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RISK FACTORS ASSOCIATED WITH HYPERGLYCEMIA IN HIV PATIENTS ON DTG-BASED ART REGIMEN RECEIVING CARE AT JINJA REGIONAL REFERRAL HOSPITAL. A CROSS-SECTIONAL STUDY.

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Abstract

Background

Increasing BMI, Central obesity, Lipodystrophy, Dyslipidemia, Metabolic syndrome, Increased baseline FBS, and ART medications as possible risk factors like hyperglycemia among PLWH. The study aims to assess the Risk Factors associated with hyperglycemia in HIV patients on a DTG-based ART regimen.

Methodology

A hospital-based cross-sectional study design. The study population included all adult PLWHIV initiated on a Dolutegravir-based ART regimen attending the ART clinic at JRRH in Eastern Uganda with a total of 96 Respondents.

Results

Physical inactivity and weight gain appeared to be the major risk factors associated with hyperglycemia in HIV patients on DTG-based ART regimens. The majority 90(93.8%) did not do physical exercise and the prevalence of hyperglycemia in that category was 18(94.7%). 66(68.8%) of the respondents registered weight gain with a prevalence rate of hyperglycemia at 16 (84.2%). 82(85.4%) have been on ART for more than 10 years and these had a prevalence rate of 9(47.4%) and 73(94.8%) of them had normal fasting blood glucose levels. 88(91.7%) had no family history of Type 2 DM and these had a DM prevalence of 15(79.0%). 84(87.5%) never smoked in their lifetime amongst them, and the prevalence of hyperglycemia among them was 15(78.9%). 88(91.7%) had never taken alcohol in their lifetime and had hyperglycemia prevalence among them was 17(89.5%). 53(55.2%) were males with 11(57.9%) prevalence and 43(44.8%) were females with hyperglycaemia prevalence of 8(42.1%).

Conclusion

The majority of HIV patients on DTG-based ART regimen receiving care at Jinja Regional Referral Hospital were predisposed to both lifestyle ART and related risk factors to hyperglycemia which could have cumulatively predisposed them.

Recommendation

More health education and sensitization campaigns should be conducted to raise awareness of the possible risk factors and measures for combating noncommunicable diseases like DM and HTN in all population categories.

Keywords: *Physical inactivity, Dolutegravir-based ART regimen, Risk Factors for hyperglycemia.*
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Background of the study

Traditional risk factors for the development of hyperglycemia among PLWH are the same as the general population. Persistent Hyperglycemia is a cardinal finding that suggests pre-existing or emerging DM among patients. HDL-C, duration of ART, hypertension, overweight, obesity, age, and educational status of participants increase the prevalence of diabetes mellitus highlighting the importance of timely screening of HDL-C level, blood pressure, and BMI for adults on HAART (Demeke, 2021).

Increasing BMI, Central obesity, Lipodystrophy, Dyslipidaemia, Metabolic syndrome, Increased baseline FBS, ART medications like Proteus inhibitors, Zidovudine, didanosine, lamivudine, Stavudine, and Nevirapine have been identified as possible risk factors like to hyperglycemia among PLWH (Nansseu JR, et al, 2018). The effect of INSTIs on the risk of development of DM has been attenuated when accounting for 12 months of weight gain in some Patients (Nansseu JR et al, 2018). In Kenya development of hyperglycemia was associated with advanced age, being female, being overweight, and obesity (Odenyo et al, 2020). The study aims to assess the Risk Factors associated with hyperglycemia in HIV patients on DTG-based ART regimens receiving care at Jinja Regional Referral Hospital.

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Methodology

Study Design

A hospital-based cross-sectional study design was conducted because it was easier to use i.e., the researcher was able to manipulate numerous variables at once. The study design was selected because it could also manipulate both the independent and dependent study variables and does not allow follow-up of study participants.

Study area

The study was conducted at Jinja Regional Referral Hospital located in Jinja City, Eastern Uganda.

Study population

The study population included all adult PLWHIV initiated on a Dolutegravir-based ART regimen attending the ART clinic at JRRH.

Sample size determination

The sample size of participants voluntarily involved in the study was determined using the Keish and Leslie (1965) method of sample size determination using the formula.

$$n = \frac{Z^2P(1-P)}{d^2}$$

Where, n =Sample size required

Z= Constant normal standard variation corresponding to 95% confidence interval (1.96).

