exposure to TDF+3TC+DTG drug therapy, either as a first therapy or a change to the first line triple therapy. 62 (14.7%) had hyperglycemia from the study participants. Our finding showed that taking Dolutegravir-based ART has no effect on the blood sugar level of patients, while adjusting for age, sex, and weight at HAART initiation (AOR=1.04, 95% CI: 0.55-1.95, p=0.896)

Conclusion: Dolutegravir-based ART regimen has no effect on the blood sugar level of patients.

Keywords: Dolutegravir • Hyperglycemia • Diabetes mellitus • Deficiency • Virus

Abbreviations: HIV: Human Immune Deficiency Virus; ART: Antiretroviral Therapy; ACSH: Ayder Comprehensive Specialized Hospital; TDF: Tenofovir; 3TC: lamivudine; DTG: Dolutegravir; HAART: Highly Active Antiretroviral Therapy; EFV: Efavirez; NVP: Nevirapin; ATV/r: ritonavir boosted Atazanavir; ABC: Abacavir; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; PIs: Protease Inhibitors; ARV: Antiretroviral; INSTIs: Integrase Strand Transfer Inhibitors; CI: Confidence Interval; SD: Standard Deviation; IRB: Institutional Review Board

Introduction

Diabetes mellitus is one of the four most prevalent diseases. Its current prevalence reaches 9.3% (463 million people) worldwide. It is expected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [1]. In Ethiopia the prevalence of diabetes mellitus is estimated to be 3.2 % and an additional 9.1% have impaired fasting glucose which makes them at risk of developing diabetes mellitus if proper preventive measures are not taken [2].

Diabetes mellitus is being related with developing communicable and non-communicable diseases as it leads to an immune compromised state and as its risk factors are also the risk factors of other non-communicable diseases. The improvement in the diagnosis and management of patients living with Human Immune Deficiency Virus (HIV) has led them to live long and develop diabetes mellitus. The increased risk of developing diabetes is related to HIV

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itself or its treatment [3]. Insulin resistance is found to be the main pathogenetic mechanism of diabetes in HIV patients making type 2 diabetes mellitus common in such kind of patients. Insulin resistance results from high levels of inflammatory cytokines that impair glucose tolerance. But recently, some patients were reported to develop autoimmune T1DM after immune restoration by treatment of the HIV with Highly Active Antiretroviral Therapy (HAART). A study has identified having high viral burden, low CD4 count, longer duration of HIV infection, advancing age, male gender, lower socioeconomic class, and accumulation of visceral fat to be risk factors for patients with HIV to develop diabetes mellitus [4].

Patients on HAART are at increased risk of developing diabetes than those who are treatment Naïve [5]. Hyperglycemia has been mentioned as the side effect of Protease Inhibitors (PIs), Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and integrase inhibitors. For instance, in a study done in Uganda in HIV patients initiated and switched to Dolutegravir, an integrase inhibitor, incidence of hyperglycemia over 12 months was found to be 4.7 per 1000 persons while the incidence in the control group was 0.32 per 1000 patients [6].

In Ethiopia the NRTIs, NNRTIs and PIs have been used as the first line and second line therapies since the introduction of Antiretroviral (ARV) in the country. But since June 2019 an integrase inhibitor, Dolutegravir has been introduced as a first line therapy and many newly diagnosed HIV patients and patients on other ARVs are being started on this medication. But there have been reports from different institutions that patients are coming with new symptoms of diabetes mellitus and the known patients are complaining of poor control of their disease after initiation of Dolutegravir.

In Ayder comprehensive specialized hospital, there are more than 1300 patients on antiretroviral therapy. Of these, 435 of them are on Dolutegravir-based regimen. Though there are reports that some patients are complaining of hyperglycemia symptoms, no study has been done to determine the magnitude and predisposing factors of this hyperglycemia in patients taking dolutegravir-based regimen.

Therefore, we assessed the incidence of hyperglycemia among patients taking Dolutegravir-based regimen in ACSH.

