Short-Term Safety and Tolerability of Didanosine Combined with High- versus Low-Dose Tenofovir Disproxil Fumarate in Ambulatory HIV-1–Infected Persons*,†

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ABSTRACT

Coadministration of didanosine (ddI) and tenofovir (TDF) results in increased ddI serum concentrations, which may lead to increased risk of ddI-associated toxicities. To evaluate the safety and tolerability of ddI/TDF, we performed a retrospective cohort analysis of patients seen in the HIV Outpatient Study, an ongoing dynamic cohort study of HIV-infected persons in clinical care. Study subjects were those who received at least 14 days of combined ddI/TDF before October 2003. Of 260 subjects who received ddI/TDF-based antiretroviral therapy, 155 (60%) received high-dose ddI (400 mg daily dose) and 105 (40%) received low-dose ddI (100–250 mg daily). Forty-two of the high-dose ddI recipients were later switched to low-dose ddI. The median time of observation for those on high-dose ddI only was 5 months, high-dose ddI switched to low-dose ddI was 16 months, and low-dose ddI only was 5 months (p < 0.05). Discontinuations because of toxicity were more frequent on high-dose ddI regimens (34/155, 22%) than on low-dose ddI regimens (9/105, 9%) (unadjusted odds ratio [ORunadj] 3.0, 95% confidence interval [95% CI] 1.30–7.09; p = 0.007). Among subjects without preexisting peripheral neuropathy, 12 (12%) of 101 subjects ever on high-dose ddI regimens had treatment-emergent peripheral neuropathy compared to 2 (4%) of 55 subjects on low-dose ddI regimens (ORunadj 3.57; 95% CI, 0.72–24.1; p = 0.14). Among patients without a history of pancreatitis, 6 (4%) of 153 subjects developed pancreatitis after starting high-dose ddI regimens, compared to none of the 103 subjects on low-dose ddI regimens (ORadj and 95% CIs undefined; p = 0.08). Severe laboratory abnormalities of creatinine, phosphorous, and bicarbonate were not different between the groups. A summary variable for any event—discontinuation for toxicity, treatment-emergent adverse event or abnormal laboratory values—indicated that 44 (28%) of 155

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†The findings and conclusions from this review are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.
‡A complete list of these investigators can be found in the Appendix.
of those on high-dose ddI versus 13 (12%) of 105 on low-dose ddI developed any event (OR\textsubscript{unadj} 2.81; 95% CI, 1.36–5.86; \(p = 0.004\)). In conclusion, high-dose ddI/TDF-based therapy was more frequently associated with drug-related toxicity, adverse events, and treatment discontinuation than low-dose ddI/TDF regimens; low-dose ddI with TDF was generally well tolerated in these HIV-infected persons.

### INTRODUCTION

The use of combination antiretroviral therapy for the treatment of HIV-1 infection has resulted in dramatic declines in disease-related morbidity and mortality.\(^1\) Recent attention in antiviral drug discovery has focused on medications with lower pill burden, dosing frequency, and toxicity without reduction in inherent antiviral potency. Enteric-coated didanosine (ddI) and tenofovir disoproxil fumarate (TDF) are commonly prescribed reverse transcriptase inhibitors approved for single daily dosing of one pill each and taking them together relaxes the need for dietary restrictions required with single-agent ddI. Because of these attributes, there had been interest in combining ddI and TDF for once-daily dosing, although this combination is no longer recommended to be given with a non-nucleoside reverse transcriptase inhibitor as first-line therapy because of reports of virologic failure.\(^2\)

After the Food and Drug Administration (FDA) approval of tenofovir in 2001, ddI/TDF was typically administered as 400 mg ddI (for those \(\geq 60 \text{ kg}\)) with 300 mg TDF both once daily. Subsequently, a significant one-way drug–drug interaction in healthy volunteers was described.\(^3,4\) When 300 mg of TDF is administered concurrently with 400 mg ddI, there are 48%–64% increases in the ddI maximum plasma concentration and area under the curve with no significant alterations in the TDF pharmacokinetic parameters. The pharmacokinetics of coadministered TDF 300 mg/ddI 250 mg was compared to ddI 400 mg alone, demonstrating similar ddI exposure.\(^5\) Since mid-2003, a dose modification of enteric-coated ddI of 250 mg daily (for persons \(\geq 60 \text{ kg}\)) when coadministered with TDF has been followed.\(^6,7\)

