Background: In clinical trials, toxicity leading to discontinuation of tenofovir (TDF) is a rare occurrence (up to 5% by 2 years). However, in clinical practice it seems to be higher. Previous studies suggested that TDF toxicity is higher when it is co-administered with ritonavir-boosted protease inhibitors (PI/r) instead of nonnucleoside reverse-transcriptase inhibitors (NNRTI). The aim of this study is to assess the rate of TDF discontinuations in clinical practice and to explore associated factors.

Methods: All previously antiretroviral-naive patients initiating a TDF-containing regimen were selected from the ICONA Foundation Study cohort, unless they were positive for hepatitis B surface antigen. The primary outcome was TDF discontinuation (>30 days) regardless of the reason; the secondary was TDF discontinuation due to toxicity. All analyses were repeated for the isolated stop of TDF (i.e., discontinuation or substitution of TDF, carrying on all other concurrent antiretrovirals). The main reason for discontinuation as reported by the treating physician was used to classify stops. Kaplan-Meier (KM) analysis and Cox proportional hazards model were used. Patients were followed from the date of starting TDF until its discontinuation or their last recorded visit. In the secondary outcome analysis, follow-up was truncated at the date of stopping for a reason other/unknown causes (20%).

Results: Three thousand six hundred and eighteen HIV-infected patients were enrolled: 1669 (46%) of NNRTI based regimen and 1949 (54%) on PI/r based regimen. Their median age was 38 years-old and 80% had baseline eGFR >90 ml/min. Black ethnicity, %, Female, %, MSM, %, Drug class, % were 7,5%, 22,6% and 37 (33-43) respectively. The 5 year KM estimates in the PI/r vs NNRTI group were 80% vs. 74.7% (log-rank p=0.0004) for discontinuation due to toxicity. A significantly higher proportion of patients co-treated with PI/r had discontinuation due to toxicity and isolated (HR 1.41 ; 95%CI 1.17-1.69).

In a multivariable Cox model, PI/r use and to have a lower eGFR at baseline were associated with increased risk of discontinuing TDF regardless of the reason. PI/r use, to be older and to have a lower eGFR at baseline was a factor associated with isolated stop of TDF. No differences in rates of TDF discontinuations between PIs were found.

A significantly higher proportion of patients co-treated with PI/r had discontinued TDF due to kidney toxicity compared to those treated with a NNRTI-based regimen. KM analysis shows a different probability of TDF discontinuation due to renal toxicity in NNRTI group and PI group (2.0% vs 6.1%). However, when discontinuation due to kidney toxicity was used as outcome measure of a separate Cox regression analysis, drug companion was not associated with the risk of TDF discontinuation. Also in this model, to have a lower baseline eGFR was an important independent predictor of TDF discontinuation (HR 1.41 ; 95%CI 1.17-1.69).

ABSTRACT

In clinical trials, toxicity leading to discontinuation of tenofovir (TDF) is a rare occurrence (up to 5% by 2 years).

In clinical practice, the frequency of TDF discontinuations due to toxicity or side effects seems to be higher.

Trial data suggested that the risk of TDF toxicity is higher when it is co-administered with PI/r vs. NNRTI.

OBJECTIVES

The aim of our study is to describe the use of TDF in clinical practice, to assess the rate of its premature discontinuation and to explore factors associated with TDF discontinuation (including use of PI/r) in the setting of people starting their first ART regimen.

METHODS

Study population

Patients of ICONA Foundation Study who started a first cART including TDF from ART-naive

Exclusion : HlA+/Ag-

Outcome - Discontinuation of TDF (with other drugs or isolated)

- The main reason for discontinuation as reported by the treating physician was used to classify TDF stops

- Steps followed by re-initiation of TDF-based regimen or 'changes in formulation' within 1 month not counted as events

Statistical analysis

Survival analysis using Kaplan-Meier (KM) and Cox proportional hazards model

In clinical trials, toxicity leading to discontinuation of tenofovir (TDF) is a rare occurrence (up to 5% by 2 years).

- Frequency of TDF discontinuations in clinical practice is 10% by 2yrs, 20% by 8yrs.

- Co-administration with PI/r vs. NNRTI is associated with an increased rate of TDF discontinuations (regardless the reason, because of toxicity and isolated).

- Renal toxicity is more frequently reported in the PI/r group.

- A lower eGFR is an independent predictor for TDF discontinuations (regardless the reason, because of toxicity and isolated).

- We also find no differences between Ps (LPV/r, ATV/r, DRV/r) in TDF discontinuations.

RESULTS

<table>
<thead>
<tr>
<th>Drug class</th>
<th>TDF use</th>
<th>NNRTI use</th>
<th>Total Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1,669</td>
<td></td>
<td>n=1,949</td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>22,6%</td>
<td>17,7%</td>
<td>20,3%</td>
</tr>
<tr>
<td>Age at enrollment, median (IQR)</td>
<td>38 (32-45)</td>
<td>37 (31-42)</td>
<td>38 (32-44)</td>
</tr>
<tr>
<td>Black ethnicity, %</td>
<td>7,7%</td>
<td>5,1%</td>
<td>6,5%</td>
</tr>
<tr>
<td>Calendar year, median</td>
<td>2011</td>
<td>2011</td>
<td>2011</td>
</tr>
<tr>
<td>eGFR, ml/min</td>
<td>106.2</td>
<td>105.9</td>
<td>106.2</td>
</tr>
<tr>
<td>CD4 count at cART, median</td>
<td>253</td>
<td>230</td>
<td>266</td>
</tr>
<tr>
<td>eGFR (Cockcroft-Gault) at cART, median</td>
<td>106.5</td>
<td>105.9</td>
<td>106.2</td>
</tr>
</tbody>
</table>

In a multivariable Cox model, PI/r use and to have a lower eGFR at baseline were associated with increased risk of discontinuing TDF regardless of the reason. PI/r use, to be older and to have a lower eGFR at baseline was a factor associated with isolated stop of TDF. No differences in rates of TDF discontinuations between PIs were found.

CONCLUSIONS

- Frequency of TDF discontinuations in clinical practice is 10% by 2yrs, 20% by 8yrs.

- Co-administration with PI/r vs. NNRTI is associated with an increased rate of TDF discontinuations (regardless the reason, because of toxicity and isolated).

- Renal toxicity is more frequently reported in the PI/r group.

- A lower eGFR is an independent predictor for TDF discontinuations (regardless the reason, because of toxicity and isolated).

- We also find no differences between Ps (LPV/r, ATV/r, DRV/r) in TDF discontinuations.