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The (no) Effect of Dolutegravir on Whole-Body Insulin Sensitivity, Lipid and Endocrine Profile in Healthy Volunteers

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*DTG treatment for 28 days was **not** associated with a statistically significant change in total body glucose disposal, as measured by euglycaemic clamp studies.*

3. RESULTS

Fourteen volunteers in total completed the study, with 6 in the TA, and 8 in the nTA.

The median glucose disposal rate for the nTA was 6.18 mg/kg/min at day 1 and 7.62 mg/kg/min at day 28 (p=0.64) (Figure 1), with a median percentage change of +23.3% (1.44 mg/kg/min). In the TA, the median glucose disposal rate for was 6.95 mg/kg/min at day 1 and 7.93 mg/kg/min at day 28 (p=0.06), with a median percentage change of +14% (0.98 mg/kg/min).

Furthermore, on day 28, no significant difference in glucose disposal rate was measured between the TA and the nTA: 7.93 mg/kg/min versus 7.62 mg/kg/min (p=0.41).

4. CONCLUSION

In summary, there were no clinically relevant changes in total body glucose disposal following 28 days of DTG, as measured by euglycaemic clamp studies.

Limitations of the study included a small sample size of 14 individuals, equipment availability, time constraints of completing the study and of two clamp studies per individual (at baseline and 28 days).

At present, there are conflicting reports regarding INSTI use and the development of diabetes and cardiovascular disease (2, 4). Given the above limitations, further studies are required to elucidate the correlation between DTG and insulin resistance.

1. BACKGROUND

Dolutegravir (DTG) is a second-generation HIV integrase strand transfer inhibitor (INSTI) prescribed in combination with nucleoside reverse transcriptase inhibitors (NRTIs) as a standard of care regimen in initial and subsequent lines of therapy.

Despite its efficacy in achieving and maintaining virological suppression, there have been reports highlighting its effects on patients' metabolic profile (1, 2), including elevated blood glucose values and the development of diabetes mellitus (3), although subsequent evidence challenge this correlation (4).

The aim of this study was to assess insulin sensitivity via measurement of glucose disposal in volunteers exposed to DTG daily for 28 days.

2. METHODS

An open-label, two-arm, single centre study randomised participants 1:1 to either 28 days of DTG (treatment arm, TA) or no therapy (no treatment arm, nTA). Participants in both arms underwent a euglycaemic clamp study to determine insulin sensitivity at baseline and 28 days.

The study protocol was approved by the National Research Ethics Service, UK and Medicines and Healthcare Regulatory Authority (Eudra CT number 2020-004395-17; ClinicalTrials.gov ID: NCT04771754).

Participants were deemed eligible for the study if they were clinically well, HIV negative, had a BMI between 18-30 kg/m^2, had no history of diabetes or metabolic syndrome and were not receiving medication deemed to alter the patient's metabolic profile or interact with the study drugs.

The clamp protocol was taken from DeFronzo and colleagues (5). This required participants to fast for a minimum of 8 hours prior to the clamp study, followed by an intravenous insulin and 20% glucose infusions respectively running simultaneously. A negative feedback formula was used to adjust the glucose infusion rate to achieve euglycaemia.

During the study, measurement of insulin sensitivity was carried out by calculating the glucose disposal rate divided by the average insulin concentration throughout the procedure.

Statistical assessments of change in estimated glucose disposal rates were carried out using Wilcoxon signed-rank test (intra-arm) and Two-sample Wilcoxon rank-sum (Mann–Whitney) test (inter-arm).

The primary study outcome was the degree of change from baseline in total body glucose disposal by euglycaemic clamp method following 28 days of treatment. Further details of the methodology can be found on clinicaltrials.gov (ID: NCT04771754).

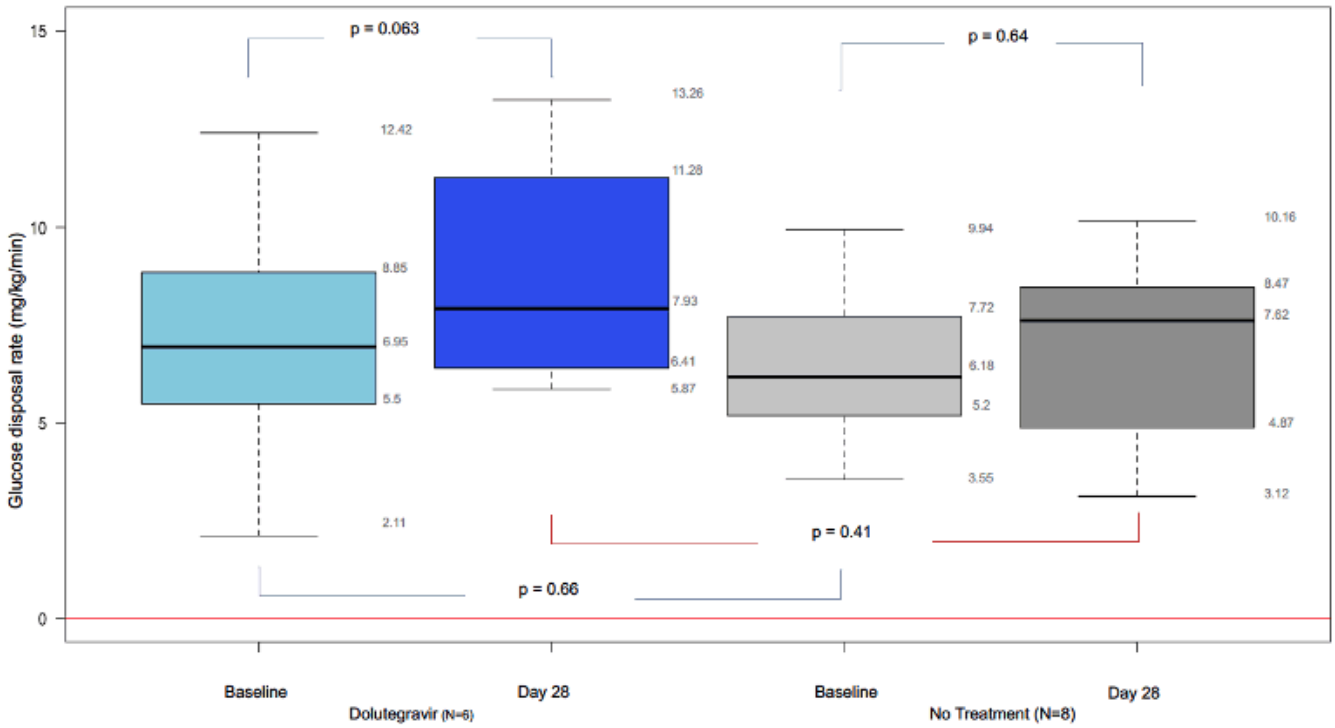

Figure 1 – Boxplot highlighting the change in glucose disposal rate from baseline to day 28 between the nTA and TA.

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