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Association of hyperglycemia with Tenofovir+Lamivudine+ Dolutegravir (TLD) or Tenofovir+Lamivudine+Efavirenz (TLE) Antiretroviral Regimens in Patients Living with HIV: A Retrospective Cohort Study

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Abstract

Background: Dolutegravir (DTG) is recommended as first-line treatment for HIV infected adults, pregnant women and children older than 12 years. However, emerging evidence suggests an association between dolutegravir and hyperglycemia. Hence, we evaluated the association of hyperglycemia in adult patients living with HIV receiving either Tenofovir+Lamivudine+Dolutegravir (TLD) or Tenofovir+Lamivudine+Efavirenz (TLE) regimens.

Methods: A retrospective cohort study was conducted wherein medical records of 250 HIV infected adults, registered at the ART Centre of a tertiary care public hospital and receiving either TLD or TLE regimens for at least 6 months were reviewed following ethical approval. Demographic details, ART drug regimen details, HbA1c values, fasting blood glucose levels, antidiabetic drug details and adverse drug reactions were captured and association between ART medications and hyperglycemia was analysed.

Results: Women were the predominant population in both cohorts with mean body weight being significantly higher in the TLD cohort (62.29 vs.58.74 kg) [p=0.02]. Significantly larger number of patients receiving TLD regimen (30.4%) were predisposed to hyperglycemic events (14.4%) [p=0.002]. Significantly higher HbA1c values and mean fasting glucose levels was observed in the TLD cohort with 13.6% patients initiated on antidiabetic treatment [p=0.02].

Conclusion: TLD regimen was found to be associated with a significant increase in hyperglycemic events and dysregulation of glucose metabolism. Thus, patients on TLD regimen should have frequent glucose monitoring and management with antidiabetic therapy, if required, so long as the benefits of these drugs in delaying HIV disease progression outweigh the risks involved

Keywords: Anti-retroviral drugs, Human immunodeficiency virus, Dolutegravir, hyperglycemia, retrospective cohort

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Introduction

The recommended treatment for HIV today is a combination of a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs).[1,2,3] The standard first line regimen for treatment of patients on antiretroviral therapy has been switched from Tenofovir + Lamivudine + Efavirenz [TLE regimen] to Tenofovir + Lamivudine + Dolutegravir [TLD regimen] wherein the drug Efavirenz was replaced with the integrase strand transfer inhibitor; Dolutegravir (DTG) due to a better pharmacological properties and minimal drug-drug interactions.[1,2,3,4]

Assessing its risk-benefit ratio, WHO (July 2019) recommended the use of DTG as the preferred first-line treatment for the adult and pediatric population aged 12 years and older as well as in pregnancy only if its benefits outweigh the risks.[3] In 2019, 82 low- and middle-income countries were reported to be transitioning to DTG-based HIV treatment regimens as DTG was found to be more effective with a high genetic barrier to drug resistance, affordable for patients and has fewer side effects than alternative drugs.[5] A case-control study by Lamorde M *et al* however observed that a higher number of patients on DTG based ART regimen reported episodes of hyperglycemia with an incidence of 4.7% per 1000 patients.[6] A retrospective cohort data analysis from 2006–2017 conducted by Summers *et al* using data from virally-controlled women living with HIV (WLWH) enrolled in the longitudinal Women's Interagency HIV study found that women who switched to or added an INSTI to their ART regimen had unfavorable changes in HbA1c and blood pressure when compared to those who received non-INSTI ART, during the short-term follow up of 6-18 months.[7]

Currently, the hyperglycemic events are medically managed by antidiabetic agents such as glimepiride/injectable insulin analogues/metformin not exceeding one gram dose/day as metformin levels were found to be increased due to inhibition of renal organic cation transporter-2 [OCT2] by Dolutegravir that led to increased gastrointestinal side effects.[8,9] The cause of hyperglycemia induced by the integrase strand inhibitors [INSTIs] is hypothesized to be due to INSTI drug binding to the DDE(D) motif of the HIV integrase enzyme with divalent metal ion catalysts, Magnesium [Mg^{2+}] and Manganese [Mn^{2+}] required for viral integration to host DNA. INSTIs chelate the essential metal cation, Mg^{2+} and induce lower levels of Mg^{2+} availability for Adenosine Tri-Phosphatase (ATP) catalyzed reaction, insulin release & signaling.[10] Few studies have shown an association between decreased levels of Mg^{2+} and decreased insulin sensitivity and/or Diabetes mellitus (DM). The hyperglycemia may not remain consistent due to turnover of HIV integrase enzymes and replenishment of divalent metal ions by physiological mechanisms in the human body. Moreover, these ART based regimens have their own toxicity profiles.[10]

With this background, we planned to evaluate the association of hyperglycemic and non-hyperglycemic adverse events induced in patients on a dolutegravir [INSTIs] based HIV treatment regimen.

