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Retraction

The article "Effect of dolutegravir on plasma glucose among human immunodeficiency virus patients in a community health center setting" is retracted by the Editor-in-Chief.[1] The article is retracted as per the corresponding author's request.

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1. Bahamdain FO. Effect of dolutegravir on plasma glucose among human immunodeficiency virus patients in a community health center setting. Int J Community Med Public Health 2022;9:1178-82. DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20220673.

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Original Research Article

Effect of dolutegravir on plasma glucose among human immunodeficiency virus patients in a community health center setting

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ABSTRACT

Background: Dolutegravir has become one of the initial backbone in antiretroviral therapy (ART) regimens for most patients with human immunodeficiency virus (HIV) in several recent clinical guidelines. However, dolutegravir has been associated with severe cases of hyperglycemia and new-onset of diabetes in multiple case reports and clinical trials. A community health center noticed an increasing number of new-onset hyperglycemia incidences in patients on dolutegravir.
Methods: Retrospective chart review of patients who started on dolutegravir or dolutegavir combination regimen (Triumreq®, Juluca®) between the dates of 1 January 2013 to 1 January 2018 who have been treated in community healthcare centers. Baseline blood sugar and/or A1C before starting dolutegravir, at 3-6 months of treatment and at end of study were compared between subjects.
Results: 422 subjects were enrolled. Dolutegravir had little effect on plasma glucose among 72% of the subjects (n=305). However, 7% of the subjects (n=28) on dolutegravir treatment with no glucose intolerance met criteria for prediabetes at 3-6 months of therapy. One subjects had developed diabetes at 3-6 months after dolutegravir was initiated. In addition, at the end of the study, thirteen percent of patients developed prediabetes (n=56) and 1.4% developed diabetes (n=6). Among the 24 subjects that had diabetes before dolutegravir was initiation, 83% required intensification of their diabetes regimen.
Conclusions: Dolutegravir may cause a moderate increase in plasma sugar after 3-6 months of therapy. Further increase has been noticed up to 12%. Due to existence of confounding variables, patient with diabetes should not be switched from dolutegravir.

Keywords: HIV, Dolutegravir, Diabetes

INTRODUCTION

Diabetes mellitus affects approximately 10% of the United States population and contributes to significant morbidity, decreased quality of life, rising health care costs, and mortality.[1] Research has demonstrated a 4-fold increase in the incidence of diabetes in men with HIV infection taking ART compared to men not infected with HIV.[2] Integrase strand transfer inhibitor (INSTI)-based regimens are recommended as an initial ART for most patients with HIV in several recent clinical guidelines.[3]

Dolutegravir is an integrase strand transfer inhibitor that has become an initial component in many ART regimens. Dolutegravir is dosed once daily with a long half-life of nearly fourteen hours, does not require a pharmacokinetic booster, high potency and barrier to resistance compared to some ART medications, and has minimum cytochrome

P450 interactions compare to other ART medications.[3] The pharmacokinetic properties of dolutegravir have made it an appealing drug in the treatment of HIV. However, hyperglycemia has been reported as one of the potential side effects of dolutegravir (up to 11%).[4,5] The severity of hyperglycemia ranged from grade 2 (plasma glucose level between 126-250 mg/dl) to grade 4 (life-threating complication like ketoacidosis) in several clinical trials that approved dolutegravir efficacy. Furthermore, dolutegravir has been associated with severe cases of hyperglycemia and new-onset of diabetes in multiple case reports.[7,8] A community health center noticed an increasing number of new-onset hyperglycemia incidences in patients on dolutegravir.

Due to the lack of clinical studies on prevalence and association between new-onset of hyperglycemia and dolutegravir in a community health center setting, the need for a study that examined this phenomenon was necessary, as results can be used to guide providers in the selection of ART. The aim of this study was to investigate the association between dolutegravir and hyperglycemia and measure the impact of dolutegravir on patients with diabetes.