Materials and Methods

The study was conducted at Ayder comprehensive specialized hospital. Ayder comprehensive specialized hospital is a tertiary care institution located at Northern part of Ethiopia, Tigray regional state. It is owned by Mekelle University and is used for clinical services, clinical teaching and research activities. It serves as a tertiary care referral center for around 10 million people coming from the whole Tigray, North-eastern parts of Amhara, vicinity areas of Afar and Eritrea. Common causes of morbidity and mortality are trauma, pneumonia, diabetes, many others.

It served around 262,176 outpatient visits, around 37,244 emergency visits, 16,841 inpatient admissions and around 842 in the year 2018/19 G.C. It has around 500 beds and is staffed with 108 (sub) specialists, 223 medical residents, 45 general practitioners, 834 nurses/midwives, 302 allied health professionals and 527 support staff. HIV care is one of the services provided in Ayder comprehensive specialized hospital. Currently, there are around 1344 patients on antiretroviral therapy and about 500 of them take Dolutegravir-based regimen.

Study design

A hospital-based cross-sectional study was conducted.

Population

Source and study population: While our source population was all patients above the age of 18 years, the study population includes adult patients on ART in Ayder comprehensive specialized hospital ART clinic.

Exclusion criteria

Patients with overt diabetes mellitus before June 2019.

Sample size determination and sampling procedure

The sample size was determined using a single proportion population formula and with a prevalence of 50% as there is no similar study done. Adding 10% non-response rate, the total sample size was 423.

A simple random sampling technique was employed using excel function to select study participants. List of patients in the database was used as a sampling reference. The numbers randomly appeared in the excel randomization were drawn from the database for data collection.

Data collection procedure

A data clerk was trained and collected the phone numbers of the patients from the patient charts. He called patients and informed them to come fasting on their appointment dates. Then patients were recruited by simple random sampling technique. Data collection tool was prepared and trained data collectors collected the data from the electronic HIV registration form and patient charts starting from 5 August 2020 to September 20, 2020. Four categories of data were collected, namely socio-economic, clinical and immunological, regimen type and outcome variables. In addition to this blood was taken for fasting blood sugar determination after getting consent. Patients with abnormal fasting blood sugar were linked to the diabetic clinic for further workup and initiation of treatment. Authors had no access to identify individual participants during or after data collection.

Data analysis

Data was transferred from excel into R-software [7]. After coding and cleaning, data was presented in descriptive

Data analysis

Data was transferred from excel into R-software [7]. After coding and cleaning, data was presented in descriptive statistics, like percentages, mean, standard deviation, median, tables and graphs. Then bivariate analysis was conducted to see the existence of association between dependent and independent variables. Those variables that showed significant association with the outcome variable (with p value of <0.2) were included in multivariable logistic regression to see if there is an independent effect of each variable on the dependent variable. Finally, only those independent variables that persistently associated with the outcome variable were used to construct the final model. A p-value<0.05 was considered statistically significant within the 95% confidence level.

Operational definition

Hyperglycemia: Patients who either have diabetes or impaired fasting glucose.

Diabetes mellitus: Patients who either have fasting blood sugar above 126 mg/dl or those who already are taking anti diabetic agents.

Impaired fasting glucose: Patients who have a fasting glucose level between 100 and 125 mg/dl.

Results

Sociodemographic characteristics

A total of 421 HIV patients were included in the study (99.5% response rate). Age of the participants ranged between 18 and 78 years with a mean and Standard Deviation (SD) of 41.15 and 10.20 years respectively. Female participants accounted for 245 (58.2%) of the patients. The vast majority (92.4%) of the participants were urban dwellers. About half (49.9%) of them had high school and above level of education. Nearly half (46.9%) of the clients were married. Regarding occupation, 87 (23.2%) of the study participants were government employees (Table 1).