Methodology

Study design: An observational, single-center, two-arm retrospective cohort study.

Study setting: This was a single center study conducted at the HIV Clinic/Outpatient department of a tertiary care teaching hospital in Mumbai, India.

Study population: Patients aged between 18-65 years of age, diagnosed with Human Immunodeficiency Virus [HIV] infection and on at least 6 months of either TLD or TLD ART drug regimen visiting the HIV clinic and who consented to allow the Study Investigators to access their outpatient department records were enrolled in either one of the two study groups. One group included patients on TLE drug regimen or those who were switched to TLE regimen in the past 6 months or more while the other group included patients who were on TLD drug regimen or switched to TLD regimen in the past 6 months at least. Patients detected to be diabetic prior to the diagnosis of HIV disease and receiving ART drugs other than TLD/TLE regimen were excluded. No intervention was given and only data records of the study participants were accessed.

Ethics: The study received approval from Ethics Committee for Academic Research Projects [ECARP/2022/166] and Mumbai Districts AIDS Control Society [MDACS] before the start of enrolment. The study was conducted in compliance with Indian Good Clinical Practice [GCP], 2013, ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017) and also in

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accordance with principles of the Declaration of Helsinki (2013).

Study Procedure for data collection: Study participant records were accessed only to collect demographic details, concomitant drug details, laboratory data, and adverse drug reaction data over a retrospective period of 12 months (June 2021 to May 2022). Laboratory data included glycated hemoglobin (HbA_1c) values, fasting and postprandial (wherever available) blood glucose levels to confirm the hyperglycemic events in patients on ART regimen. Only those patient case records which were complete with respect to the study related details (HIV disease history, ART & antidiabetic drug details, blood glucose and HbA_1c reports) were documented in a study proforma and considered for analysis.

Case definition for Pre-diabetic and Diabetes Mellitus: In accordance with the American Diabetic Association (ADA) 2020 guidelines for Diabetes mellitus, patients with HbA_1c values between 5.7–6.4% and fasting blood glucose values between 100–125 mg/dL were considered to be Pre-diabetic (predisposed to hyperglycemia) whereas patients with HbA_1c values ≥6.5% and fasting blood glucose values ≥126 mg/dL were considered to be diagnosed as suffering from Diabetes mellitus.[11]

Sample size calculation: The study had only two groups; Participants on TLD regimen or switched to TLD regimen from any other ART treatment regimen in the past 6 months & those on TLE regimen or those switched to TLE regimen from any other ART treatment regimen in the past 6 months, with every patient receiving the prescribed ART regimen for at least 6 months. Considering the ART patient load of approximately 3000 per year at our HIV clinic with an equal chance of a hyperglycemic event occurring in either study group [50%] with 90% confidence level and 5% precision, the estimated sample size was calculated to be 249.[12] Thus, a sample size of 250 patients [125 patients in each cohort] was considered for this study.

***Outcome measures*:** These were measured at the end of 6 months of treatment on either TLD or TLE regimen.

Primary outcome measures:

- Number of patients with hyperglycemic events across the TLD and TLE cohorts

Secondary outcome measures:

- Mean HbA_1c values of study participants across the TLD and TLE cohorts
- Mean fasting blood glucose levels of study participants across the TLD and TLE cohorts
- Nature of ADRs reported by the study participants on TLD or TLE based ART regimen.

***Statistical Analysis*:** The data collected in the study proforma was entered into Microsoft Excel and analysed using GraphPad InStat Version 3.06, GraphPad Software Inc. Categorical variables [gender, proportion of patients with ADRs, proportion of hyperglycemic patients] were expressed as percentages [descriptive] and Chi-square test was used to test the difference in proportions, with the relative risk and 95% Confidence Interval. Quantitative data was checked for normality by the Kolmogorov Smirnov test and as the data was found to be normally distributed, Student's unpaired 't' test was used to test for the difference in the means between the two groups, with the mean difference and 95% Confidence Interval. A p-value of less than or equal to 0.05 was considered to be statistically significant.

