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Evaluating the glycemic effects of Dolutegravir and its predictors among people living with HIV in Uganda: A prospective cohort study.

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Introduction: Dolutegravir (DTG), a key component of the recommended HIV treatment regimens in Uganda, has been associated with hyperglycemia. We evaluated its influence on hyperglycemia risk to create a hyperglycemia risk stratification tool for patient monitoring.

Methods: We conducted a prospective cohort study at three sites with 628 HIV patients on Tenofovir Disoproxyl Fumarate, Lamivudine, and Dolutegravir (TLD). Participants included both Nucleoside reverse transcriptase inhibitors-experienced (exposed) and ART-naïve (non-exposed) groups. Follow-ups occurred every six months with Random Blood Sugar(RBS)every three months. Participants with RBS $\geq$ 7 mmol/L were classified as hyperglycemic and underwent HbA1c testing, confirming diabetes with a 6.5% cut-off.

Results: The study found a hyperglycemia incidence rate of 24.5 cases per 100 person-years (95% CI: 19.3-31.1) and a diabetes incidence rate of 5.8 cases per 100 person-years (95% CI: 3.6-9.3). Hyperglycemia incidence was slightly lower in non-exposed (20.8 cases per 100 person-years) vs. exposed groups (25.2 cases per 100 person-years). Multivariable analysis indicated a trend towards lower hyperglycemia risk in non-exposed (adjusted HR = 0.78, 95% CI: 0.37-1.66, p = 0.52) and substantially lower diabetes incidence (adjusted HR = 0.34, 95% CI: 0.04-2.82, p = 0.32).

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Significant factors for hyperglycemia included age ($p < 0.001$), study site ($p < 0.001$), and DTG-based ART duration ($p = 0.02$).

Conclusion: Our study showed an increased incidence of hyperglycemia with age, study site, and duration of DTG exposure in HIV patients on TLD. We suggest integrated screening and care for hyperglycemia and diabetes in HIV services, especially when initiating DTG regimens.

Key words: Dolutegravir; Hyperglycemia; Diabetes; HIV; Antiretroviral therapy.

BACKGROUND

Diabetes Mellitus (DM) is a leading cause of death in adults globally(1). Prolonged hyperglycemia signals early diabetes risk, crucial for monitoring, especially in predisposed individuals(2). In 2019, global diabetes prevalence was 9.3% (20-79 years) and 19.9% (65-79 years), with Uganda's 2014 survey at 1.4%(1). The DM-HIV treatment association in sub-Saharan Africa is understudied(3). ART use may influence DM development, complicating HIV/AIDS management(4,5). Uganda reports symptomatic hyperglycemia with DTG regimens, but data on incidence are limited(6,7). Dolutegravir (DTG) is believed to chelate and reduce serum magnesium levels, potentially affecting glucose transport via GLUT-4 receptor, leading to increased liver glucose production(8,9)

Uganda's HIV guidelines recommend DTG with TLD as the preferred first-line regimen for people living with HIV (PLHIV), aligning with global trends(10,11). Prioritizing new HIV diagnoses and treatment readiness, TLD is chosen for its high resistance barrier (10,12–14). However, DTG regimens may present hyperglycemia risks, as observed in studies like SPRING-2 and SINGLE. There have been reports of grade 2 (6.95 to 13.88 mmol/L) and grade 3 (blood glucose >13.88 mmol/L) hyperglycemia associated with DTG use, though the extent of these findings remains unclear(15–17). Despite widespread DTG adoption, concerns about hyperglycemia and other adverse effects persist (18).

Despite DTG's efficacy in HIV treatment, limited hyperglycemia data in Uganda hinders risk assessment. This study aims to address this gap by systematically assessing hyperglycemia incidence among PLHIV on DTG-based regimens. The World Health Organization (WHO) underscores the importance of staying informed about drug risks and encourages integrating emerging evidence into clinical guidelines (19).

Therefore, this study addresses a critical knowledge gap and aligns with WHO recommendations, contributing to evidence-based decision-making in HIV care. The study evaluated the association between prior exposure to nucleoside reverse transcriptase inhibitors (NRTIs) and the risk of hyperglycemia or DM in order to guide risk stratification and tailored interventions, ultimately enhancing the quality of HIV care and treatment in Uganda and beyond.