P=Prevalence attribute of hyperglycemia in a recent study. (Estimated prevalence of 50% (0.5) stated by Larmorde M, et al, 2020 in a case study)

Q= (1-P)

d=Error allowed [desired level of precision at a percentage of 10%] =0.1

$$N = \frac{(1.96)^2 0.5(1-0.5)}{(0.1)^2}$$

$$N = \frac{0.9604}{0.01}$$

N =96.04 which approximated 96 participants. Therefore 96 participants participated in this research study.

Sampling Techniques

A simple random sampling technique was used. Patients on a DTG-based regimen were continuously sampled until the required sample size was reached. Those who fulfilled the eligibility criteria were included in the study.

Sampling procedure

Respondents were given numerical values ranging from one to twenty and the participants to participated in the study were randomly selected from the numerical values and were instructed to fast for at least 8 hours before the glucose tests on the following morning. An FPG test and a 2-hour OGTT were done by trained personnel at the clinic according to the 2021 American Diabetes Association guidelines 23. The fasting glucose capillary blood sample was collected by a needle prick using lancets and immediately Fasting glucose level was determined using a glucometer.

Inclusion Criteria

All adult HIV patients on DTG- a based regimen for at least four months, those who were willing to participate in the study, and those who came after overnight fasting met the Inclusion Criteria

Exclusion criteria

PLWHIV on non-DTG ART regimen, Known DM patients, Patients taking corticosteroids treatment for any reason, and Patients taking chemotherapeutic agents were excluded from the study.

Dependent variable

Prevalence of hyperglycemia

Independent variables

The risk factors of hyperglycemia in HIV patients on a Dolutegravir ART regimen

Data collection tools

The researcher used a questionnaire that will consist of closed-ended and open-ended questions written in simple English language and filled by the researcher herself and an assistant. The questionnaire written by the researcher was pre-tested to adjust for any ambiguity or errors and corrections were made accordingly. A lab request form, sample logs, and study register, in addition to a glucometer, glucose test strips, and stationeries [books, pens, pencils, rulers, Ream of papers] were used.

Reliability and validity of the research

The questionnaire was first approved by the supervisor of my research together with the proposal. The questions were pre-tested on selected clients on the DTG ART regimen to check out any ambiguous questions and errors. Corrections were made accordingly.

Data collection procedure

I obtained data on socio-demographic characteristics, lifestyle, and medical history from individual participants using interviewer-administered questionnaires. I cross-checked information on the medical history, ART regimens, and dates of ART initiation by reviewing participants' clinical records and also when they were Initiated on the DTG ART regimen. A 5ml blood sample was collected from participants to test for Fasting glucose levels.

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Quality Control
Pre-tested questionnaires were designed with the consultation and guidance of my institute research supervisor, pre-tested in a similar study setting, and corrections made before use in the final data collection.

Pilot Study
Before conducting the study, the designed tools, laboratory investigation forms, and sample logs were subjected to the supervisor and lab to improve the tool, and where applicable changes were made.

Data Management
After data collection, every questionnaire was checked for completeness and any gaps were filled immediately before the clients (participants) left the clinic. The questionnaires were kept under key and lock only accessible to the researcher and my assistant on request after which it was directly entered into Excel Software.

Data Analysis
Data obtained will be entered directly into Excel Software Package data analysis and will be analyzed starting with the demographic information and the other objectives. The analyzed data will be presented in percentages, and frequencies in tables, pie charts, and bar graphs.

Ethical Considerations
My research proposal was submitted to the research and ethical Committee of the school for approval and thereafter introductory letter from the school was taken to the administrators of JRRH to seek authorization for pre-testing of the questionnaires and thereafter the letter was taken to the management of JRRH ART clinic to seek permission and authority for data collection. A consent letter was also provided to clients and was filled voluntarily and total confidentiality was observed. In addition, other ethical considerations like privacy were highly applied and sample codes were availed to avoid display of patients' identities to unauthorized persons.

Results
Socio-demographic characteristics of respondents receiving care at JRRH ART clinic.