Hyperglycaemia				
Characteristics	**No (n=359)**	**Yes (n=62)**	**Total (N=421)**	***Chi-square***
	n (row %)	**n (row %)**	**n (column %)**	**p value**
Age, years, mean ± SD	40.9 ± 10.1	42.6 ± 10.8	41.15 ± 10.20	0.136
Sex				
Male	141 (80.1)	35 (19.9)	176 (41.8)	0.011
Female	218 (89.0)	27 (11.0)	245 (58.2)	
Total	359 (85.3)	62 (14.7)	421 (100.0)	
Residence				
Urban	332 (85.3)	57 (14.7)	389 (92.4)	0.881
Rural	27 (84.4)	5 (15.6)	32 (7.6)	
Total	359 (85.3)	62 (14.7)	421 (100.0)	
Religion				
Orthodox	330 (85.1)	58 (14.9)	388 (93.0)	0.312
Protestant	2 (66.7)	1 (33.3)	3 (0.7)	
Muslim	22 (91.7)	2 (8.3)	24 (5.8)	
Catholic	1 (50.0)	1 (50.0)	2 (0.5)	
Total	355 (85.1)	62 (14.9)	417 (100.0)	
Education				
Unable to read and write	51 (83.6)	10 (16.4)	61 (14.9)	0.208
Can read and write	11 (68.8)	5 (31.3)	16 (3.9)	
Elementary	113 (88.3)	15 (11.7)	128 (31.3)	
High school and above	174 (85.3)	30 (14.7)	204 (49.9)	
Total	349 (85.3)	60 (14.7)	409 (100.0)	
Marital status				

Single	63 (81.8)	14 (18.2)	77 (18.6)	0.125
Married	162 (83.5)	32 (16.5)	194 (46.9)	
Divorced/Separated	64 (86.5)	10 (13.5)	74 (17.9)	
Widowed	65 (94.2)	4 (5.8)	69 (16.7)	
Total	354 (85.5)	60 (14.5)	414 (100.0)	
Occupation				
Farmer	6 (75.0)	2 (25.0)	8 (2.1)	0.805
Housewife	64 (88.9)	8 (11.1)	72 (19.2)	
Daily laborer	51 (87.9)	7 (12.1)	58 (15.5)	
Merchant	79 (84.0)	15 (16.0)	94 (25.1)	
Government employee	74 (85.1)	13 (14.9)	87 (23.2)	
Other	46 (82.1)	10 (17.9)	56 (14.9)	
Total	320 (85.3)	55 (14.7)	375 (100.0)	

Table 1. Baseline socio-demographic characteristics of the study participants at Ayder comprehensive specialized hospital, Mekelle, Northern Ethiopia, 2020 (n=421).

ART regimen related characteristics

While the majority (60.9%) of the patients were taking TDF+3TC +EFV based ART regimen, only few (6.8%) of them were using TDF +3TC+DTG as their first line course of therapy. In the upcoming period, 237 (56.3%) of the ART users changed their first line regimen. Remarkably, 125 (52.7%) of them shifted their regimen into Dolutegravir based triple therapy, TDF+3TC+DTG. Overall, more than one-third (36.1%) of the subjects had an exposure to TDF+3TC+DTG drug therapy, either as a first therapy or a change to the first line triple therapy (Table 2). Duration of HIV and duration of HAART had no significant effect on the occurrence of hyperglycemia (Table 3).

Hyperglycemia				
Characteristics	**No (n=359)**	**Yes (n=62)**	**Total (N=421)**	***Chi-square***
	n (row %)	**n (row %)**	**n (column %)**	**p value**
First ART regimen				
AZT+3TC+EFV	15 (75.0)	5 (25.0)	20 (4.8)	0.704
AZT+3TC+NVP	61 (85.9)	10 (14.1)	71 (17.1)	
D4T+3TC+EFV	3 (100.0)	0 (0.0)	3 (0.7)	
D4T+3TC+NVP	11 (84.6)	2 (15.4)	13 (3.1)	
TDF+3TC+DTG	25 (89.3)	3 (10.7)	28 (6.8)	
TDF+3TC+EFV	214 (84.9)	38 (15.1)	252 (60.9)	
TDF+3TC+NVP	25 (92.6)	2 (7.4)	27 (6.5)	
Total	354 (85.5)	60 (14.5)	414 (100.0)	
Regimen changed				
Yes	198 (83.5)	39 (16.5)	237 (56.3)	0.256
No	161 (87.5)	23 (12.5)	184 (43.7)	
Total	359 (85.3)	62 (14.7)	421 (100.0)	
Regimen after change				
ABC+3TC+ATV	0 (0.0)	1 (100.0)	1 (0.4)	0.458