METHODS AND MATERIALS

Study Design: This prospective cohort study evaluated the incidence of hyperglycemia among adults receiving DTG as part of their ART regimen. The study spanned 14 months, from July 2021 to September 2022. Participants were enrolled and followed for six months, with clinical and laboratory assessments every three months to evaluate hyperglycemia related to ART history.

Study Sites and Study Population: Electronic lists from Mildmay Uganda Hospital (Site 1), Luwero Hospital (Site 2), and Nyimbwa Health Centre IV (Site 3) ART clinics were used to sample participants. Cluster sampling organized the lists into study groups, followed by random sampling. The exposed group comprised participants on TLD who had prior exposure to NRTI and Non-nucleoside reverse transcriptase inhibitors (NNRTIs), while the Exposed group included ART-naïve participants on TLD, representing their first ART regimen. Adults on TLD with undetectable viral loads and no history of diabetes were included. Inclusion criteria required consent and an adult above 18years of age, while exclusion criteria included history of hyperglycemia, detectable HIV viremia, unclear ART history, and pregnancy. A proportionate sample size was selected to ensure representation across different settings: urban, peri-urban, and rural.

Sample Size Calculation: The study opted to use data for Protease inhibitors due to lack data on Integrase strand inhibitors. Past research indicated Protease Inhibitors independently associated with hyperglycemia (IRR 5, 95% CI 1.3–19.4) (20). Sample size for this study (n=628) was determined using Open Epi software to achieve 80% power, considering potential follow-up losses with two groups in the study and two-sided 95% confidence interval.

Data Collection and Management: Data on participants' socio-demographic characteristics, medical history and examination was collected using a combination of participant interviews and abstraction of data from ART registers, patient cards, and Electronic Medical Records (EMR). All data were entered into the Open Data Kit (ODK) platform for electronic storage and analysis. To ensure data accuracy, regular checks were conducted against hard copies of study materials.

Laboratory Procedures and interpretation of Laboratory results: At each three-month study visit, participants underwent Random Blood Sugar (RBS) testing using an On Call® Plus glucometer, chosen for its cost-effectiveness and lack of dietary restrictions. Participants with RBS levels ≥ 7 mmol/L had additional glycated hemoglobin (HbA1c) testing to confirm diabetes, using a 6.5% HbA1c cut-off (21). HbA1c analysis was conducted with the AFI 6000 Fluorescence Immuno Assay Analyzer or Cobas C311 at the ISO 15189 certified Mildmay Uganda Hospital laboratory. The 7 mmol/L hyperglycemia cut-off is supported by Michael E. Bowen et al. (2015), who found elevated RBS levels (≥ 5.6 mmol/L) strongly linked to undiagnosed diabetes (OR: 31.2), persisting after adjustment (OR: 20.4) (22). Diabetes likelihood increased with higher RBS: 100–119 mg/dL (5.6–6.6 mmol/L) (OR: 7.1), 120–139 mg/dL (6.7–7.7 mmol/L) (OR: 30.3), and ≥ 140 mg/dL (≥ 7.8 mmol/L) (OR: 256). Additionally, the Division of AIDS (DAIDS) grading

system classifies high non-fasting blood glucose levels from 6.44 to less than 8.89 mmol/L as mild (23).

Data Analysis: Data analysis was performed using Stata version 15 software. Descriptive statistics were used to summarize participant characteristics, and Cox regression models were employed to assess the association between variables. Multivariable models were adjusted for potential confounders.

Ethical Considerations: Ethical approval was obtained from the Mildmay Uganda Research Ethics Committee (#REC REF 0812-2020) and the Uganda National Council for Science and Technology (HS1273ES). Participants were treated with confidentiality, and a written informed consent was obtained prior to enrollment in the study.

RESULTS

The majority of the participants were; female (n=419, 67%), aged 40 years and above (n= 327, 52%), none alcohol users (n= 453, 72%), none smoker (n= 601, 96%), of normal BMI (n= 347, 56%), of normal waist circumference (n=322, 52%), of normal waist to Hip ratio (n=367, 59%), normotensive (n=386, 63%), previously exposed TDF NRTI backbone ART regimen (n=407, 65%), ART experienced for five years or more (n=404, 64%), euglycemic at baseline (n=605, 96%), and asymptomatic (n=366, 58%) as shown in Table 1 below.