Table 1 shows socio-demographic factors

Variable	Category	Frequency (N=96)	Percentage (%)	With Hyperglycaemia	Without Hyperglycaemia
Age (Years)	18-30	18	18.8	3(15.8%)	15(19.5%)
	31-45	30	31.2	4(21.0%)	26(33.8%)
	46-60	45	46.9	9(47.4%)	36(46.7%)
	>60	3	3.1	5(15.8%)	0(0.0%)
Total		**96**	**100**	**19(100%)**	**77(100%)**
Gender	Female	43	44.8	8(42.6%)	35(45.5%)
	Male	53	55.2	11(57.9%)	42(54.5%)
Total		**96**	**100**	**19(100%)**	**77(100%)**
Educational Level	Illiterate	6	6.3	2(10.5%)	4(5.2%)
	Elementary school	24	25	8(42.1%)	16(20.8%)
	Secondary school	46	47.9	8(42.1%)	38(49.3%)
	Diploma & above	20	20.8	1(5.3%)	19(24.7%)
Total		**96**	**100**	**19(100%)**	**77(100%)**
Occupation	Unemployed	25	26	5(26.3%)	20(26.0%)
	Civil Servant	31	32.3	4(21.0%)	27(35.0%)
	Private Business	37	38.5	9(47.4%)	28(36.4%)
	Healthcare Worker	3	3.2	1(5.3%)	2(2.6%)
Total		**96**	**100**	**19(100%)**	**77(100%)**

Results obtained in Table 1 showed that the majority 45(46.9%) of the respondents were in the age group of 46-60years with hyperglycemia prevalence of 9(47.4%) followed by the age group of 31-45years 30(31.2%) with hyperglycemia prevalence of 4(21.0%), followed by the age group of 18-30years that were

18(18.8%) with the prevalence of hyperglycemia being 3(15.8%) and the minority of the respondents 3(3.1%) were in the age category of above 60years with hyperglycemia prevalence of 3(15.8%).

Regarding gender, majority of the respondents 53(55.2%) were males with 11(57.9%) prevalence and the minority 43(44.8%) were females with hyperglycaemia prevalence of 8(42.1%).

Regarding respondents' educational level, the majority 46(47.9%) of the respondents attended secondary school education with a prevalence of 8(42.1%), followed by those who attended elementary school who was 24(25.0%) with a prevalence of 8(42.1%), followed by those who attended diploma and higher education that were 20(20.8%) with a lower prevalence of 1(5.3%), followed by the illiterates who were 6(6.3%) with hyperglycemia prevalence of 2(10.5%).

Concerning respondents' occupation, the majority 37(38.5%) had a private business, followed by civil servants who were 31(32.3%), followed by unemployed who were 25(26.0%) and the minority 3(3.1%) were healthcare workers.

Table 2 Shows risk factors associated with hyperglycemia among HIV patients on DTG (n=96)

VARIABLE	CATEGORY	FREQUENCY	HYPERGLYCAEMIC	NONE HYPERGLYCAEMIC
Smoking History	Yes	12	4(21.1%)	8(10.4%)
	No	84	15(78.9%)	69(89.6%)
	Total	**96**	**19(100%)**	**77(100%)**
Alcohol drinking history	Yes	8	2(10.5%)	8(10.4%)
	No	88	17(89.5%)	69(89.6%)
	Total	**96**	**19(100%)**	**77(100%)**
Physical exercise habit	Yes	6	1(5.3%)	5(6.5%)
	No	90	18(94.7%)	72(93.5%)
	Total	**96**	**19(100%)**	**77(100%)**
Duration on ART (yrs.)	>10	82	9(47.4%)	73(94.8%)
	02-Oct	9	7(36.8%)	2(2.6%)
	<1	5	3(15.8%)	2(2.6%)
	Total	**96**	**19(100%)**	**77(100%)**
Duration on DTG (yrs.)	>2	18	7(36.8%)	11(14.3%)
	1 to 2yrs	74	11(57.9%)	63(81.8%)
	<1	4	1(5.3%)	3(4.0%)
	Total	**96**	**19(100%)**	**77(100%)**
Other medical conditions	HTN	11	3(15.8%)	8(10.4%)
	Dyslipidaemia	4	3(15.8%)	1(1.3%)
	other	81	13(68.4%)	68(88.3%)
	Total	**96**	**19(100%)**	**77(100%)**
weight changes after starting ART	Weight gain	66	16(84.2%)	50(64.9%)
	Weight loss	27	2(10.5%)	25(32.5%)
	No change	3	1(5.3%)	2(2.6%)
	Total	**96**	**19(100%)**	**77(100%)**
Family history of type 2 DM	Yes	8	4(21.0%)	4(5.2%)
	No	88	15(79.0%)	73(94.8%)
	Total	**96**	**19(100%)**	**77(100%)**
Respondent reports with symptoms of DM	Yes	21	17(89.5%)	4(5.2%)
	No	75	2(10.2%)	73(94.8%)
	Total	**96**	**19(100%)**	**77(100%)**