METHODS

This study was a retrospective chart review of patients who started on dolutegravir or dolutegavir combination regimen (Triumreq®, Juluca®) with or without the diagnosis of diabetes who have been treated in Tucson, Arizona, United States: El Rio community healthcare centers between the dates of January 2013 to January 2018. We included participants who were 18 years or older with HIV infection and were on dolutegravir between January 2013 to January 2018. Patients had to have at least one blood sugar and/or A1C, at 3-6 months after initiation of dolutegravir and at end of study or after dolutegravir discontinued. We excluded individuals who were on protease inhibitor. Protease inhibitors acutely and reversibly inhibited the insulin-responsive glucose transporter Glut 4, leading to peripheral insulin resistance and impaired glucose tolerance.[8] Children (age <17) and patients with documented pregnancy during the study period were also excluded. The study was approved by the research oversight committee of El Rio community healthcare centers and university of Arizona, Tucson, Arizona, United States. Patients were identified using medication prescription records. Electronic health record (EHR) was utilized to collect patients' data using a data collection form. Baseline blood sugar and/or A1C before starting DTG, at 3-6 months of treatment and at end of study was compared between groups. A further examination at how many patients in the non-diabetic group have developed diabetes mellitus or prediabetes was done. Finally, the number of patients in the diabetes group requiring escalation in therapy were identified. Only average and percentage of patients were reported without the need for further analysis.

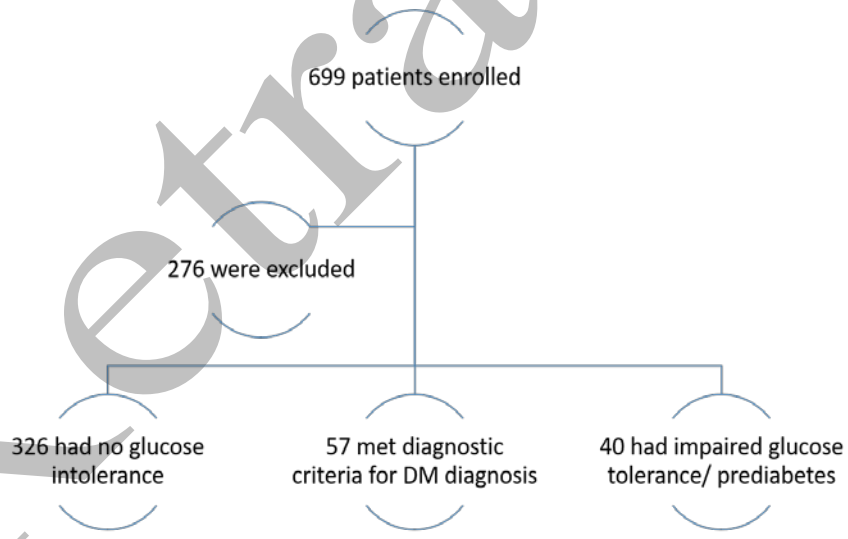

Figure 1: Study profile.

RESULTS

Between 1 January 2013 and 1 January 2018, 699 individuals were screened for inclusion of which 423 were enrolled (Figure 1). Baseline characteristics shown below and for the 423 subjects (Table 1). The majority of subjects were male (85%). Forty-six percent of the subjects were of white/non-Hispanic heritage, with thirty-six were of subjects were Hispanic/Latino and 1% of African American descent. Some patients (n=24) had diabetes before dolutegravir was initiation and others had prediabetes (n=13). Majority of the subjects had chronic co-morbidities; defined as diagnoses of one of these diseases (diabetes, dyslipidemia, hypertension, polycystic ovary syndrome, any mental health disease, BMI of >24).

Only 6% of the study population (n=24) did not have any chronic co-morbidities.

As shown in Figure 2, dolutegravir did not have any effect on plasma glucose at the end of the study among 72% of the subjects (n=305). However, 7% of the subjects (n=28) on dolutegravir treatment with no glucose intolerance met criteria for prediabetes at 3-6 months of therapy. Moreover, one subjects had developed diabetes at 3-6 months after dolutegravir was initiated. In addition, at the end of the study, thirteen percent of patients developed prediabetes (n=56) and 1.4% developed diabetes (n=6).

Among the 24 subjects that had diabetes before dolutegravir was initiation, 83% of required intensification of their diabetes regimen (Figure 3). Intensification of diabetes regimen was defined as any increase in their current dose or the addition of new diabetes medication to the subjects' regiment before dolutegravir was initiated.