Incidence of hyperglycemia

The study found an overall hyperglycemia incidence of 24.5 per 100 person-years. The incidence was higher in the exposed group (25.2) compared to the non-exposed group (20.8) (HR=0.74, 95%CI: 0.36-1.50, p=0.38). Hyperglycemia risk was associated with increasing age, marital status, study site and duration on TLD. However, the increased risk of hyperglycemia was linked to the duration of DTG exposure and not the overall duration on ART as shown in Table 2 below.

Association between previous NRTI exposure and the incidence of hyperglycemia among patients on TLD.

The multivariable analysis showed lower hyperglycemia risk in the non-exposed group, but this was not statistically significant. (adjusted HR=0.78, 95% CI: 0.37-1.66, p=0.52). Influencing factors included study site, age, marital status, and alcohol consumption, but not BMI. The relationship was modified by alcohol (interaction p=0.09) and sex (interaction p=0.14), with non-drinkers and women showing lower incidence rates (22.5 (16.6-30.4)compared to their counterparts (28.7 (19.6-42.2)).

Incidence of Diabetes Mellitus

The study found a diabetes incidence of 5.8 per 100 person-years, higher in the exposed group (6.5) than the non-exposed group (2.2). Incidence varied by dolutegravir duration, age, marital status, alcohol, smoking, BMI, waist measures, hypertension, and study site as shown in Table 3.

Flow chart for Random glucose and HbA1C

In the study, 90 hyperglycemic RBS test results were identified, with 17 cases classified as diabetic among 68 unique participants. Among these, 23 RBS results ≥7 mmol/l were found during the first visit, 34 during the second, and 33 during the third. Out of these, 7, 12, and 5 were classified as diabetic during the respective visits as shown below in figure 1.

Association between previous ART exposure and incidence of diabetes

After adjusting for potential confounders, the study found that being in a non-exposed group was associated with a 66% lower incidence of diabetes compared to the exposed group (adjusted HR=0.34, 95%CI: 0.04-2.82, p=0.32). The association between previous ART exposure and diabetes incidence was confounded by various factors, including study site, duration on Dolutegravir-based ART, age, and marital status.

Predictors of hyperglycemia among patients on TLD.

Factors associated with hyperglycemia included age (p<0.001), study site (p<0.001), and duration of Dolutegravir-based ART (p=0.02). Hyperglycemia incidence was higher among those older, married, and with prolonged ART. Site 2 participants had a 3.5 times higher incidence (Table 4).

DISCUSSION

In Uganda, the main considerations for ART initiation include a new diagnosis of HIV infection and patient's readiness to start ART. The standard initial regimen should be TLD unless any of the components of this regimen are contraindicated. This is principally because DTG offers a higher genetic barrier to drug resistance as compared to Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and has not yet been extensively used previously in this setting(13). However, alongside the benefits of this preferred regimen, come challenges with adverse effects, among which the risk of hyperglycemia is highest(18).

This multisite prospective cohort study observed 68 hyperglycemia events (11%) among 628 participants over six months, with an incidence rate of 24.5 per 100 person-years. This aligns with the SAILING trial, which reported hyperglycemia-related lab abnormalities in 10% of participants, both with similar follow-up periods and ART-experienced participants (17).

However, these results contrast with the SPRING 2 and SINGLE studies, which reported lower hyperglycemia incidence rates of 7% (26/411) and 8% (34/414) respectively(15,16). This difference could be attributed to several factors such as the study design, participant selection criteria and study setting. Our study employed an observational design reflecting real-world data and clinical practice, where ART prescription follows public health approach and pre-treatment comorbidity screening is often more clinical than laboratory based. In contrast, SPRING 2 and SINGLE studies were rigorous clinical trials with strict eligibility criteria (15,16). This difference in participant selection could have influenced the observed hyperglycemia rates.