An early analysis of treatment-experienced HIV-1–infected individuals who received ddI/TDF in two short-term clinical trials (using the 400 mg ddI dose) did not reveal an increased incidence of drug-related adverse events.\(^8\) However, growing evidence suggests that this combination as a backbone to combination antiretroviral therapy may be suboptimal with reports of virologic breakthrough,\(^9–11\) blunted CD4\(^+\) cell count response,\(^12–15\) and increased reports of the potential for the ddI/TDF-containing treatments to cause excess toxicity.\(^16–21\)

We undertook an analysis of the tolerability and safety of ddI/TDF in a dynamic, longitudinal cohort of HIV-1–infected persons. Because ddI/TDF therapy was initiated in this cohort of patients both before and after the modified dose recommendation, this analysis provides an opportunity to compare the adverse event profiles of high-dose ddI/TDF with low-dose ddI/TDF.

### PATIENTS AND METHODS

The HIV Outpatient Study

The HIV Outpatient Study (HOPS) is a dynamic, longitudinal cohort of HIV patients attending 10 HIV clinics in 8 U.S. cities; approximately 3000 such patients are seen every year, as has previously been described.\(^22\) The ethical conduct of this study undergoes yearly review by federal and local institutional research review boards. HOPS data from 1993 through December 31, 2003 were used for this analysis.

Inclusion criteria and definitions

To be included in the analysis, subjects had to be taking ddI and TDF for at least 14 consecutive days starting in 2000 through October 2003. Two groups of subjects were defined; one that had ever been exposed to high-dose ddI (400 mg/d if weight \(\geq 60 \text{ kg}\); 250 mg if weight < 60 kg), whether they eventually switched to low-dose ddI or not, and the second group consisted of patients that had only been on a low-dose of ddI (250 mg if \(\geq 60 \text{ kg}\);
100–200 mg if < 60 kg). Baseline CD4⁺ cell count and plasma HIV viral load were based on the values obtained within the six months prior to the start of the ddI/TDF regimen or within 1 month after regimen start, and then selecting the value obtained closest to the start date. Patient follow-up was defined as the length of time from the start of the ddI/TDF regimen to the earlier of December 31, 2003 or date corresponding to the date of last contact plus 90 days. Length of time on ddI/TDF therapy for those who switched from high-dose to low-dose ddI was the sum of time spent on high and low dose while on TDF.

The specific incident clinical adverse events that were examined in this analysis were peripheral neuropathy, pancreatitis, renal failure, and hyperlactatemia. Evidence of these adverse events was determined by scanning reasons for discontinuing therapy; diagnoses, symptoms, or initiation of treatment for peripheral neuropathy (for example, gabapentin), reported after starting the ddI/TDF regimen. Only incident specific adverse events that occurred at least 14 days after starting the ddI/TDF regimen were included for analysis.

Abnormal laboratory values were also evaluated. The on-treatment value had to have been obtained during treatment or no later than 7 days after ending the ddI/TDF regimen. We examined severe elevations in creatinine as AIDS Clinical Trials Group (ACTG) grade 3 (3.1–6.0 mg/dL) or grade 4 (> 6.0 mg/dL) and decreases in serum phosphorous as ACTG grade 3 (1.0–1.4 mg/dL) or grade 4 (< 1.0 mg/dL). Serum bicarbonate values were considered as adverse events if the on-treatment value was less than 18 mEq/L.

All reasons for discontinuation were evaluated to identify reasons for ddI or TDF treatment stops due to any toxicity. A summary adverse event variable was created to indicate whether TDF or ddI was discontinued for any toxicity, or whether there was evidence of clinical adverse event or abnormal laboratory values after ddI/TDF treatment began.

Statistical analyses

Statistical analyses were performed using the Statistical Analysis System (SAS) version 8.2 (SAS Institute, Cary, NC). Differences in groups were tested using the Pearson χ² test for categorical data and the Wilcoxon rank-sum test for quantitative data. Logistic regression was used to evaluate the differences in “any adverse advent” between the high- and low-dose treatment groups, adjusting for treatment duration. P values were noted as statistically significant if the value was less than 0.05. A Cox proportional hazards model analysis comparing persons on high-dose ddI to low-dose ddI was performed on the time to: (1) discontinuation for any toxicity, (2) any incident clinical adverse event, or (3) any event (either 1, 2, or any laboratory adverse event).

