

The Impact of Tenofovir on Insulin Sensitivity and Lipids in Healthy Volunteers

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Introduction

- Effective antiretroviral therapy has resulted in a dramatic improvement in HIV associated morbidity and mortality
- Certain antiretrovirals are associated with metabolic side effects including dyslipidaemia, body fat changes and insulin resistance¹
- These effects are variable not only between different drug classes but between drugs in the same class

Background

- The hyperinsulinaemic euglycaemic clamp² is considered the gold standard for investigating insulin sensitivity and a number of trials have used the clamp methodology to investigate antiretrovirals
- The development of insulin resistance in healthy volunteers has been seen with lopinavir/ritonavir³, ritonavir⁴, indinavir⁵ and stavudine⁶ but not with amprenavir⁴ or atazanavir³
- Insulin resistance associated with protease inhibitors appears to be mediated through the inhibition of the glucose transporter GLUT4⁷
- Mitochondrial toxicity is implicated in the development of insulin resistance with nucleoside reverse transcriptase inhibitors⁸

Objectives

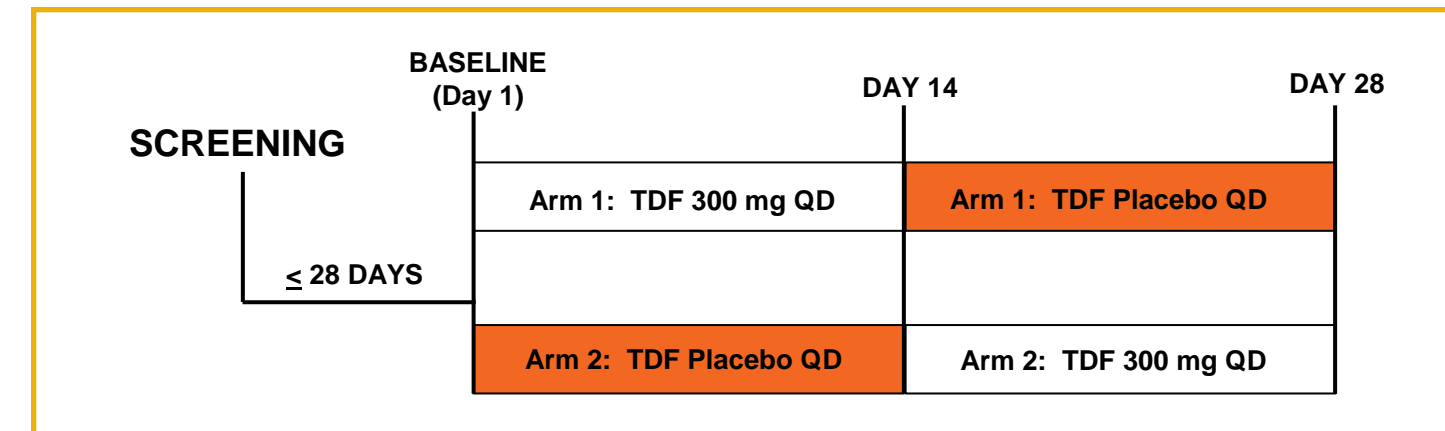
- To investigate the impact of tenofovir disoproxil fumarate (TDF) on insulin sensitivity as assessed by the peripheral glucose disposal rate during the last hour of the hyperinsulinaemic euglycaemic clamp
- To investigate the impact of TDF on lipid parameters

Methods

- Single centre, randomised, double blinded, placebo-controlled study that utilised a 2 sequence, 2 period crossover design
- HIV negative subjects were recruited and randomised 1:1 as shown (fig 1)

Methods (cont'd)

Figure 1. Study Design



- Important exclusion criteria were BMI >28kg/m², waist:hip ratio >0.97 and any medication or disease process likely to cause a marked disturbance in glucose and lipid homeostasis. Fasting glucose, cholesterol and triglycerides also had to be within normal limits
- A hyperinsulinaemic euglycaemic clamp and fasting bloods were performed at baseline, after 2 weeks of treatment and after 4 weeks of treatment (2 weeks after treatment switch)
- Peripheral glucose disposal rate was assessed during the last hour (120-180 min) of the clamp