In a six months' period, this study observed an overall diabetes incidence of 5.8 cases per 100 person-years (95% CI: 3.6-9.3)which is comparable to 4.7 cases per 100 person-years reported in a four years' follow up in the Multicenter AIDS Cohort Study (MACS) among HIV-infected men receiving Highly Active Antiretroviral Therapy (HAART)(24). Our study captured more incident diabetes cases than MACS population at four years therefore extending the follow-up period in future studies could potentially yield even higher diabetes incidence rates. Despite diabetes being an exclusion criterion at enrollment, the study identified 23 participants with hyperglycemia and 7 with diagnosed diabetes who were unaware of their condition (figure 1). These findings are consistent with a study carried out in Tanzania, where 95% of HIV-infected adults with diabetes were not aware of their diagnosis(25). Similarly, low diabetes awareness rates have been reported in other African studies (25).

Our study revealed an increased risk of hyperglycemia with increasing age. Participants aged 40 years or older had a 4.6-fold increased risk of hyperglycemia compared to those aged 18-29 years (adjusted HR = 4.6, 95% CI: 1.8-12.1). This age-related risk was further amplified by factors such as obesity, daily alcohol consumption, abnormal waist-to-hip ratio, and moderate/severe hypertension. These findings align with previous research demonstrating that increasing age, along with associated genetic changes and lifestyle factors, can contribute to a higher risk of hyperglycemia(26). This observation suggests that initiating DTG-based regimens in older adults might present a double burden: the risk of HIV and the potential increased risk of hyperglycemia. Consequently, it highlights the importance of vigorous hyperglycemia screening for HIV-infected individuals within these high-risk groups before starting DTG therapy.

The duration on DTG based regimen was one of the factors that we found to be predictive of hyperglycemia. Compared to participants who had been on Dolutegravir-based ART for less than one year, those with a duration of at least 2 years were associated with an increased incidence of hyperglycemia of 5.7 times (adjusted HR=5.7, 95% CI: 1.5-21.2). These findings are similar to those in a study by Namara et al. (2021). where PLHIV who had previously been prescribed DTG based regimen had seven times greater odds of having hyperglycemia(26). This similar trend has been suggested in the pivotal DTG trials which indicate an increased risk of hyperglycemia with extended exposure to DTG combination treatment as well as treatment duration(17).

Uniquely, Study site 2 was found to have an association with hyperglycemia compared to study sites 1 and 3. There was a significantly higher incidence of hyperglycemia 20% [46.9 (34.0-64.8)] at site 2 (Luwero hospital) compared to other sites Nyimbwa HCIV 6% [13.4 (4.3-41.6)] (Site 3) and Mildmay Uganda hospital 7.2% [15.9 (11.0-23.0)] (Site1). Compared to participants recruited from site 1, those recruited from site 2 were associated with an increased incidence of hyperglycemia of 3.5 times (adjusted HR=3.5, 95% CI: 2.0-6.2).

However, there have not been many studies to ascertain how a study setting could influence the incidence of hyperglycemia. Such an observation could be attributed to the fact that study site 2 is at hospital level with a much wider catchment area in terms of access to ART services compared to its counterpart in the same rural setting (site 3, HCIV). The diversity in participant composure enrolled in the study could have clouded the true reflection of findings at site 2. Despite having almost, the same catchment area or participant composure, the same phenomenon was not observed at site 1.

This could be explained by the difference in the study participants' composure considering that site 1 is in a peri-urban setting where access to screening services and health information is improved compared to a rural setting. Therefore, this would warrant a study to understand the site related factors that could have contributed to these findings.

The study found no significant association between prior NRTI exposure and hyperglycemia among TLD users (p=0.52), with a wide confidence interval indicating insufficient power. Age, alcohol use, waist circumference, marital status, and DTG-based ART duration (but not overall ART duration) were confounders. Enhanced hyperglycemia screening for older adults and long-term DTG users is recommended, alongside tailored public health strategies.

Strength and Limitations of this study

Our study's prospective cohort design allowed for precise monitoring of newly occurring events and clear differentiation between hyperglycemia and diabetes, enhancing the reliability of our findings. However, limited literature during the study's preparation and resource constraints may have affected sample size estimation and follow-up duration, respectively. Consequently, we relied on past studies on ART, specifically Protease Inhibitors, which may have affected the accuracy of our sample estimate. Nonetheless, our study provides valuable insights into the glycemic effects of Dolutegravir-based regimens, offering crucial information for HIV programming stakeholders.