RESULTS

Of 260 patients who met the inclusion criteria for this analysis, 155 (60%) started on high-dose ddI, and 105 (40%) low-dose ddI (Table 1). There were no significant differences in the HIV transmission risk categories, race or ethnic minority status, or in baseline plasma HIV-1 RNA viral load, CD4⁺ cell counts or diagnosis of AIDS. There were significant differences in length of observation, length of time taking ddI/TDF at any dose and median number of previous antiretroviral regimens; in general, these were all longer or more frequent for those who had switched from high-dose to low-dose ddI/TDF compared to patients who were maintained on either high-dose or low-dose ddI/TDF only (Table 1).

The occurrence of any incident clinical adverse effect and discontinuation of ddI or TDF therapy were more frequent for those who ever took high-dose ddI/TDF compared to those who had only taken low-dose ddI/TDF (Table 2). Abnormalities in creatinine, phosphorous, and bicarbonate were infrequent and not significantly different between the high-dose and low-dose ddI/TDF-receiving patients. Of high-dose ddI/TDF patients with adequate laboratory values recorded, 2 (2%) of 122 had elevated creatinine, 8 (14%) of 57 had hypophosphatemia, and 6 (6%) of 104 had low serum bicarbonate levels. Comparable percentages for the low-dose ddI/TDF patients were 2 (3%) of 80 with elevated creatinine; 2 (11%) of 19 with
hypophosphatemia; and 1 (2%) of 51 with low serum bicarbonate. Overall, 44 (28%) patients in the high-dose group had any event compared to 13 (12%) of those who only took low-dose ddI/TDF (relative hazard adjusted for number of previous antiretroviral regimens [RHadj] 1.87; 95% CI [1.00, 3.48]; p = 0.05).

Change in CD4 cell count from baseline to assessment closest to 6 months from initiation of that regimen (range, 4–8 months) was not

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics:</th>
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<tbody>
<tr>
<td><strong>Age, median (yrs)</strong></td>
<td>42</td>
</tr>
<tr>
<td>Male</td>
<td>104 (92.1%)</td>
</tr>
<tr>
<td>Minority race/ethnicity</td>
<td>37 (32.7%)</td>
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<tr>
<td>Men who have sex with men</td>
<td>90 (79.7%)</td>
</tr>
<tr>
<td>AIDS (CDC Class C)</td>
<td>72 (63.6%)</td>
</tr>
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</table>

At start of therapy or switch (median [range]):

| Plasma HIV-1 RNA, log copies/mL | 3.51 (< 2.60, 5.88) | 3.86 (< 2.60, 5.59) | 4.35 (< 2.60, 5.88) |
| CD4<sup>+</sup> cell count, cells/mm<sup>3</sup> | 337 (0, 1447) | 361 (3, 1285) | 282 (1, 1610) |
| Nadir CD4<sup>+</sup> cell count, cells/mm<sup>3</sup> | 167 (0, 1441) | 187 (2, 890) | 152 (1, 707) |

Duration of therapy (median):

| Months on any ddI/TDF<sup>a</sup> | 5 | 16 | 5 |
| Months on HD ddI/TDF<sup>a</sup> | 5 | 7 | — |
| On that therapy as of December 2003<sup>a</sup> | 38 (33.6%) | 23 (54.8%) | 81 (77.1%) |
| Months of observation on therapy<sup>a</sup> | 15 | 20 | 9 |
| Number of previous antiretroviral regimens<sup>a</sup> | 7 | 9 | 6 |


<sup>a</sup>Statistically significant differences between groups (p < 0.05), by Pearson χ² or Wilcoxon rank-sum test.

HD ddI = 400 mg daily if weight > 60 kg, or 250 mg if weight ≤ 60 kg.
LD ddI = 250 mg if weight > 60 kg, or 100–200 mg if weight ≤ 60 kg.
ddi, didanosine; TDF, tenofovir; CDC, Centers for Disease Control and Prevention.