Information about smoking history

Most of the respondents 84(87.5%) never smoked in their lifetime amongst them, the prevalence of hyperglycemia among them was 15(78.9%) while 69(89.6.5%) of them had normal fasting blood sugar levels. 12(12.5%) had ever smoked in their lifetime and the prevalence of hyperglycemia among them was 4(21.1%) with 8(10.4%) of them being non-hyperglycaemic.

Alcohol drinking history

The majority 88(91.7%) had never taken alcohol in their lifetime and had hyperglycemia prevalence among them was 17(89.5%). the minority of the respondents 8(8.3%) had ever taken alcohol in their lifetime and there was a prevalence of hyperglycemia of 2(10.5%) among them.

The habit of physical exercise

Out of the 96 respondents, the Majority 90(93.8%) did not do physical exercise, and the prevalence of hyperglycemia in that category was 18(94.7%) while the minority 6(6.2%) who made physical exercise a habit, only 1(5.3%) of the respondents had hyperglycemia.

Duration on ART (Yrs.)

Most of the respondents 82(85.4%) have been on ART for more than 10 years and these had prevalence rates of 9(47.4%) and 73(94.8%) of them had normal fasting blood glucose levels. Respondents who have been on ART for 1-2 years were 9(9.4%) with a prevalence rate of 7(36.8%). 5(5.2%) have been on ART for less than a year. These groups had a hyperglycemia prevalence of 3(15.8%).

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Duration of DTG-based ART regimen

Out of the 96 respondents, the majority 74(77.1%) have been on a DTG ART regimen for about 1-2 years and these have a prevalence rate of 11(57.9%). Those on DTG for above 2years were 18(18.8%) with a prevalence rate of 7(36.8%) and the minority 4(4.2%) have been on DTG for less than a year and these had hyperglycemia prevalence of 1(5.3%).

Other medical conditions

Most of the respondents 81(84.4%) had other medical conditions, for example, hepatitis B, TB infection, and so on, and out of these 13(68.4%) had hyperglycemia, 11(11.5%) had hypertension and 4(4.2%) had dyslipidemia and out of these, they category registered the same prevalence rate of hyperglycemia being 3(15.8%).

Information on weight changes

The majority of 66(68.8%) of the respondents registered weight gain with a prevalence rate of hyperglycemia at 16 (84.2%). Respondents who registered weight loss 27(28.1%) had a prevalence rate of 2(10.5%). Minority 3(3.1%) never registered any weight changes, and these had a prevalence rate of 1(5.3%).

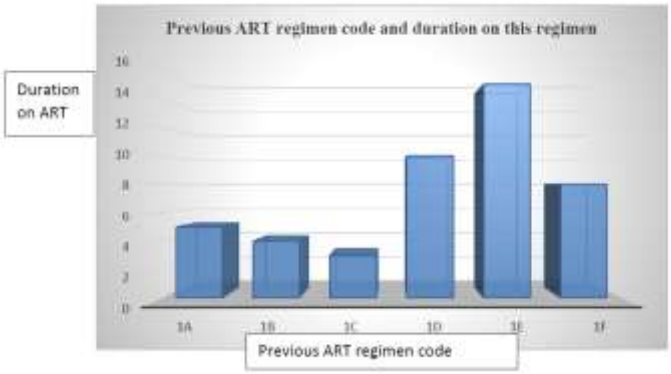
Family history of hyperglycemia

Out of the 96 respondents, 88(91.7%) had no family history of Type 2 DM and these had a DM prevalence of 15(79.0%). 8(8.3%) had a family history of type 2 DM and out of these 4(21.0%) had hyperglycemia.

Respondents reporting symptoms of hyperglycemia

The majority 75(78.1%) of the respondents had no symptoms of hyperglycemia and had a lower prevalence of 2(10.5%). 21(21.9%) registered symptoms of hyperglycemia and these had a high hyperglycemia prevalence of 17(89.5%).