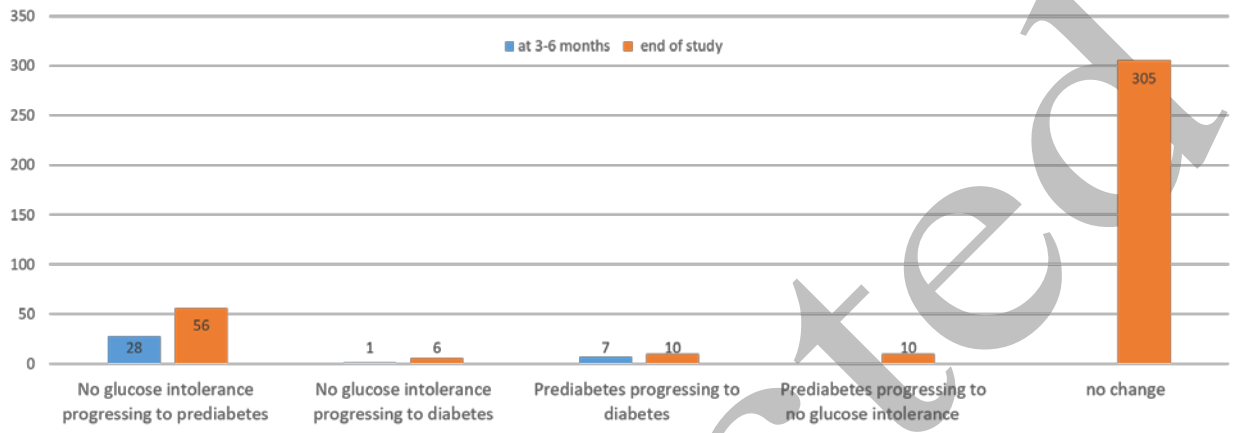

Figure 2: Effect of dolutegravir on plasma glucose at 3-4 months and end of study; data are in numbers (number of patients).

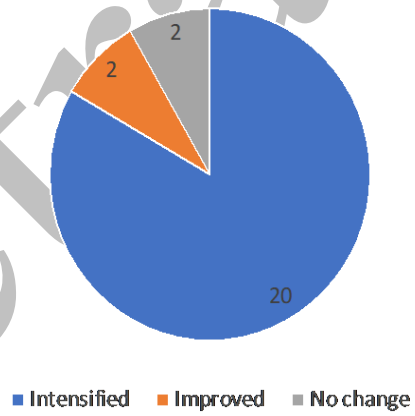

Figure 3: Number of patients that required intensification of their diabetes regimen.

Table 1: Baseline characteristics and demographic data of patients; data are in numbers (%).

Characteristics	N (%)
Male	358 (85)
Initial diagnosis of diabetes	24 (6)
Initial diagnosis of prediabetes	14 (3)
White/non-Hispanic	196 (46)
Hispanic/Latino	153 (36)
African American	43 (1)
Chronic co-morbidities	397 (94)

DISCUSSION

Combination ART for the treatment of HIV infection was associated with a risk of developing diabetes, mainly in subjects with signs of metabolic syndrome before initiating ART.[2] Dolutegravir had become one of the initial backbone in ART regimens for most patients with HIV in several recent clinical guidelines.[3] In this study we examined the association between new-onset of hyperglycemia and dolutegravir.

While only 1.4% of subjects on dolutegravir treatment developed diabetes (n=6), 7% of the subjects (n=28) on dolutegravir treatment with no glucose intolerance met criteria for prediabetes at 3-6 months. The number of subjects on dolutegravir treatment with no glucose intolerance who met criteria for prediabetes increased to thirteen percent (n=56) by the end of the study. This study had similar results to the SINGLE study. In the SINGLE study, the dolutegravir/abacavir/lamivudine group had 9% in the grade 2 hyperglycaemia classification (serum plasma glucose between 126 and 250 mg/dl) and 2% in the grade 3 classification (serum plasma glucose >25). Moreover, hyperglycemia was reported in SPRING-2, SAILING, SINGLE and VIKING-36-8. Furthermore, the package inserted for dolutegravir had information regarding plasma glucose abnormalities.[5] A mechanism for the INSTI-induced hyperglycaemia was hypothesized to be due to chelation of magnesium, thereby inhibiting the release and signalling of insulin.[14] On the other hand, hyperglycaemia was not reported in the original VIKING trial; however, it was included in the package insert.[7]

This study had several limitations. The study did not exclude patients with pancreatic cancer or chronic pancreatitis and patients on additional medication therapy known to cause hyperglycemia (antipsychotics). Moreover, the study was done in a small but diverse population limiting the generalizability of results. Majority of the subjects were white men. Additionally, the study did not measure medications using prescription fill history or viral load. Finally, the 83% of the diabetic patients who required escalation in antidiabetic therapy could be due to economic, social and behavior factors. Besides that, diabetes was a progressive disease could account for some of the diabetes medication escalation.

CONCLUSION

Dolutegravir may cause a moderate increase in plasma sugar after 3-6 months of therapy. Due to existence of confounding variables, patients with diabetes should not be switched from dolutegravir. Further sub-analysis of this study should be done to examine patient predictors of dolutegravir-associated hyperglycemia, different dolutegravir regimens (Tivicay® vs Triumeq®) and long-term effect of dolutegravir should be assessed.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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