Higher Risk of Hyperglycemia in HIV-Infected Patients Treated with Didanosine Plus Tenofovir

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ABSTRACT

The combination of didanosine (ddI) and tenofovir (TDF) has potential advantages, but because of several pitfalls (unexpected decreases in CD4+ T cells, increased risk of pancreatitis) its use has been questioned. Since anecdotal cases of transient insulin-dependent diabetes mellitus were seen in our clinic in patients on ddI + TDF-containing regimens, we explored the rate of this complication in more detail. Retrospective analysis of plasma glucose levels in patients who completed 12 months of treatment with three different triple antiretroviral regimens including ddI + TDF, TDF, or ddI was done. Patients taking antidiabetic drugs and/or those with baseline glucose levels >125 mg/dl were excluded. Weight, age, concomitant antiretrovirals, and ddI dose were assessed. At 12 months without treatment changes, fasting glucose levels were compared to baseline. A multivariate analysis was performed to evaluate which variables were associated with glucose elevations. A total of 177 HIV-infected patients were assessed (78 on ddI + TDF, 42 on TDF, and 57 on ddI). Mean baseline features were well balanced between groups for age (mean, 39 years), gender (78% male), CD4+ count (mean, 507 cells/mm3), weight (mean, 67 kg), and glucose level (mean, 95 mg/dl). There were only significant differences between groups for baseline viral load and protease inhibitor (PI) use (13% in the ddI + TDF arm vs. 7% and 9% in the TDF and ddI arms, respectively). At 12 months, 60% of the patients in the ddI + TDF arm were taking ddI 250 mg/day and the rest were on ddI 400 mg/day. At 12 months, hyperglycemia was significantly more frequent in the ddI + TDF arm (33%) when compared to patients on TDF or ddI separately (5% and 10%, respectively). In the multiple linear regression analysis, a lower weight (β = −0.35; 95% CI = −0.67 to −0.03; p = 0.033) and use of ddI + TDF (β: 13.05; 95% CI: 0.2 to 26; p = 0.047) were independently associated with a higher risk of developing hyperglycemia. The risk of hyperglycemia is increased in patients treated with ddI + TDF, particularly in those with lower weight. As high ddI exposure has been associated with endocrine pancreatic dysfunction and diabetes, ddI “overdosing” as result of concomitant TDF use and low weight might explain our findings. These results add a further note of caution to the use of TDF and ddI in combination.

INTRODUCTION

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. Moreover, regimens with low pill burden are preferred for patients with increased problems of treatment adherence, i.e., intravenous drug users (IDU). 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 (one pill daily each). However, as TDF significantly increases ddI plasma levels, reduction in the dose of ddI has been recommended when
combining both drugs.\textsuperscript{7} Despite ddI dose adjustments, several reports have stressed the risk of unexpected decreases in CD4\textsuperscript{+} T cells\textsuperscript{6,7} and pancreatitis\textsuperscript{8} 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/day, respectively.\textsuperscript{9} In addition to exocrine pancreatic toxicity, reversible hyperglycemia and insulin-dependent diabetes have also been associated with ddI use.\textsuperscript{10,11} Following several cases of transient insulin-dependent diabetes mellitus in our clinic in patients taking ddI plus TDF, we decided to determine if glucose abnormalities were particularly more frequent when taking this combination.

**MATERIALS AND METHODS**

We retrospectively analyzed three groups of patients on regular follow-up at one single HIV referral hospital between September 2002 and June 2003. Only subjects who had completed 12 months of an unmodified antiretroviral regimen based on ddI, TDF, or ddI + TDF, and had available glucose levels during the entire follow-up, were assessed. Moreover, all had been previously exposed to other antiretroviral regimens, and prior drug-naive patients were excluded from this analysis.