Figure 1: Previous ART regimen code for respondents currently on DTG



1a=d4T+3TC+NVP, 1b=d4T+3TC+EFV, 1c=AZT+3TC+NVP, 1d=AZT+3TC+EFV, 1e=TDF+3TC+EFV, 1f=TDF+3TC+NVP

From Figure 3 above, results indicated the previous ART regimen codes of respondents before starting the DTG ART regimen. Most of the respondents were on 1e and they had been on this regimen for over 10 years, followed by ART regimen 1d where respondents have been on this regimen for over 10 years, followed by ART regimen 1f,1a,1b where respondents have been on this regimen for 2 to 10 years and very few had been on ART regimen of 1c before initiation on DTG ART regimen.

Discussion

Findings reveal that out of 96 respondents that participated in the study,84/96(87.5%) had no smoking history in their lifetime 12/96(12.5%) had a smoking history, and hyperglycemia prevalence was found to be 78.9%, and 21.1% respectively. There's not much correspondence between smoking history and hyperglycemia. The study also revealed that the duration of ART and duration of the Dolutegravir ART regimen were risk factors. The findings showed that 82/96 of the respondents had been on ART for over 10 years hyperglycemia prevalence in this category was high at 47.4% and duration on Dolutegravir ART regimen revealed 74/96 respondents who had been on DTG-containing ART regimen for about 1-2years and this category had the highest hyperglycemia prevalence (57.9%). This high prevalence could have been attributed to the fact that a DTG-containing ART regimen contributes a great deal to hyperglycemia prevalence. This study's findings were in line with a case-control study in Uganda, 8 of 16 (50%) cases with hyperglycemia diagnoses were older than 50 years and most of these cases were taking ART medication for more than five years. (Larmorde M, *et al*, 2018).

The risk factors of other medical conditions (hypertension, Dyslipidaemia & others), weight changes (gain, loss &no change), family history of type 2 DM (yes, no), symptomatic hyperglycemia (yes, no) revealed the following hyperglycemia prevalences. (15.8%,15.8%,68.4%), (84.2%,10.5%,5.3%),

(21.0%,79.0%), (89.5%,10.5%) respectively. This study's findings show similarity with a systematic review and meta-analysis of 44 high-quality articles published all over the world from January 2000 to April 30, 2017, assessing the incidence of Prediabetes and diabetes in PLHW, the major risk factors identified were: older age, Family history of DM, Increasing BMI, Central obesity, Lipodystrophy, Dyslipidaemia, Metabolic syndrome, Increased baseline FBS, ART medications. ART medications found to increase the risk of Prediabetes and diabetes were Proteus inhibitors, Zidovudine, didanosine, lamivudine, Stavudine, and Nevirapine. (Nansseu JR, *et al*, 2018).
Additionally, the findings correlate with a case series where hypertension was seen in two of the three case series reported from Gondar. The time from initiation of DTG-based ART regimen to development of symptomatic hyperglycemia ranged from 1 month to 12 months in this case series. Additionally, all three cases were on other ART regimens for more than ten years (Hailu W, Tesfaye T and Tadesse, 2021).

Conclusion
The majority of HIV patients on DTG-based ART regimen receiving care at Jinja Regional Referral Hospital were predisposed to both lifestyle ART and related risk factors to hyperglycemia which could have cumulatively predisposed them.

Recommendation
More health education and sensitization campaigns should be conducted to raise awareness of the possible risk factors and measures for combating noncommunicable diseases like DM and HTN in all population categories.

Acknowledgment
First and foremost, I would like to express my sincere gratitude to the almighty God who is my source of knowledge, wisdom, and understanding and for giving me the strength to complete this study satisfactorily.
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LIST OF ABBREVIATIONS
ART: Anti-Retroviral Treatment
D.M : Diabetes Mellitus
DTG **:** Dolutegravir
FBS: Fasting blood sugar
HIV: Human Immunodeficiency Virus
JRRH: Jinja Regional Referral Hospital
NNRTI: Non-nucleoside Reverse Transcriptase Inhibitors
NRTI: Nucleoside Reverse Transcriptase Inhibitors
PLWH: People Living With HIV
WHO: World Health Organization
HDL-C: High-Density Lipoprotein Cholesterol
HAART: Highly Active Anti-Retroviral Therapy
BMI: Body Mass Index

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No conflict of interest

Author Biography
Annet Mugoya is a student pursuing a Diploma in Medical Laboratory Technology at St Francis School of Health Sciences.

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