Compromised Immunologic Recovery in Treatment-Experienced Patients with HIV Infection Receiving Both Tenofovir Disoproxil Fumarate and Didanosine in the TORO Studies

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The effect of therapy with a combination of tenofovir and full-dose didanosine on increases in CD4+ cell count was examined in 2 large trials of treatment-experienced patients with human immunodeficiency virus (HIV) infection (the T-20 versus Optimized Regimen Only [TORO] 1 and 2 clinical trials). Individuals receiving both agents showed little additional increase in CD4+ cell count after week 8 of therapy, whereas those receiving 1 or neither of the agents had continuous increases over a 48-week period.

We have recently reported that HIV-infected patients receiving combinations containing both the nucleotide reverse-transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF) (300 mg/day) and full dosages (400 mg/day in patients weighing ≥60 kg and a reduced dosage of 250 mg/day in patients weighing <60 kg) of the NRTI didanosine (ddI) experience unexpected decreases in CD4+ cell count, despite maintaining undetectable plasma viral loads [1]. At 48 weeks, >50% of the 302 patients in this study showed a decrease of >100 CD4+ cells/mm3, and up to 30% had a decrease of >200 cells/mm3. This finding is further supported by a recent retrospective analysis of patients with controlled viremia [2]. Patients receiving both ddI and TDF had a significant decline in CD4+ cell count over a 1-year treatment period, compared with those who took either drug alone or neither drug.

To investigate the effect of concomitant TDF and ddl therapy in a larger and more antiretroviral-experienced patient set, we examined changes from baseline in CD4+ cell count at week 48 of therapy in 2 phase III studies of the HIV-1 fusion inhibitor enfuvirtide (ENF).

Patients and methods. The T-20 versus Optimized Regimen Only (TORO) 1 and TORO 2 studies recruited highly treatment-experienced patients with detectable HIV-1 RNA loads who had received therapy for a mean duration of 7 years and had received a median of 12 previous antiretrovirals from all 3 conventional classes (NRTIs, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors) [3]. Patients were randomized 2:1 to receive treatment with ENF plus an optimized background (OB) of other antiretrovirals (selected on the basis of resistance testing) or treatment with an OB regimen without ENF. The genotypic susceptibility of virus to antiretrovirals was determined by the baseline genotypic sensitivity score (GSS), defined as the number of drugs in a patient’s OB regimen to which their virus was genotypically susceptible. Positive prognostic factors have been identified that can predict outcomes of treatment with ENF [4]. These have been identified as baseline CD4+ cell count >100 cells/mm3, baseline HIV-1 RNA load <5 log10 copies/mL, prior treatment with ≤10 antiretrovirals, and ≥2 active antiretrovirals in the OB regimen (based on baseline phenotypic sensitivity score, defined as the number of drugs in a patient’s OB regimen to which their virus is phenotypically sensitive).

Similar study designs and patient baseline characteristics allowed pooled analyses to be performed from a combined dataset of 995 patients. For the current analysis, patients from both the ENF plus OB arm and the OB only arm of the pooled TORO 1 and 2 trials were divided into 4 mutually exclusive treatment groups. Group 1 consisted of 113 patients with TDF and ddl in their OB regimen; 85% of these patients received a modal ddl dosage of 400 mg/day, 10% received a reduced modal dosage of 250 mg/day, and ~5% received a modal dosage that was neither 400 nor 250 mg/day. Group 2 consisted of 144 patients receiving TDF without ddl. Group 3 consisted of 393 patients receiving ddl without TDF. Group 4 consisted of 345 patients receiving neither TDF nor ddl.