Patients already taking antidiabetic drugs and/or those whose baseline glucose levels were above 125 mg/dl were excluded from the analysis. Hyperglycemia and diabetes were defined as repeated measurements of fasting plasma glucose levels over 110 and 125 mg/dl, respectively.\textsuperscript{12}

Demographics, weight, fasting glucose levels, concomitant antiretroviral drugs, and ddI doses were assessed at 3, 6, 9, and 12 months. Fasting glucose levels were compared with baseline and between groups at each time point. As recommended, the dose of ddI was 400 mg daily if weight was above 60 kg and 250 if lower. Following the recommendation to reduce the ddI dose in subjects taking TDF concomitantly in early 2003,\textsuperscript{5} subjects weighting more than 60 kg switched to 250 mg/day. Moreover, we reduced ddI to 200 mg daily in subjects weighing less than 60 kg.

Insulin and peptide C were further determined in patients who developed diabetes during the study period, to ascertain the type of diabetes.\textsuperscript{12}

| Table 1. Baseline Characteristics of the Study Population\textsuperscript{a} |
|---------------------------------|--------|--------|--------|--------|
|                                | ddI + TDF | TDF     | ddI     | p       |
| No. of patients             | 78      | 42      | 57      | NS      |
| Mean age (years)            | 39 ± 6  | 40 ± 7  | 37 ± 7  | NS      |
| Male gender                  | 78\%    | 75\%    | 84\%    | NS      |
| Mean weight (kg)            | 67 ± 11 | 60 ± 9  | 70 ± 16 | NS      |
| Mean CD4\textsuperscript{+} count (cells/mm\textsuperscript{3}) | 564 ± 311 | 536 ± 315 | 476 ± 320 | NS |
| Median plasma HIV-RNA        | 1.69    | 1.69    | 3.73    | 0.001   |
| (log\textsubscript{10} copies/ml) | (1.69–3.29) | (1.69–3.18) | (1.69–4.46) |       |
| No. of patients on PI      | 73      | 60      | 16      | NS      |
| No. of patients on ddI 250 mg/day | 7 (7\%) | 3 (7\%) | 5 (9\%) | 0.02 |

\textsuperscript{a}ddI, didanosine; TDF, tenofovir; PI, protease inhibitors; NS, not significant.

**Statistical analyses**

Continuous variables were expressed as mean and standard deviation and median plus interquartile range when convenient. Categorical data were expressed as percentages. Univariate analysis was performed to compare the baseline characteristics of the distinct treatment groups. Categorical data were compared using the chi-square test (with Yates and Fisher corrections when appropriate). Changes in glucose levels were assessed for each patient with respect to baseline. Mean glucose levels at each time point in the different treatment arms were compared using the ANOVA test. Mean glucose levels at each time point in the different treatment arms were compared using the ANOVA test. The Student’s t test for related variables was used to compare baseline glucose values and those recorded during the follow-up.

To assess which variables were independently associated with changes in glucose levels, a multivariate analysis (multiple linear regression) was performed at the different time points. The variation in glucose levels was considered as the dependent variable and treatment modality (ddI and/or TDF), weight, age, viral load, and use of protease inhibitors (PI) as independent factors. All statistical analyses were conducted using the SPSS package (v9.0, Chicago, IL) and only p values below 0.05 were considered significant.

**RESULTS**

A total of 177 individuals were assessed. All were antiretroviral-experienced patients before beginning the current regimen and the mean time on antiretroviral drugs was of 27 ± 13 months, without significant differences between treatment groups. Around 82\% of all patients had been exposed to stavudine (d4T) before beginning the current study, and the mean time of exposure to d4T was 8 ± 5 months, without significant differences between treatment arms.