CONCLUSION

Our study found hyperglycemia incidence among HIV patients on TLD, influenced by age, marital status, study site, and duration on DTG-based regimens. Integration of hyperglycemia and diabetes screening into HIV services is essential, particularly for high-risk groups such as the elderly, hypertensive, and obese individuals before DTG initiation. Additionally, continued blood glucose

monitoring for individuals already on DTG should be emphasized to enable early detection and prompt management of hyperglycemia/diabetes. Larger cohort studies and investigations into site-related factors are recommended for targeted interventions in HIV programming.

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Conflict of interest: All authors have no conflict of interests to declare.

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Contributors: CA*, CA, YK, SN conceived and designed the study. CA*, CA, SN, SN2, IK SMC, PK and JE did the data collection and interpretation. IK, and SN participated in analysis. MO, IM, DNK, VN, HBN and BM participated in the interpretation of results and writing the final manuscript. All authors read and approved the final version of the manuscript.

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Table 1: Baseline characteristics of study participants.

Characteristic	Category	n (%)
All respondents		628
Study site	Site 1	390 (62.1)
	Site 2	188 (29.9)
	Site 3	50 (8.0)
Gender	Female	419(67%),
	Male	209(33%),
Age in years	18-29	124 (19.7)
	30-39	177 (28.2)
	40 and more	327 (52.1)
Marital status	Single	312 (49.7)
	Married	221 (35.2)
	Separated/Divorced/Widow	95 (15.1)
Alcohol intake	No	453 (72.2)
	Weekly or Occasionally	162 (25.8)
	Daily	12 (1.9)
Smoking status	Yes	26 (4.1)
	No	601 (95.9)
Body Mass Index (kg/m2)	<=24.9(Normal BMI)	347 (56.1)
	25-29.9(Overweight)	168 (27.1)
	>=30 (Obesity)	104 (16.8)
Abnormal waist circumference	>=94cm(men)/>=80cm(women)(Abnormal)	301 (48.3)
	< 94cm(men)/<80cm(women) (Normal)	322 (51.7)
Abnormal waist/hip ratio	>0.95(men)/>0.85(women) (Abnormal)	252 (40.7)
	<0.95(men)/< 0.85(women) (Normal)	367 (59.3)
Hypertension level	Normal (110-129/70-79)	386 (62.5)
	Mild(130-139/ 80-89)	188 (30.4)

	Grade 2/3 hypertension(≥140/≥90)	44 (7.1)
ART regimen exposure	TDF NRTI backbone	407 (64.8)
	Zidovudine (AZT) NRTI backbone	121 (19.3)
	Abacavir (ABC) NRTI backbone	4 (0.6)
	TLD at Initiation	96 (15.3)
Overall duration on ART	<2 years	76 (12.1)
	2 - <5 years	148 (23.6)
	5+ years	404 (64.3)
Duration on current ART	<1 year	172 (27.4)
	1 - <2 years	240 (38.2)
	2+ years	216 (34.4)
Random blood glucose (mmol/l)	<7.0 mmol/l	605 (96.3)
	7.0+ mmol/l	23 (3.7)

Table 2: Incidence of hyperglycemia and relative risks

Characteristic	**Number with hyperglycemia/ person-years**	**Incidence of hyperglycemia (95% CI)**	**Hazard Ratio (95% CI)**	**p-value**
All respondents	68/277.4	24.5 (19.3-31.1)		
Exposure to DTG previously				0.38
Exposed	59/234.0	25.2 (19.5-32.5)	1	
Non-Exposed	9 /43.4	20.8 (10.8-39.9)	0.74 (0.36-1.50)	
ART regimen prior to the current regimen				0.58
TDF NRTI backbone	45/178.0	25.3 (18.9-33.9)	1	
AZT NRTI backbone	14/54.4	25.8 (15.3-43.5)	1.03 (0.56-1.90)	
ABC NRTI backbone	0 /1.7	-	-	
TLD at Initiation	9 /43.4	20.8 (10.8-39.9)	0.74 (0.36-1.52)	
Study site				<0.001
Site 1	28/176.2	15.9 (11.0-23.0)	1	
Site 2	37/78.8	46.9 (34.0-64.8)	2.71 (1.58-4.65)	
Site 3	3 /22.3	13.4 (4.3-41.6)	0.66 (0.19-2.24)	