Results

- 19 subjects were randomised. 16 male subjects completed all 3 clamp procedures (3 withdrew prior to baseline visit)
- Subjects had mean age of 27.4 years and mean BMI of 23.02 kg/m²
- 7 subjects received TDF followed by placebo and 9 received placebo followed by TDF
- No significant change from baseline in the mean peripheral glucose disposal rate was seen after 2 weeks of TDF (fig 2b) or placebo (fig 2a)
- No significant difference between placebo and TDF
- Statistically significant decreases from baseline in total cholesterol and LDL cholesterol were seen after 2 weeks of TDF (fig 3)

Results (cont'd)

Figure 2. Glucose Disposal Rate

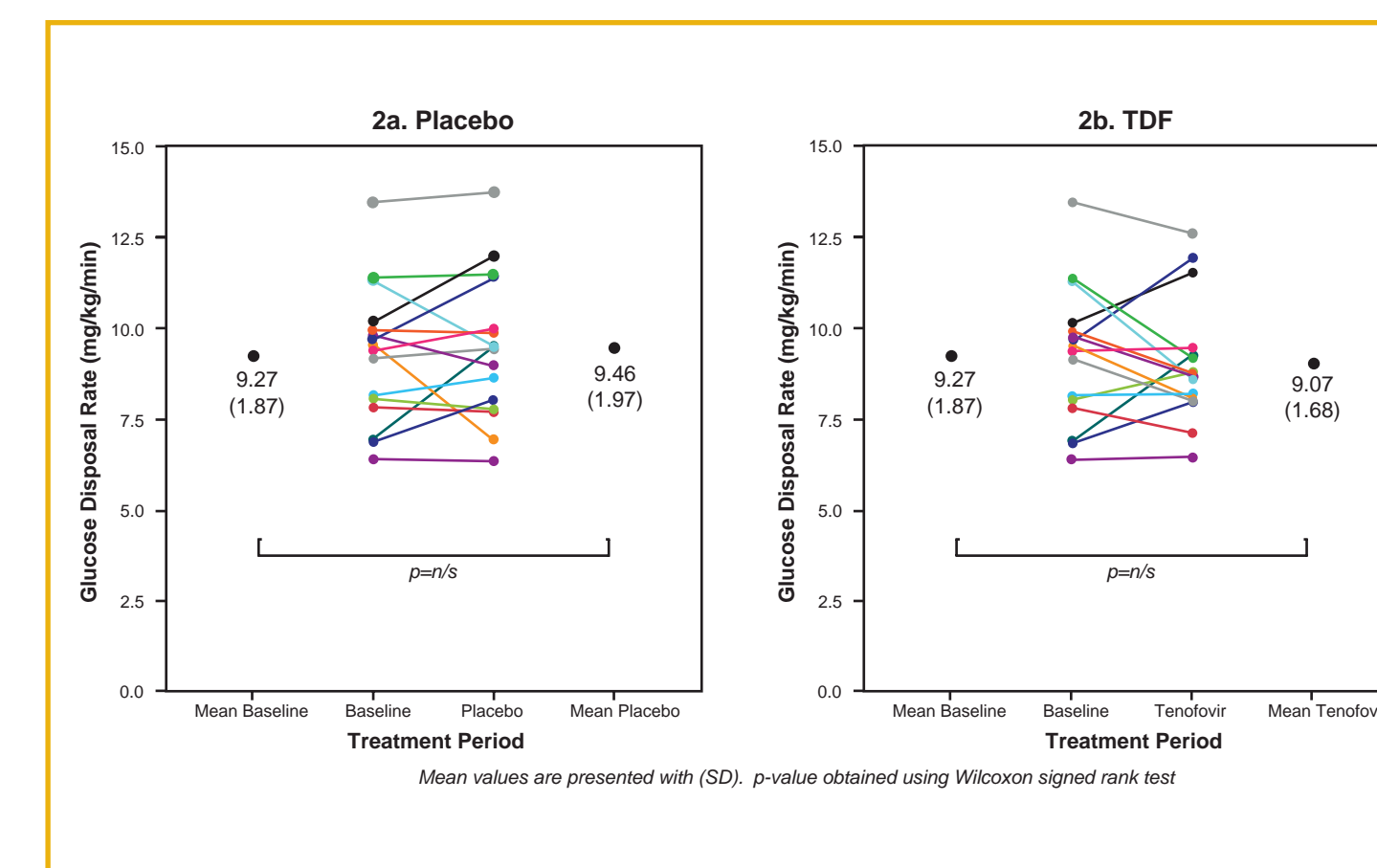
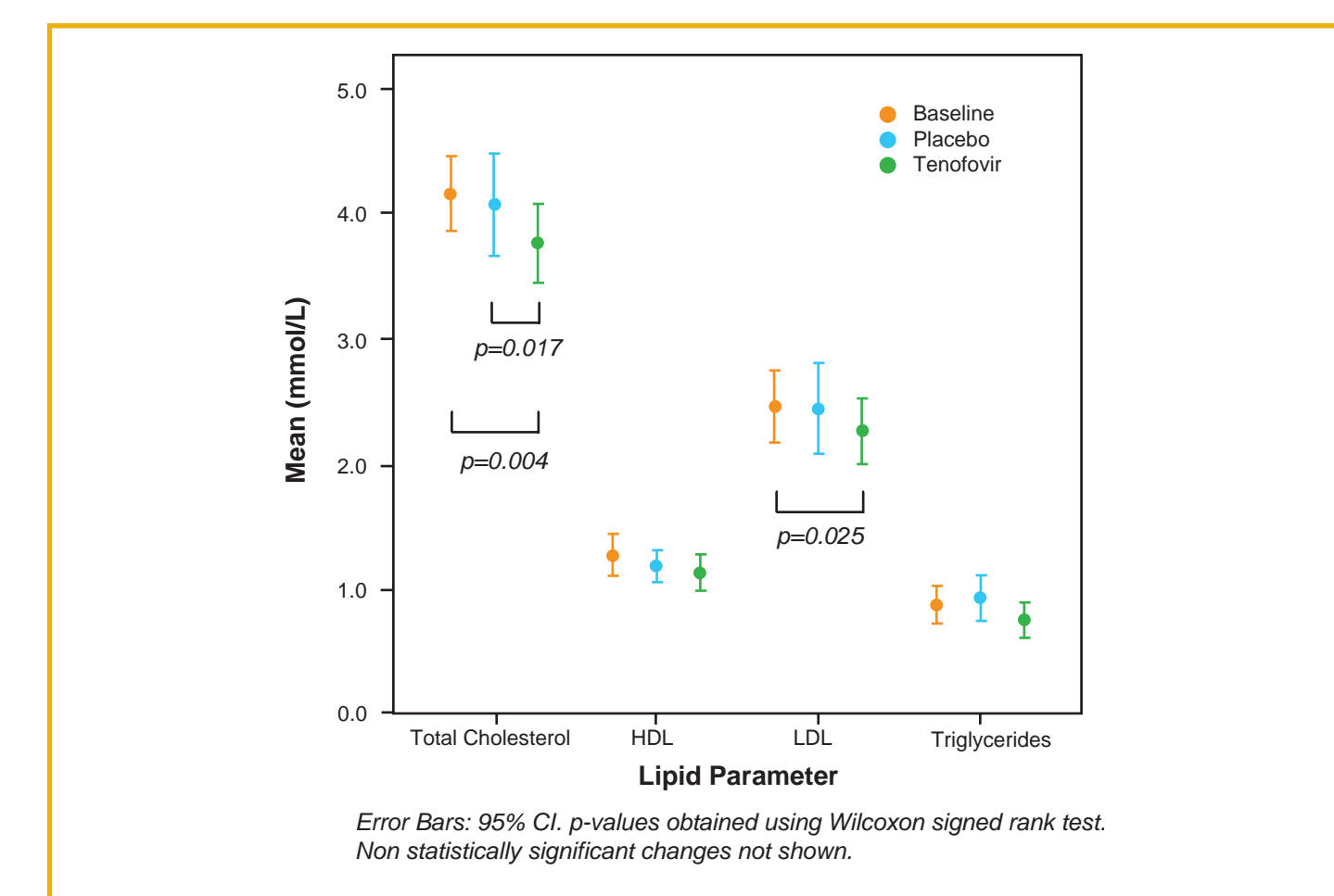


Figure 3. Fasting Lipid Parameters



Conclusions

- Two-week dosing with TDF did not have a significant impact on insulin sensitivity
- Statistically significant reductions in total cholesterol and LDL cholesterol were seen after 2 weeks of TDF
- These study results are consistent with previous observations that no significant mitochondrial toxicity was associated with TDF⁸

References

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