The majority of patients had undetectable plasma HIV-RNA (<50 copies/ml) before beginning the current regimen with either ddI, TDF, or both in combination. Thus, simplification strategies were the main cause of initiating the current regimen. Overall, baseline characteristics were well balanced between groups and are summarized in Table 1. There were significant differences regarding baseline viral load and the proportion of patients taking PI concomitantly (13\% in the ddI + TDF arm vs. 7\% and 9\% in the TDF and ddI arms, respectively). By far,
lopinavir/ritonavir was the most frequently prescribed PI in all treatment arms. There were no significant differences in the use of other antiretroviral drugs along with the study medications comparing distinct treatment arms (data not shown). Overall, the daily dose of ddl was 400 mg in 68% and 40% of patients at baseline and at 12 months, respectively. At the time the study was initiated, the recommendation to reduce the ddl dose had not been released.

A significant increase in fasting glucose levels was recognized in the ddl + TDF arm only during follow-up (Fig. 1). At month 12 both hyperglycemia and diabetes were significantly more frequent in ddl + TDF recipients when compared to patients on either TDF or ddl (Table 2). The difference in the incidence of hyperglycemia persisted after excluding from the analysis the subset of patients taking PI; the rate of hyperglycemia at month 12 was 28%, 9%, and 4% in patients on ddl + TDF, ddl, and TDF, respectively \( (p = 0.03) \).

Overall, 18 of 22 patients who developed hyperglycemia in the ddl + TDF arm and 6 of 7 patients taking ddl without TDF where taking ddl 400 mg/day.

To explore which variables were associated with a higher risk of developing hyperglycemia, multiple linear regression was performed considering the variation of glucose levels at month 12 as the dependent variable and treatment with ddl and/or TDF, weight, age, viral load, and concomitant PI use as independent factors. A lower baseline weight \( (\beta: -0.35; 95\% \text{ CI: } -0.67 \text{ to } -0.03; p = 0.033) \) and ddl + TDF use \( (\beta: 13.05; 95\% \text{ CI: } 0.2 \text{ to } 26; p = 0.047) \) were independently associated with higher glucose values. In contrast, no correlation was found between time on higher ddl doses, PI use \( (\beta: -0.133; 95\% \text{ CI: } -22.7 \text{ to } 5.7; p = 0.24) \), and hyperglycemia. Prior prolonged d4T exposure and/or low baseline CD4 counts were not associated with a higher risk of hyperglycemia in the univariate analysis.

In all nine patients who developed diabetes in the ddl + TDF arm, insulin and C peptide levels were measured in plasma during the follow-up. Their values were within normal range at baseline in all cases, but became abnormal progressively during follow-up (data not shown). Interestingly, all returned to normal values following the discontinuation of ddl, along with normalization of glucose levels. Figure 2 records the outcome in four cases in which substitution of lamivudine for ddl was made, keeping the rest of the medication unchanged.

**DISCUSSION**

We demonstrate that the risk of hyperglycemia and diabetes is significantly increased in HIV-infected patients treated with ddl + TDF-based combinations when compared to subjects ex-

### TABLE 2. INCIDENCE (%) OF HYPERGLYCEMIA AND DIABETES IN DIFFERENT TREATMENT ARMS

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Month 3</th>
<th></th>
<th>Month 6</th>
<th></th>
<th>Month 12</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>Diabetes</td>
<td>Hyperglycemia</td>
<td>Diabetes</td>
<td>Hyperglycemia</td>
<td>Diabetes</td>
</tr>
<tr>
<td>ddl + TDF</td>
<td>14*</td>
<td>3.3</td>
<td>18.2</td>
<td>2.6</td>
<td>33*</td>
<td>11.4*</td>
</tr>
<tr>
<td>ddl</td>
<td>6.2</td>
<td>0</td>
<td>10.2</td>
<td>1.7</td>
<td>10.5</td>
<td>5.3</td>
</tr>
<tr>
<td>TDF</td>
<td>3.4</td>
<td>0</td>
<td>16.4</td>
<td>1.8</td>
<td>4.8</td>
<td>0</td>
</tr>
</tbody>
</table>

\*\( p < 0.05 \) between groups.
posed to the two drugs separately. This toxicity was more frequent in patients with low weight. Moreover, as more than 60% of patients on ddI/H11001/TDF were initially treated with higher than recommended ddI doses, a direct toxicity of ddI on endocrine pancreatic cells is the most likely cause of hyperglycemia in this population, as was suggested in earlier reports of transient insulin-dependent diabetes mellitus in subjects treated with ddI.13–15 Moreover, since we excluded from our retrospective analysis subjects with missing data while being on TDF-ddI for 12 months, it is likely that our results may underestimate the rate of hyperglycemia in patients exposed to this drug combination.