Results

Demographics: The study population predominantly included women in both cohorts [TLE (54.4%) & TLD (52%)]. The mean body weight ranged between 58-62 kg in both cohorts with the TLD cohort having a significantly higher body weight [p=0.02]. The mean duration of HIV infection in each cohort was 12 years with a majority of the patients receiving different ART regimens over the last 9-10 years. About 22.4% & 25.6% of the study patients were receiving the TLD & TLE regimens respectively as de-novo therapy while 77.6% and 74.4% patients had their regimens switched from TLE to TLD or *vice versa* respectively over the last 3-4 years. About 13.6% of study participants on TLD regimen were started on antidiabetic treatment, although not statistically significant compared to the TLE cohort (p=0.09). [Refer Table 1].

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Table 1: Demographic characteristics and treatment details of patients on Tenofovir + Lamivudine + Dolutegravir (TLD) regimen and Tenofovir + Lamivudine + Efavirenz (TLE) cohorts.

Demographic Characteristics of study participants	TLD drug regimen cohort (N=125) n (%/Mean ±SD)	TLE drug regimen cohort (N=125) n (%/Mean ±SD)	Relative Risk; 95% CI]	p-value
Gender distribution				
Male	60 (48)	57 (45.6)	1.05 [0.82 to 1.34]	0.79
Female	65 (52)	68 (54.4)		
Age (years)	47.92 ± 7.33	46.53 ± 7.09	-1.39 [-3.19 to 0.41]	0.13
Body weight (kg)	62.29 ± 11.99	58.74 ± 12.24	-3.55 [-6.57 to -0.53]	**0.02**
Duration of HIV disease (in years)	12.06 ± 3.29	12.02 ± 3.36	-0.94 [-0.86 to 0.80]	0.94
Duration of ART treatment (in years)	9.34 ± 2.71	10.00 ± 3.09	0.07 [-0.06 to 1.39]	0.07
% participants on de-novo ART regimen	28 (22.4)	32 (25.6)		
% participants who were switched from one regimen to the other	97 (77.6)	93 (74.4)	0.91 [0.67 to 1.24]	0.66
% participants started on anti-diabetic agents after initiation of ART regimen	17 (13.6)	8 (6.4)	1.42 [1.05 to 1.92]	0.09
Duration of ART treatment prior to diagnosis of Diabetes mellitus (in years)	2.37 ± 0.88	3.71 ± 1.65	1.34 [1.01 to 1.67]	**<0.0001**

Association between hyperglycemic events in those started or switched to TLD and TLE drug regimens

The total number of pre-diabetic and diabetic participants together was used to analyze the data. A significantly larger number of study participants receiving TLD drug regimen (38/125) had experienced hyperglycemic events compared to TLE cohort when assessed at the end of 6 months therapy with either regimen (18/125) [p=0.003] [Table 2]. All patients confirmed to be diabetics were started on antidiabetic agents for the treatment of hyperglycemia.

Table 2: Association of hyperglycemic events with the anti-retroviral drug regimens.

Study Participants on ART drug regimen	Number of study Participants who experienced hyperglycemic events at the end of 6 months of ART therapy n (%)	Number of study Participants who did not experience hyperglycemic events at the end of 6 months of ART therapy n (%)	Relative Risk (95% Confidence Interval	p-Value
On/switched to TLD drug regimen [N=125 cases]	38 (30.4)	87 (69.6)	2.11 (1.27-3.49)	**0.003**
On/switched to TLE drug regimen [N=125 controls]	18 (14.4)	107 (85.6)		
Total	56	194		

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Comparative assessment of HbA1c values and mean fasting blood glucose levels (mg/dl) across the TLE/TLD cohorts.
Significantly higher HbA1c values [p=0.02] and mean fasting glucose levels [p=0.005] was observed in the TLD cohort as compared to the TLE cohort, indicating that dolutegravir did affect glucose metabolism to a greater extent than the TLE regimen. [Table 3].

Table 3: Comparative assessment of mean HbA1c values and fasting blood glucose levels (mg/dl) across the Tenofovir + Lamivudine + Dolutegravir (TLD) regimen and Tenofovir + Lamivudine + Efavirenz (TLE) cohorts.