ABC+3TC+ATV/r	18 (78.3)	5 (21.7)	23 (9.7)	
ABC+3TC+EFV	4 (100.0)	0 (0.0)	4 (1.7)	
ABC+3TC+kaltria	2 (100.0)	0 (0.0)	2 (0.8)	
Azt+3TC+ABC	1 (100.0)	0 (0.0)	1 (0.4)	
Azt+3TC+ATV	1 (100.0)	0 (0.0)	1 (0.4)	
AZT+3TC+ATV/r	23 (88.5)	3 (11.5)	26 (11.0)	
Azt+3TC+EFV	1 (100.0)	0 (0.0)	1 (0.4)	
AZT+3TC+NVP	1 (50.0)	1 (50.0)	2 (0.8)	
TDF-3TC-kalitre	1 (100.0)	00 (0.0)	1 (0.4)	
TDF+3TC+ATV/r	14 (77.8)	4 (22.2)	18 (7.6)	
TDF+3TC+DTG	102 (81.6)	23 (18.4)	125 (52.7)	
TDF+3TC+EFV	28 (93.3)	2 (6.7)	30 (12.7)	
TDF+3TC+NVP	2 (100.0)	0 (0.0)	2 (0.8)	
Total	198 (83.5)	39 (16.5)	237 (100.0)	
DTG based regimen				
Yes	126 (82.9)	26 (17.1)	152 (36.1)	0.301
No	233 (86.6)	36 (13.4)	269 (63.9)	
Total	359 (85.3)	62 (14.7)	421 (100.0)	

Table 2. ART regimen related characteristics of the study participants at Ayder Comprehensive Specialized Hospital, Mekelle, Northern Ethiopia, 2020 (n=421).

Characteristics	Normal blood sugar		Hyperglycemic	
	Median	IQR	Median	IQR
Duration of HIV (years)	8	6	8	8
Duration of HAART	7.1	6.8	8	8
Weight at initiation of HAART	50	14	50	18
CD4 count at initiation of HAART	169	89	176	159
Weight during change of HAART regimen	54	18	61	19
CD4 during change of HAART regimen	326	334	408.5	342

Table 3. Clinical characteristics of the study participants at Ayder comprehensive specialized hospital, Mekelle, Northern Ethiopia, 2020 (n=421).

Predictors of hyperglycemia among patients taking Dolutegravir-based ART

In this study, 62 (14.7%) had hyperglycemia from the total 421 HIV patients who were on ART. To assess predictors of hyperglycemia, a multivariable logistic regression model consisted of four explanatory variables (age, sex, weight at HAART initiation, and exposure to Dolutegravir-based ART) were fitted and sex was found to be the only statistically significant predictor of hyperglycemia. Accordingly, the likelihood of being hyperglycemic was higher among males than females (AOR=2.32, 95% CI: 1.22-4.50, p=0.011). Our finding showed that taking Dolutegravir-based ART has no effect on the blood sugar level of patients, while adjusting for age, sex, and weight at HAART initiation (AOR=1.04, 95%CI: 0.55-1.95, p=0.896) (Tables 4 and 5).

