

# 829 HIGHER RISK OF HYPERGLYCAEMIA IN PATIENTS UNDER DIDANOSINE AND TENOFOVIR-CONTAINING REGIMENS

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## Background

Nucleoside analogues (NA) continue to be the cornerstone of anti-HIV therapy. The selection of the most convenient NA backbone for a given individual is based on particular features of both patients and drugs. The safety profile widely differs for distinct NA and the risk of toxicities increases in some populations, i.e. zidovudine-induced anemia in cirrhotics or tenofovir-related tubular dysfunction in patients with prior renal impairment. Regimens with low pill burden are preferred for patients with more problems of treatment adherence. In this context, the combination of didanosine (ddi) and tenofovir (TDF) has emerged as one of the most attractive NA backbones, given the high potency of these drugs, their relative high genetic barrier for resistance, good safety profile, and easy dosing. However, as TDF significantly increases ddi plasma levels, the dose of ddi has been recommended to be reduced when combining both drugs. Despite ddi dose adjustment, several reports have stressed about the risk of unexpected CD4 T cell drops and pancreatitis when combining both drugs.

Pancreatic dysfunction associated with ddi therapy is known to be dose-dependent, and the incidence of pancreatitis was 10% and 1.1% when ddi was initially administered at doses of 750 and 400 mg per day, respectively. In addition to exocrine pancreatic toxicity, reversible hyperglycaemia and insulin-dependent diabetes have also been associated with ddi use.

Several cases of transient insulin-dependent diabetes mellitus were diagnosed in our clinic in patients taking ddi plus TDF, and so we decided to explore if glucose abnormalities were more frequent taking this combination.

## Patients and Methods

**Retrospective analysis** of data of [these groups](#) of patients that were controlled at our clinic between September 2002 and June 2003 and had completed a **12 month follow-up** with recorded basal and at 12 months glucose levels. They all received triple antiretroviral combinations including: ddi, tenofovir or ddi+TDF.

Patients under antidiabetic drugs and/or those whose baseline glucose levels were above 125 mg/dl were excluded for the analysis. Hyperglycaemia and diabetes were defined as fasting plasma glucose level over 110 mg/dl and 125 mg/dl respectively. Demographic parameters, weight, fasting glucose levels, concomitant antiretrovirals and ddi dosage were assessed at 3, 6, 9 and 12 months. No treatment changes were performed during follow up. Fasting glucose levels were compared with baseline and between groups at each time point.

Individuals who received ddi took 400 mg if their weight was above 60 kg and 250 mg if lower than 60 kg. After the release of the recommendation to reduce the dose in subjects taking TDF concomitantly, subjects weighing more than 60 kg switched to 250 mg per day and those weighing less than 60 kg switched to 200 mg per day.

In 4 patients who developed diabetes during follow-up both insulin and C peptide plasma levels were determined in order to document type of diabetes.

**Univariate analysis** was performed to compare baseline characteristics in patients according to the use of ddi, TDF or ddi+TDF. Changes in glucose levels were assessed for each patient with respect to baseline. Mean glucose levels at each time point in different treatment arms were compared using ANOVA test. The Student's T test for related variables was used to compare baseline glucose values with those recorded during follow up.

In order to assess variables independently associated with changes in glucose levels, a **multivariate analysis** was performed at different time points. Only p values below 0.05 were considered as significant.

## Results

A total of 177 individuals were assessed. Table 1 summarises baseline characteristics.