Sex of respondent				0.96
Men	26/90.5	28.7 (19.6-42.2)	1	
Women	42/186.9	22.5 (16.6-30.4)	1.01 (0.59-1.73)	
Age in years				<0.001
18-29	5 /57.1	8.8 (3.6-21.0)	1	
30-39	14/81.1	17.3 (10.2-29.2)	1.90 (0.68-5.29)	
40 and more	49/139.2	35.2 (26.6-46.6)	3.56 (1.39-9.09)	
Marital status				0.04
Single	23/139.3	16.5 (11.0-24.9)	1	
Married	29/97.1	29.9 (20.8-43.0)	1.78 (1.02-3.09)	
Separated/Divorced/Widowed	16/40.5	39.5 (24.2-64.5)	2.09 (1.09-4.01)	
Alcohol intake				0.33
No	45/199.2	22.6 (16.9-30.3)	1	
Weekly or Occasionally	20/72.9	27.4 (17.7-42.5)	1.15 (0.68-1.95)	
Daily	3 /4.8	63.0 (20.3-195.3)	2.01 (0.61-6.63)	
Smoking status				0.30
NoYes	63/265.0	23.8 (18.6-30.4)	1	
	5 /11.9	42.1 (17.5-101.1)	1.63 (0.65-4.10)	
Body Mass Index (kg/m2)				0.77
<=24.9	40/152.1	26.3 (19.3-35.9)	1	
25-29.9	16/74.5	21.5 (13.2-35.1)	0.85 (0.48-1.53)	
>=30	12/47.0	25.5 (14.5-45.0)	1.11 (0.58-2.14)	
Abnormal waist circumference				0.50
Normal>=94cm(men)/>=80cm(women)	34/140.4	24.2 (17.3-33.9)	1	
	34/132.8	25.6 (18.3-35.8)	1.19 (0.73-1.94)	
Abnormal waist/hip ratio				0.93
Normal>0.95(men)/>0.85(women)	41/159.2	25.7 (19.0-35.0)	1	
	27/111.9	24.1 (16.5-35.2)	1.02 (0.62-1.68)	
Hypertension level				0.34
Normal	41/169.2	24.2 (17.8-32.9)	1	
Mild	19/82.5	23.0 (14.7-36.1)	0.97 (0.56-1.67)	
Grade 2/3 hypertension	8 /19.0	42.2 (21.1-84.3)	1.75 (0.81-3.75)	

Overall duration on ART				0.55
<2 years	6 /34.1	17.6 (7.9-39.1)	1	
2 - <5 years	17/65.4	26.0 (16.2-41.8)	1.45 (0.55-3.79)	
5+ years	45/177.3	25.4 (18.9-34.0)	1.58 (0.66-3.79)	
Duration on TLD				0.01
<1 year	15/77.5	19.3 (11.7-32.1)	1	
1 - <2 years	19/107.9	17.6 (11.2-27.6)	1.69 (0.67-4.27)	
2+ years	34/91.4	37.2 (26.6-52.0)	6.09 (1.80-20.61)	

Table 3: Incidence of Diabetes Mellitus and relative risks.