Parameters	Study Participants on/switched to TLD drug regimen [N=125 cases] (%/Mean ±SD; 95% CI)	Study Participants on/switched to TLE drug regimen [N=125 controls] (%/Mean ±SD; 95% CI)	Mean difference [95% Confidence Interval]	p-Value
Mean HbA1c values (%)	6.20 ± 0.37 (95% CI 6.14 - 6.27)	6.11 ± 0.23 (95% CI 6.02-6.20)	-0.09 [-0.17 to -0.01]	**0.020**
Mean fasting blood glucose level (mg/dl)	200.62 ± 57.74* (95% CI:190-218)	180.17 ± 58.66 (95% CI:170-210)	20.45 [-34.95 to -5.95]	**0.005**

Association between adverse events other than hyperglycemia across TLE & TLD cohorts and nature of adverse events reported
When adverse events other than hyperglycemia were comparatively assessed across the TLD and TLE cohorts, there was a higher number of adverse events reported by patients on the TLD regimen (9.6%) compared to those in the TLE cohort (4.8%) although this difference was not statistically significant [p=0.22]. One case of neurotoxicity [seizure disorder] was reported only in the TLE cohort, but there were more cases of hypertension and hyperlipidemia reported in the TLD cohort [Table 4].

Table 4: Association between the adverse events other than hyperglycemia across Tenofovir + Lamivudine + Dolutegravir (TLD) regimen and Tenofovir + Lamivudine + Efavirenz (TLE) cohorts and nature of adverse events reported.

Study Participants on ART drug regimen [N=125/cohort]	Proportion of study participants developing adverse events other than hyperglycemia n/N (%)	Proportion of study participants not experiencing any adverse events n/N (%)	Relative Risk (95% Confidence Interval]	p-Value
On/switched to TLD drug regimen [N=125]	12 (9.6)	113 (90.4)	1.37 [0.96 to 1.95]	0.22
On/switched to TLE drug regimen [N=125]	6 (4.8)	119 (95.2)		
Nature of adverse events reported other than hyperglycemia	Flatulence-1 (0.8) Hypertension-9 (7.2) Hyperlipidemia-2 (1.6)	Neurotoxicity-1 (0.8) Hypertension-5 (4)		

Discussion

Our study supports the hypothesis of a significantly higher number of hyperglycemic events being reported with the TLD drug regimen compared to the TLE regimen. Patients in the TLD cohort reported significantly higher HbA1c values and mean fasting glucose levels as compared to the TLE cohort. Our results are in concordance with other reported studies wherein it was observed that patients receiving dolutegravir developed hyperglycemic events within a

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short duration of initiation of treatment with dolutegravir. Lamorde M *et al* reported the development of severe hyperglycemia [16/3417, 0.47%, p=0.0004] in patients receiving dolutegravir within a median duration of 4 months (incidence of 4.7% per 1000 patients in DTG based ART regimen group *vs* 0.32% per 1000 patients in non-DTG based ART regimen group).[7]

A case report by Fong PS *et al* (2017) also revealed a patient developing hyperglycemia when switched on TLR [Raltegravir] regimen and was treated with glargine insulin injection with an improvement in HbA1c and C-peptide levels seen ten weeks after discontinuing Raltegravir & six weeks after discontinuing insulin glargine.[13] Hailu W *et al* discussed three cases of human immunodeficiency disease when switched to TLD drug regimen having experienced hyperglycemic events managed by injection insulin and later switched to metformin for better glycemic control.[14] Another similar three case reports of TLD drug regimen associated hyperglycemia have been documented by Hirigo AT *et al*.[15] Nolan S *et al* also described three cases of hyperglycemia and ketoacidosis that developed within months of being switched to bictegravir-based ART.[16] The study by O'Halloran JA *et al* reported that the use of INSTI was associated with an increased risk of new-onset diabetes mellitus/hyperglycemia within 6 months following ART initiation. The highest risk was associated with the use of elvitegravir and the least with raltegravir.[17] McLaughlin M *et al* reported the case of an African-American male living with HIV who was switched to abacavir/lamivudine and dolutegravir after 16 years of treatment with abacavir/lamivudine and efavirenz due to neuropsychiatric effects attributed to efavirenz. Approximately 3 weeks after the switch from efavirenz to dolutegravir, the patient presented with polyuria, polydipsia, and visual changes diagnosed to be severe hyperglycemia on further evaluation.[18] Several clinical trials have demonstrated the efficacy of dolutegravir. Of these trials, hyperglycemia has been reported in the SPRING-2, SAILING, SINGLE, and VIKING-3 trials, although not reported to be a clinically significant adverse event.[19-22]