Table 1. Baseline characteristics of study population

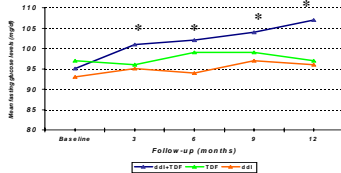
	ddi+TDF	TDF	ddi	p
No. of patients	78	62	27	NS
Mean age (years)	39 ± 6	40 ± 7	37 ± 7	NS
Male gender (%)	78	75	84	NS
Mean weight (kg)	67 ± 11	69 ± 9	70 ± 16	NS
Mean CD4 <sup>+</sup> count (cells/mm <sup>3</sup> )	564 ± 311	558 ± 315	678 ± 355	NS
Median plasma HIV RNA	1.65	1.65	3.73	0.001
CD4<sup>+</sup>CD8<sup>-</sup>	11.00 (3.76)	11.00 (3.98)	11.00 (4.40)	0.32
No. patients on PI	100 (100%)	100 (100%)	100 (100%)	NS
No. patients on ddi ≥250 mg/dl	32	—	—	—

ddi: didanosine; TDF: tenofovir; PI: protease inhibitor; NS: non significant

ddi daily doses were 400 mg per day in 68% and 40% of patients at baseline and 12 months respectively (ddi dose reduction with concomitant TDF use had not been advised at the initiation of the follow up).

A significant increase in fasting glucose levels was only achieved in ddi+TDF arm during follow up (figure 1).

Figure 1. Evolution of mean fasting glucose levels in different treatment arms



\*p<0.05 between groups

At 12 months, hyperglycaemia and diabetes were significantly more frequent in ddi+TDF recipients (table 2).

Table 2. Rate (%) of hyperglycaemia and diabetes in treatment arms over time

Treatment	Month 3		Month 6		Month 12	
	Hyperglycaemia	Diabetes	Hyperglycaemia	Diabetes	Hyperglycaemia	Diabetes
ddi+TDF	14*	3.3	18.2	3.6	32*	11.4*
TDF	3.4	0	16.4	1.8	4.8	0
ddi	6.2	0	19.2	1.7	16.5	3.3

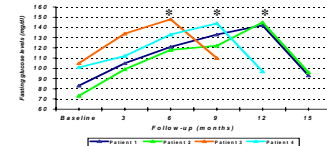
\*p<0.05 between groups

Regarding **ddi doses**, 18 of the 22 patients that developed hyperglycaemia in the ddi+TDF treatment arm, and 6 of the 7 patients that developed diabetes in the same group at 12 months where under ddi doses of 400 mg per day.

**Multiple linear regression** was performed. Variation of glucose levels was considered as dependent variable and treatment with ddi and/or TDF, weight, age, viral load and PI concomitant treatment as independent factors. A **lower baseline weight** (β = -0.35, 95% CI -0.67 to -0.03; p=0.033) and use of **regimens including ddi+TDF** (β 13.05, 95% CI 0.2 to 26; p=0.047) were independently associated with **higher glucose values**. No correlation was found between time under ddi higher doses and hyperglycaemia.

In 4 of the patients who developed diabetes in the ddi+TDF arm, C peptide and insulin plasma levels were measured during follow up. The values of both parameters were under normal range (data not shown) and improved when 3TC was substituted for ddi, while complete normalization of glucose levels was achieved with this change (figure 2). Of note, the weight of these 4 patients was less than 60 kg.

Figure 2. Evolution of fasting glucose levels in 4 patients on ddi+TDF in which development of transient insulinopenic diabetes mellitus occurred and resolved after substitution of 3TC for ddi.



\*Substitution of 3TC for ddi

We hypothesize **that direct endocrine pancreatic toxicity of ddi might be the cause of hyperglycaemia and diabetes** in ddi+TDF recipients for several reasons:

- 1) the use of higher than currently recommended ddi doses prescribed in most patients who developed glucose abnormalities
- 2) presence of low levels of insulin and C peptide whenever they were measured in this subset of patients
- 3) normalization of glucose levels after ddi substitution for 3TC in patients who developed diabetes

## Conclusions

The risk of hyperglycaemia and diabetes mellitus is increased in patients treated with ddi+TDF, particularly among those with lower weight and when using high ddi doses. A direct toxicity of ddi on endocrine pancreatic cells rather than peripheral insulin resistance is the most reasonable cause of this toxicity. Our findings add a further note of caution to the use of ddi+TDF. Thus, when possible this combination should be discouraged.