Predictors		COR (95% CI)	P value	AOR (95% CI)	P value
Age, years, mean ± SD		1.02 (0.99, 1.04)	0. 223	1.01 (0.98, 1.04)	0.476
Sex	Male	2.00 (1.17, 3.48)	0.012	2.32 (1.22, 4.50)	0.011
	Female	1		1	
DTG based regimen	Yes	1.34 (0.77, 2.30)	0.302	1.04 (0.55, 1.95)	0.896
	No	1		1	
Weight at HAART initiation		1.02 (1.00, 1.05)	0.064	1.01 (0.98, 1.04)	0.404

Note: The final model was good fit for the data; Hosmer-Lemeshow test: X^2 (df=8)=3.38, p value=0.908. The final model has no multicollinearity issue (maximum VIF=1.13).

Table 4. Predictors of hyperglycemia among patients taking Dolutegravir-based ART at Ayder Comprehensive Specialized Hospital, Mekelle, Northern Ethiopia, 2020 (n=421).

Predictors of impaired fasting glucose among patients taking Dolutegravir-based ART

Predictors		COR (95% CI)	P value	AOR (95% CI)	P value
Age, years, mean ± SD		1.00 (0.97, 1.02)	0. 777	1.01 (0.98, 1.02)	0.794
Sex	Male	0.79 (0.52, 1.18)	0.254	0.82 (0.53, 1.24)	0.349
	Female	1		1	
DTG based regimen	Yes	0.80 (0.52, 1.22)	0.303	0.94 (0.58, 1.50)	0.788
	No	1		1	
First ART regimen changed	Yes	1		1	0.222
	No	1.37 (0.92, 2.05)	0.122	1.32 (0.84, 2.07)	

Note: The final model was good fit for the data; Hosmer-Lemeshow test: X^2 (df=8)=12.74, p value=0.1211. The final model has no multicollinearity issue (maximum VIF=1.27).

Table 5. Predictors of impaired fasting glucose among patients taking Dolutegravir-based ART at Ayder Comprehensive Specialized Hospital, Mekelle, Northern Ethiopia, 2020 (n=421).

Discussion

Antiretroviral drugs have shown to improve the life expectancy of patients with HIV by mounting their immunity. Combination of 3 drugs from 2 classes has been used to treat HIV and the second generation Integrase Strand Transfer Inhibitors (INSTIs) have been included as the first or second line choices of ART in many countries including Ethiopia [8,9]. These classes of drugs are selected due to their high potency, low toxicity, good tolerability and high genetic barrier to resistance [10]. Case reports from Gonder, Ethiopia and Chicago, USA have shown that Dolutegravir based regimen is associated with the development of new diabetes mellitus and poor glycemic control of known diabetic patients who already were on anti-diabetic agents [11,6].

Though our study has shown that there is a higher prevalence of hyperglycemia in HIV patients taking ART which is 14.7%, patients taking Dolutegravir based regimen where not at higher risk of developing diabetic range hyperglycemia or impaired fasting glucose as compared to the patients taking other regimen. But gender had a role as male participants were found to be at higher risk of hyperglycemia than females. This difference could be due to the different study methods. Most studies were either case reports or case series while our study was cross sectional study with a representative sample.

Conclusion

In this study patients taking ART drugs were found to have high risk of hyperglycemia but Dolutegravir based regimen was not associated with increased risk of diabetes or impaired fasting blood glucose.

Limitation of the Study

A single fasting blood sugar level was taken to know the glycemia level and hemoglobin A1C measurement, immune markers and c peptide level were not done.

Ethical Approval and Consent to Participate

Ethical clearance was obtained from Institutional Review Board (IRB) of Mekelle University College of Health Sciences. All methods were performed in accordance with relevant guidelines and regulations.

Data was collected after getting permission letter from the chief clinical director of Ayder Comprehensive Specialized Hospital and verbal informed consent from the participants.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Declaration of Computing Interest

All authors declare that they have no conflict of interest.

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The authors received no specific funding for this work.

Authors' Contributions

MAA selected the topic, planned the study protocol, oversaw the study, entered the data, and reviewed the literature. MAA, MHT and EB conducted the analysis and interpreted the results. MAA, ALW, HEA and MME drafted the final manuscript. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

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