Changes from baseline in CD4+ cell count at week 48 of treatment were assessed using an analysis of covariance model for an intent-to-treat (ITT) population, with last observation carried forward for patients discontinuing randomized treatment (D/C=LOCF). Mean changes over time were assessed using observed data.
Table 1. Baseline demographic and clinical characteristics of 995 highly treatment-experienced patients with detectable HIV-1 RNA levels, by treatment regimen.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TDF and ddI (n = 113)</th>
<th>TDF only (n = 144)</th>
<th>ddI only (n = 393)</th>
<th>Neither TDF nor ddI (n = 345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous antiretroviral therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median no. of drugs received</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Median duration of therapy, months</td>
<td>95.8</td>
<td>85.4</td>
<td>82.1</td>
<td>83.2</td>
</tr>
<tr>
<td>Median genotypic sensitivity score</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>HIV RNA load, median log10 copies/mL</td>
<td>5.1</td>
<td>5.2</td>
<td>5.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Median CD4+ cell count, cells/mm³</td>
<td>93</td>
<td>79.5</td>
<td>110.5</td>
<td>76</td>
</tr>
</tbody>
</table>

NOTE. ddI, didanosine; TDF, tenofovir disoproxil fumarate.

Table 2. Week 48 least squares mean change from baseline in CD4+ cell count of 995 patients grouped according to the presence or absence of didanosine (ddI) and/or tenofovir disoprophyl fumarate (TDF) in the optimized background (OB) regimen.

<table>
<thead>
<tr>
<th>Group</th>
<th>OB regimen</th>
<th>All (n = 995)</th>
<th>Receiving enfuvirtide and OB regimen (n = 661)</th>
<th>Receiving OB regimen alone (n = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∆ CD4+ cell count</td>
<td>No. (%) of patients</td>
<td>P</td>
<td>∆ CD4+ cell count</td>
</tr>
<tr>
<td>1</td>
<td>TDF and ddI</td>
<td>59 (11.4)</td>
<td>...</td>
<td>71 (10.9)</td>
</tr>
<tr>
<td>2</td>
<td>TDF only</td>
<td>82 (14.5)</td>
<td>.123</td>
<td>103 (15.7)</td>
</tr>
<tr>
<td>3</td>
<td>ddI only</td>
<td>83 (39.5)</td>
<td>.059</td>
<td>105 (38.9)</td>
</tr>
<tr>
<td>4</td>
<td>Neither TDF nor ddI</td>
<td>75 (34.7)</td>
<td>.223</td>
<td>94 (34.5)</td>
</tr>
</tbody>
</table>

NOTE. Changes from baseline in CD4+ cell count at week 48 of treatment were assessed using an analysis of covariance model for an intent-to-treat population, with last observation carried forward for patients discontinuing randomized treatment. P values are for group 1 vs. groups 2, 3, and 4. Boldface type indicates statistical significance (P < .05).

Results. Baseline characteristics of the 4 treatment groups were comparable with respect to plasma HIV-1 load, CD4+ cell count, and median number of prior antiretrovirals received (table 1). Patients in group 1 had longer treatment histories than did patients in groups 2, 3, and 4 (median duration, 95.8 months vs. 82.1–85.4 months, respectively) and were classed as susceptible to fewer drugs in their OB regimen by resistance testing (median GSS, 1 for group 1 vs. 2 for each of the other groups).

Least squares mean changes from baseline in CD4+ cell count at week 48 are shown in table 2. After adjusting for baseline prognostic factors (GSS, CD4+ cell count, HIV-1 RNA load, and number of positive prognostic factors), other antiretrovirals in the OB regimen, and randomization to ENF, group 1 consistently had the lowest gain in CD4+ cell count. This difference reached statistical significance between groups 1 and 3 in patients receiving a combination of ENF and OB.

The lower CD4+ cell response at week 48 in group 1, compared with the other groups, was not associated with having a virologic response. Overall, fewer patients in group 1 had undetectable viral loads (i.e., <400 copies/mL) at week 48 than in the other groups (19% vs. 27%–30% [ITT population], respectively). However, when only those patients with undetectable viral loads were considered (n = 269), the week 48 least squares mean change in CD4+ cell count was still lower in patients receiving a combination of ddI and TDF, compared with the other 3 groups (+119 vs. +164, +152, and +150 cells/mm³ for groups 1 vs. groups 2, 3, and 4, respectively; P = .279, .367, and .409, respectively).