### Table 1. Characteristics of HIV-Infected Persons Who Took Either High-Dose ddI with TDF, Low-Dose ddI/TDF, or Who Switched from High-Dose to Low-Dose ddI/TDF, HIV Outpatient Study, January 2000 to December 2003

<table>
<thead>
<tr>
<th>Dosages of ddI/TDF taken:</th>
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<tbody>
<tr>
<td><strong>High-dose ddI/TDF</strong></td>
<td>Switched from High-dose to Low-dose ddI/TDF</td>
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<tr>
<td>(n = 113)</td>
<td>(n = 42)</td>
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Duration of therapy (median):

| Months on any ddI/TDF<sup>a</sup> | 5 | 16 | 5 |
| Months on HD ddI/TDF<sup>a</sup> | 5 | 7 | — |
| On that therapy as of December 2003<sup>a</sup> | 38 (33.6%) | 23 (54.8%) | 81 (77.1%) |
| Months of observation on therapy<sup>a</sup> | 15 | 20 | 9 |
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HD ddI = 400 mg daily if weight > 60 kg, or 250 mg if weight ≤ 60 kg.
LD ddI = 250 mg if weight > 60 kg, or 100–200 mg if weight ≤ 60 kg.
ddi, didanosine; TDF, tenofovir; CDC, Centers for Disease Control and Prevention.

### Table 2. Adverse Events Experienced by Patients with HIV Who Started on Either High-Dose or Low-Dose ddI with TDF, HOPS Cohort<sup>a</sup>

<table>
<thead>
<tr>
<th>Patients who started with:</th>
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<tbody>
<tr>
<td><strong>High-dose ddI/TDF</strong></td>
<td><strong>Low-dose ddI/TDF</strong></td>
</tr>
<tr>
<td>(n = 155)</td>
<td>(n = 105)</td>
</tr>
</tbody>
</table>

| Discontinued ddI or TDF for any toxicity | 34 (21.9%) | 9 (8.6%) | 3.00 (1.30, 7.09) | 0.007 | 1.99 (0.95, 4.17) | 0.068 |

| Peripheral neuropathy | 12/101 (12%) | 2/55 (4%) | 3.57 (0.72, 24.1) | 0.140 |
| Acute pancreatitis | 6/153 (4%) | 0/103 (0%) | -undefined- | 0.084 |
| Renal insufficiency | 2/153 (1%) | 0/104 (0%) | -undefined- | 0.516 |
| Hyperlactemia | 3/152 (2%) | 1/102 (1%) | 2.03 (0.19, 51.5) | 0.651 |

Any of the above | 18 (12%) | 3 (3%) | 4.47 (1.20, 16.9) | 0.021 | 3.44 (1.00, 11.8) | 0.050 |

Any event<sup>b</sup> | 44 (28%) | 13 (12%) | 2.81 (1.36, 5.86) | 0.004 | 1.87 (1.00, 3.48) | 0.050 |

<sup>a</sup>By Yates-corrected or Fisher’s exact (two-tailed) test.

<sup>b</sup>Any event, any discontinuation for toxicity, incident clinical adverse event, or any grade 3 or 4 serum creatinine, phosphorus, or bicarbonate concentration.

High-dose ddI = 400 mg daily if weight > 60 kg, or 250 mg if weight ≤ 60 kg.
Low-dose ddI = 250 mg if weight > 60 kg, or 100–200 mg if weight ≤ 60 kg.

OR<sub>unadj</sub> unadjusted odds ratio; 95% CI, 95% confidence intervals; RH<sub>adj</sub>, relative hazard, adjusted for number of previous antiretroviral regimens.
significantly different across groups: in the HD group -5 cells/mm³ (n = 92, range, -477–679), in the high-dose to low-dose group +11 cells/mm³ (n = 41, range, -272–318), and in the low-dose group +15 cells/mm³ (n = 67, range, -342–254). A crude assessment of the most recent viral load (or last viral load prior to treatment discontinuation) showed no significant differences between groups. Rigorous stratified analyses of immunologic and virologic responses were not undertaken because of the small numbers and heterogeneous nature of the cohort.

DISCUSSION

In combination with TDF, ddI dosed at 400 mg daily (or 250 mg for those < 60 kg) is associated with more frequent drug-related toxicity and treatment discontinuation than when ddI was dosed at 250 mg daily (or 100–150 mg for those < 60 kg). Patients in this study who received high-dose ddI/TDF were nearly twice as likely to develop toxicity and more than three times more likely to develop at least one of the following incident adverse events—peripheral neuropathy, pancreatitis, renal insufficiency or hyperlactatemia—than patients who received low-dose ddI/TDF. Low-dose ddI/TDF appears generally well tolerated in this cohort of HIV-infected persons, consistent with what others have reported.

