Renal Impairment Associated with the Use of Tenofovir

James D. Heffelfinger, Debra L. Hanson, Andrew C. Votey, A.D. McNagnach, and Patrick S. Sullivan, Centers for Disease Control and Prevention, Atlanta, GA

INTRODUCTION

• Tenofovir disoproxil fumarate (TDF), a potent nucleoside reverse transcriptase inhibitor, is being approved for use by the U.S. Food and Drug Administration in 2001 for HIV infection. It is currently a common component of antiretroviral therapy (ART) regimens.

• Cidofovir and adefovir, which are closely related to TDF, have been associated with increased risk of acute renal insufficiency [1, 2].

• Several case reports and a case series indicate that tenofovir disoproxil fumarate (TDF) may be associated with renal failure or severe renal impairment [3-6]. However, a case-control study and two longitudinal cohort-studies found that TDF was associated with only a low risk of renal impairment (7-9).

OBJECTIVES

To examine the risk factors for the development of renal impairment and the effects of TDF use on renal function among HIV-infected persons being treated with ART during 2000-2003 using longitudinal data from a large cohort study.

METHODS

Data source

• The Adult AIDS Spectrum of Disease (AIDS) project, a longitudinal medical records-based cohort study conducted at 110 facilities in 10 U.S. states during 1990-2004.

• ASD participants: HIV-infected persons ≥18 years who attended participating clinics. Medical record abstraction occurred over the 12-month period prior to enrollment and at 6-month intervals until patient death or loss to follow-up.

• Data collected include: Demographic characteristics, HIV risk mode, prescription of antiretroviral medications, CD4+ cell counts, HIV ribonucleic acid (RNA) levels (viral load), undetectable and incident medical conditions, and basic laboratory values including creatinine and hemoglobin.

RESULTS

• The analysis includes follow-up data from 9,535 patients with 34,814 6-month person-observations (17,257 person-years median = 1.5 years per person) of follow-up.

• Estimation of percentage of persons with defined GFR severity:
  • Any renal impairment: 3,842 (43.8%)
  • Mild renal impairment: 3,026 (33.7%)
  • Moderate renal impairment: 584 (6.5%)
  • Severe renal impairment: 232 (2.4%)

• Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [10].

• TDF (mean [SD] GFR 0.203 ± 0.165 mL/min) may be associated with renal failure or severe renal impairment (7-9).

• Our findings differ from those of recently published longitudinal cohort studies that have found the TDF is associated with only a small risk of renal impairment among ART-naïve patient – possible explanations include:
  1) Treatment-experienced patients may be more susceptible to renal toxicity from TDF than treatment-naïve patients.
  2) Subjects prescribed TDF may have had more progressive HIV disease or greater susceptibility to renal impairment than patients who were prescribed other ART which were not completely controlled for by the covariates available in the study – particularly during the study period before the Food and Drug Administration approved TDF for treatment of HIV disease, when TDF was often prescribed to persons who were failing to respond to other ART regimens.

• Further studies should be conducted to assess the effect of TDF on the renal function of patients with varying experience with ART.

DISCUSSION

• We found that prescription of TDF was associated with all categories of renal impairment among HIV-infected persons with varying experience with ART.

TABLE 3. Multivariable analysis evaluating risk factors for renal impairment (RI). Separate logistic regression models with robust variance estimates were used to evaluate risk factors categories of RI. GFR indicates glomerular filtration rate (mL/min). ART indicates antiretroviral therapy. TDF indicates tenofovir disoproxil fumarate. OR indicates odds ratio. 95% CI indicates 95% confidence intervals. Red font indicates estimates are statistically significant.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TDF Prescribed</th>
<th>Age &lt;25 years</th>
<th>Age 25-49 years</th>
<th>Age ≥50 years</th>
<th>Hispanic</th>
<th>Other Referent</th>
<th>Race</th>
<th>Other Referent</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR decline to &lt;90 mL/min</td>
<td>0.9 (0.8, 1.0)</td>
<td>0.8 (0.7, 0.9)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.8 (1.1, 2.8)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.7 (0.5, 1.0)</td>
<td>0.8 (0.6, 1.0)</td>
<td>0.7 (0.6, 0.9)</td>
</tr>
<tr>
<td>Any: GFR decline to &lt;90 mL/min</td>
<td>2.3 (1.4, 1.5)</td>
<td>1.3 (1.1, 1.5)</td>
<td>3.0 (2.2, 4.1)</td>
<td>3.5 (2.1, 5.9)</td>
<td>2.8 (2.2, 3.5)</td>
<td>1.8 (1.4, 2.3)</td>
<td>2.1 (1.7, 2.7)</td>
<td>2.1 (1.7, 2.7)</td>
</tr>
<tr>
<td>Mild: GFR decline to 60-89 mL/min</td>
<td>0.9 (0.8, 1.0)</td>
<td>0.8 (0.7, 0.9)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.8 (1.1, 2.8)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.7 (0.5, 1.0)</td>
<td>0.8 (0.6, 1.0)</td>
<td>0.7 (0.6, 0.9)</td>
</tr>
<tr>
<td>Moderate: GFR decline to 30-59 mL/min</td>
<td>0.9 (0.8, 1.0)</td>
<td>0.8 (0.7, 0.9)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.8 (1.1, 2.8)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.7 (0.5, 1.0)</td>
<td>0.8 (0.6, 1.0)</td>
<td>0.7 (0.6, 0.9)</td>
</tr>
<tr>
<td>Severe: GFR decline to &lt;30 mL/min</td>
<td>0.9 (0.8, 1.0)</td>
<td>0.8 (0.7, 0.9)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.8 (1.1, 2.8)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.7 (0.5, 1.0)</td>
<td>0.8 (0.6, 1.0)</td>
<td>0.7 (0.6, 0.9)</td>
</tr>
</tbody>
</table>

• Any: GFR decline to <90 mL/min

• Mild: GFR decline to 60-89 mL/min

• Moderate: GFR decline to 30-59 mL/min

• Severe: GFR decline to <30 mL/min

• Information about adherence to medications is unknown

• Analysis was not accounted for other nephrotoxic drugs

• Correlation was observed among patients prescribed TDF and having adverse conditions like wasting syndrome, congestive heart failure, diabetes mellitus, hypertension, and prescribed TDF.

• Timevarying covariates representing indicators during the current or previous 6-month interval period included: Weight loss <10% or >10% body weight, diagnosis of wasting syndrome, congestive heart failure, diabetes mellitus, hypertension, and prescribed TDF.

REFERENCES