For patients receiving a combination of ENF and OB, continuous increases in CD4+ cell count over a 48-week period were noted in patients receiving either TDF or ddI (figure 1A). In contrast, patients receiving TDF and ddI together essentially ceased having increases in the CD4+ cell count after weeks 8–12. Similar results were noted for group 1 patients receiving OB alone (figure 1B).

Discussion. Patients receiving TDF and full-dosage ddI treatment showed consistently poorer immune responses over a 48-week period in the TORO trials than did those patients receiving either 1 drug or neither of the drugs, even when adjusting for differences in baseline characteristics. The poorer responses observed were not associated with the degree of virologic suppression attained. The difference in immune response at week 48 only reached statistical significance in patients receiving a combination of ENF and OB (P = .045). However, the high degree of early treatment switching for virologic suppression in group 1 patients may have contributed to the differences observed.
Figure 1.  A, Median changes from baseline in CD4+ cell counts over time for 661 patients randomized to receive a combination of enfuvirtide (ENF) and an optimized background (OB) of other antiretroviral drugs (observed data). B, Median changes from baseline in CD4+ cell counts over time for 334 patients receiving OB alone (observed data, censored at switch to a combination of ENF and OB). ddI, didanosine; TDF, tenofovir disoproxil fumarate.

These findings are consistent with our previous observations [1] and with a number of recent retrospective data analyses that show compromised immune responses in patients receiving combination therapy with ddI and TDF [2, 5]. In one report, decreases in CD4+ cell count were more pronounced in patients receiving full-dosage ddI treatment than they were in those receiving the reduced dosage [2].

The mechanism for the phenomenon of a compromised immunologic response is not known, but several factors may be involved. Purine nucleoside phosphorylase (PNP) may play a central role, because it is involved in metabolism of endogenous...
purines and catabolizes ddl [6, 7]. At present, the favored hypothesis is that TDF metabolites inhibit the degradation of ddl by PNP, resulting in elevated intracellular concentrations of ddl [6, 7]. This could, in turn, increase ddl-mediated cellular toxicity of CD4+ cells that may be induced by increased mitochondrial toxicity [8]. We recently observed that the addition of TDF to a full-dosage ddl-based regimen decreased mitochondrial mass and adversely affected cytochrome C oxidase function [8, 9], which may cause an imbalance in the intracellular adenosine pool and, in turn, cause CD4+ cell cytotoxicity [6].

An autosomal recessive deficiency in PNP results in cellular, but not humoral, immunodeficiency [10]. It has also been reported that elevated levels of certain adenosine analogues cause depletion of lymphocytes [11]. Thus, the combination of full dosages of ddl and TDF (both adenosine analogues) together may also be sufficient to directly cause CD4+ cell cytotoxicity and be responsible for the poorer immunologic response [6].

Concomitant TDF therapy is known to elevate systemic exposure to ddl by 40%–60% [12]. Reducing the dose of ddl to 250 mg when taken with TDF provides drug exposure comparable to that achieved with the 400-mg dose taken without TDF [13]. Preliminary data from a small number of patients suggested that such dose reductions may allow CD4+ cell recovery [1]. However, more-recent data have shown that patients displaying compromised immunologic recovery while receiving full-dose ddl regimens who switched to reduced-dosage ddl underwent a progressive recovery of CD4+ cells over 36 weeks of monitoring, but CD4+ cell levels did not return to baseline [1, 14]. A longer follow-up period is necessary to clarify whether a complete recovery of CD4+ cells is achievable with reduced-dosage ddl in these patients.

In addition to the compromised immunologic response observed in patients receiving a combination of ddl and TDF, a higher rate of early virologic failure in treatment-naive patients receiving this combination with efavirenz has been reported [15, 16]. This effect was seen in patients with viral loads >5 log10 copies/mL and <200 CD4+ cells/mm3, and it highlights the need for careful consideration of drug combinations in both treatment-naive and treatment-experienced patients.

In conclusion, treatment-experienced patients receiving TDF with full dosages of ddl experience substantially poorer immune responses to antiretroviral therapy, independent of virologic suppression. Therefore, we only recommend the use of TDF with a low dosage of ddl in subjects who have undetectable viral loads and only if other strategies are not available.

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**References**