Our interest was in the relative safety of the low-dose ddI compared to high-dose ddI when combined with TDF. The ddI-related toxicities peripheral neuropathy, pancreatitis, and hyperlactemia occurred almost exclusively among those on high-dose ddI in our analysis suggesting that elevated concentrations of ddI was the primary reason for the effects. We only found two cases of elevated serum creatinine (grade 3), presumably a TDF-related toxicity, both among those on high-dose ddI and TDF. We only examined relatively major changes in renal function in this analysis as we felt that we would be unable to evaluate more subtle changes confidently. Others have reported renal dysfunction among persons on combined ddI and TDF. Whether ddI enhances TDF renal dysfunction is not clear at this time.

The combination of TDF and ddI has never been among the preferred or alternative recommended nucleoside reverse transcriptase inhibitor backbones in authoritative guidelines, although its use was desirable because of the apparent relative ease of coadministration. However, the combination has come under increasing scrutiny over the past few years with reports of suboptimal virologic control when part of some triple nucleoside reverse transcriptase inhibitor regimens and in combination with a non-nucleoside reverse transcriptase inhibitor leading to the recent recommendation against the use of ddI/TDF with these drugs. These virologic failures are likely results of suboptimal potency of this combination at the cellular or viral level and are likely not due to an alterations in pharmacokinetics. Additionally, there have been reports of declines in CD4⁺ cell counts not attributed to loss of virologic control. It is unclear if the CD4⁺ cell count decline in those reports was a result of increased ddI concentrations or an effect of the two drugs at the cellular level that resulted in lymphopenia.

The potential limitations of these data from this observational cohort include selection or acquisition bias. Moreover, given the different chronological periods in which the two ddI dosing strategies were used, it is possible that other clinical parameters are not equivalently distributed in the study groups. Although we had information on virologic and immunologic parameters, given the heterogeneous nature of this cohort, we had limited ability to analyze antiviral response among the groups.

In combination with TDF, ddI at the adjusted dose recommended since 2003 appears to be better tolerated than when used at unadjusted doses prior to that. These data highlight how unexpected drug–drug interactions among antiretroviral drugs can result in significant adverse reactions. Given recent revelations about pharmacokinetic interactions within and across antiretroviral classes, caution should be exercised in implementing novel or untested treatment combinations.
ACKNOWLEDGMENTS

The authors thank the thousands of HOPS subjects across the United States for their continued support and participation in the study.

APPENDIX

The HOPS Investigators include the following investigators and sites: Anne C. Moorman, Tony Tong, John T. Brooks, and Kate Buchacz, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention (NCHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, GA; Scott D. Holmberg, Research Triangle Institute (formerly of CDC); Kathleen C. Wood, Rose K. Baker, Carl Armon, James T. Richardson, Cerner Corporation., Vienna, VA; Frank J. Palella, Joan S. Chmiel, Katharine A. Kirby, Janet Cheley, and Tiffany Murphy, Feinberg School of Medicine, Northwestern University, Chicago, IL; Kenneth A. Lichtenstein, University of Colorado Health Sciences Center, Denver, CO; Kenneth S. Greenberg, Benjamin Young, Barbara Widick, Cheryl Stewart, and Peggy Zellner, Rose Medical Center, Denver, CO; Bienvenido G. Yangco, Kalliope Halkias, and Arletis Lay, Infectious Disease Research Institute, Orlando, FL; Douglas J. Ward and Charles A. Fiorentino, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, and Jane Esteves, State University of New York (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, and Linda Walker-Kornegay, Temple University School of Medicine, Philadelphia, PA; Joseph B. Marzouk, Roger T. Phelps, and Mark Rachel, Adult Immunology Clinic, Oakland, CA; Silver Sisneros and Mark Rachel, Fairmont Hospital, San Leandro, CA; Richard M. Novak, Jonathan P. Uy and Andrea Wendrow, University of Illinois at Chicago, Chicago, IL.

B.Y. has been a consultant to Gilead Sciences, Bristol Myers Squibb, and GlaxoSmithKline.

REFERENCES


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