Characteristic	Number with Diabetes Mellitus/ person-years	Incidence of diabetes per 100 person-years, (95% CI)	Hazard Ratio (95% CI)	p-value
All participants	17/292.6	5.8 (3.6-9.3)		
Previous exposure to ART				0.17
Exposed	16/246.5	6.5 (4.0-10.6)	1	
Non-Exposed	1 /46.1	2.2 (0.3-15.4)	0.31 (0.04-2.33)	
ART backbone among the Exposed				0.54
TDF NRTI backbone	12/188.3	6.4 (3.6-11.2)	1	
AZT NRTI backbone	4 /56.5	7.1 (2.7-18.9)	0.95 (0.30-3.04)	
ABC NRTI backbone	0 /1.7	-	-	
TLD at Initiation	1 /46.1	2.2 (0.3-15.4)	0.30 (0.04-2.33)	
Study site				0.03
Site 1	9 /181.8	5.0 (2.6-9.5)	1	
Site 2	8 /87.2	9.2 (4.6-18.3)	1.98 (0.68-5.76)	
Site 3	0 /23.6	-	-	
Sex of respondent				0.77
Men	6 /96.8	6.2 (2.8-13.8)	1	
Women	11/195.8	5.6 (3.1-10.1)	1.17 (0.40-3.40)	
Age in years				0.16
18-29	1 /57.9	1.7 (0.2-12.3)	1	

30-39	4 /83.8	4.8 (1.8-12.7)	2.81 (0.31-25.28)	
40 and more	12/150.8	8.0 (4.5-14.0)	4.08 (0.51-32.36)	
Marital status				0.11
Single	6 /144.0	4.2 (1.9-9.3)	1	
Married	5 /105.0	4.8 (2.0-11.4)	1.08 (0.33-3.59)	
Separated/Divorced/Widowed	6 /43.1	13.9 (6.3-31.0)	3.41 (1.05-11.04)	
Alcohol intake				0.14
No	15/207.6	7.2 (4.4-12.0)	1	
Weekly or Occasionally	2 /78.5	2.5 (0.6-10.2)	0.32 (0.07-1.38)	
Daily	0 /6.0	-	-	
Smoking status				0.94
No	16/278.6	5.7 (3.5-9.4)	1	
Yes	1 /13.5	7.4 (1.0-52.6)	1.08 (0.14-8.23)	
Body Mass Index (kg/m2)				0.31
<=24.9	7 /161.6	4.3 (2.1-9.1)	1	
25-29.9	5 /78.6	6.4 (2.6-15.3)	1.49 (0.47-4.72)	
>=30	5 /48.6	10.3 (4.3-24.7)	2.55 (0.80-8.20)	
Abnormal waist circumference				0.07
Normal	5 /149.0	3.4 (1.4-8.1)	1	
>=94cm(men)/>=80cm(women)	12/139.4	8.6 (4.9-15.2)	2.68 (0.93-7.73)	
Abnormal waist/hip ratio				0.11
Normal >0.95(men)/>0.85(women)	7 /169.5	4.1 (2.0-8.7)	1	
	10/117.4	8.5 (4.6-15.8)	2.24 (0.84-6.00)	
Hypertension level				0.78
Normal	10/179.2	5.6 (3.0-10.4)	1	
Mild	5 /86.2	5.8 (2.4-13.9)	1.04 (0.35-3.05)	
Grade 2/3 hypertension	2 /20.5	9.7 (2.4-39.0)	1.78 (0.38-8.27)	
Overall duration on ART				0.75
<2 years	1 /35.8	2.8 (0.4-19.8)	1	
2 - <5 years	5 /69.3	7.2 (3.0-17.3)	2.21(0.24-20.60)	
5+ years	11/187.0	5.9 (3.3-10.6)	1.93 (0.24-15.79)	
Duration on TLD				0.03

<1 year	2 /81.1	2.5 (0.6-9.9)	1
1 - <2 years	6 /111.2	5.4 (2.4-12.0)	12.79(1.57-103.8)
2+ years	9 /99.8	9.0 (4.7-17.3)	20.09 (1.08-372.3)

Table 4: Factors associated with the incidence of hyperglycemia.

Characteristic	Category	Hazard Ratio (95% CI)	p-value
Study site	Site 1	1	<0.001
	Site 2	3.48 (1.96-6.18)	
	Site 3	0.66 (0.19-2.25)	
Age in years	18-29	1	<0.001
	30-39	1.75 (0.62-4.93)	
	40 and more	4.61 (1.76-12.08)	
Marital status	Single	1	0.062
	Married	1.99 (1.12-3.52)	
	Separated/Divorced/Widow(er)	1.47 (0.75-2.87)	
Duration on current ART(TLD)	<1 year	1	0.024
	1 - <2 years	1.40 (0.57-3.46)	
	2+ years	5.74 (1.54-21.20)