Bahamdain conducted a retrospective chart review of 422 patients started on dolutegravir/ dolutegravir combination regimens at community healthcare centers, Mecca. Baseline blood sugar and/or HbA1c before starting dolutegravir, at three to six months of treatment, and at the end of the study were compared. It was observed that Dolutegravir had little effect on plasma glucose among 72% (305) of the patients. However, 7% (28) patients on dolutegravir treatment with no glucose intolerance met the criteria for prediabetes at three to six months of therapy with one patient developing diabetes 3-6 months after dolutegravir was initiated. Additionally, at the end of the study, 13% (n=56) patients developed prediabetes and 1.4% (n=6) developed diabetes. Among the 24 subjects that had diabetes before dolutegravir was initiated, 83% required intensification of their diabetes regimen.[23] The results of a case–control study conducted by Namara et al (2022) to assess the risk of hyperglycemia associated with use of DTG among PLHIV attending Mulago ISS Clinic in Kampala, Uganda demonstrated a strong association between prior DTG exposure and subsequent diagnosis of hyperglycemia. Of the 204 cases and 231 controls, it was seen that patients with prior DTG use had seven times greater odds of subsequent diagnosis of hyperglycemia compared to those who had non-DTG-based regimens. The odds of hyperglycemia also increased with age and hypertension.[24]
A systematic review and meta-analysis by Kajogoo *et al* (2023) investigated the excess risk of developing Diabetes mellitus (DM) among people living with HIV on INSTIs-based regimens compared to those with other combination antiretroviral therapies (cART). The results demonstrated that there was no significant difference in the incidence of DM in patients receiving INSTIs-based regimens compared to other regimens. However, there was a lower incidence of DM in the INSTIs group compared to the NNRTIs-based and PIs compared to the NNRTIs-based. When the INSTIs drugs dolutegravir, raltegravir, and elvitegravir were compared, there was a lower incidence of DM in raltegravir compared with elvitegravir.[25]

One possible explanation for the variation reported in this metanalysis as compared to individual studies was the variation in the degree of heterogeneity noted in four studies that compared DM in INSTIs vs. other drugs *viz*. two studies, there was no prior exposure to other medications[26,27] while in the other 2 studies[28,29] the participants were previously exposed to other cARTs before the switch to INSTIs. However, an important finding in all these studies was the association of weight gain with INSTIs and weight gain is an important risk factor in the development of DM. In our study too, the

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weight observed in the TLD group was significantly higher than the TLE group which could possibly be one risk factor for the development of hyperglycemia.

Limitations

Being a retrospective, short term study, the glycated hemoglobin and fasting sugar levels were analysed only at one time point over the 6–8-month intervals as done in routine clinical practice, due to which it was not possible to monitor the progressive changes in these parameters with time. Moreover, we could not evaluate the blood glucose levels after stopping of antidiabetic therapy as the treatment was continued in majority of the study participants at the time of analysis. Similarly, as we could only analyze the data available in the case records of the study participants, information regarding alcohol intake & family history of Diabetes mellitus, which was not documented in many of the patients' case records, could not be reviewed and analyzed for the study. Thus, there could be other factors like family history predisposing to the development of diabetes mellitus or lifestyle factors, co-morbid conditions and/or concomitant medications that could contribute to the development of the diabetic condition in our study patients. Prospective randomized long-term clinical studies would provide greater evidence on the cause-effect relationship between the ART drug regimens and hyperglycemia.

Conclusion

Currently, TLD regimen is the first-line antiretroviral regimen for patients on ART drugs. So long as the benefits of these drugs outweigh the risks, the TLD regimen may continue. However, regular monitoring of glycated hemoglobin and blood sugar levels and reporting of adverse events associated with ART regimen is required. Reversal of hyperglycemia after stopping the antidiabetic treatment may be in favor of TLD regimen, however this needs further evaluation and there may be better treatment options in the future.

Declarations

Ethical Consideration: The study received approval from Ethics Committee for Academic Research Projects [ECARP/2022/167] and Mumbai Districts AIDS Control Society [MDACS/1609/APD].

Authors' Contribution: All the authors contributed to the conceptualization, literature review and development of the protocol; MMR contributed to data acquisition; RM & MM contributed to data analysis; MM drafted the manuscript, and all authors reviewed it critically for its scientific content and approved the final manuscript for publication.

Conflict of interest: None

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