Glucose plasma concentrations are normally maintained within narrow limits through balanced insulin secretion and action. Hyperglycemia and diabetes are well known adverse events associated with the use of certain antiretroviral drugs.16,17 In a longitudinal cohort study, the risk of developing diabetes mellitus was 3.1-fold in a group of HIV-infected men receiving combination antiretroviral therapy with respect to untreated controls over a 3-year period of observation.18 However, insulin resistance is the most frequent finding in these cases, which is often associated with body-shape changes and use of certain PIs.19

A greater percentage of patients under ddI/H11001/TDF received PI when compared with the other two groups. Although this fact might bias the results, adjustments for PI use were made in the multivariate analysis. Moreover, the analysis was also performed excluding the subset of patients taking PI and the differences in the incidence of hyperglycemia were likewise statistically significant.

Since recent reports20 have linked d4T use with insulin resistance, we examined whether prior d4T exposure could influence our results, and this was not the case, since all treatment arms had experienced similar prior d4T exposure.

All nine individuals in our series who developed diabetes mellitus on ddI/H11001/TDF had low C peptide and insulin plasma levels, suggesting that endocrine pancreatic dysfunction rather than peripheral insulin resistance was the mechanism leading to glucose abnormalities when taking ddI + TDF. Given that lipoatrophy in both congenital and acquired lipodystrophies may cause insulin resistance, our results do not support their involvement in the development of hyperglycemia in patients taking ddI + TDF.

Pancreatic dysfunction has traditionally been linked to ddI therapy. Exocrine damage and a higher rate of pancreatitis have recently been reported in association with the use of ddI/H11001/TDF combinations, particularly in subjects with low weight.8 Endocrine pancreatic dysfunction was also noticed in patients treated with ddI monotherapy in the pre-HAART era.10,11 In our study, several facts support the hypothesis that direct endocrine pancreatic toxicity of ddI might be the cause of hyperglycemia and diabetes in ddI + TDF recipients. First was the use of higher than currently recommended ddI doses prescribed in most patients who developed glucose abnormalities. Second was the presence of low levels of insulin and C peptide whenever they were measured in this subset of patients. Third was the normalization of glucose plasma levels after ddI substitution for lamivudine in patients who developed diabetes mellitus.

The fact that low weight was associated with a higher risk of hyperglycemia in our study needs further explanation. We hypothesize that as many patients were under higher than currently recommended ddI doses prescribed in most patients who developed glucose abnormalities, individuals with a lower weight were the most susceptible to the toxic effects of ddI “overdosing.” Moreover, lipoatrophy body shape changes were not assessed in our population, which might have contributed to insulin resistance and hyperglycemia. However, low weight is not a feature considered in the lipodystrophy case definition.21 An interesting finding was that both glucose elevations and normalizations occurred relatively rapidly. Significant increases in glucose levels were noticed as early as 3 months after initiation of ddI + TDF-containing regimens. On the other hand, normalization of glucose levels in the four patients in whom lamivudine replaced ddI occurred within the next 3 months. This is in agreement with prior reports of glucose abnormalities associated with ddI use.13–15 Moreover, it suggests that the
mechanism of toxicity is quite different from the one that explains declines in CD4 T cells, which requires a median of 9 months to become manifest.

In conclusion, the risk of hyperglycemia and diabetes mellitus is increased in patients treated with ddI + TDF, particularly among those with lower weight and using high ddI doses. The 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 avoided.

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REFERENCES


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