Disproportionality Analysis of Antiretrovirals with Suicidality using FDA Adverse Event Reporting System (FAERS) Data

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INTRODUCTION

Psychiatric events, including depression, suicidal ideation, suicide attempts, and completed suicide have been reported in patients receiving efavirenz since 1998. 

Recently, a pooled analysis of four AIDS Clinical Trial Group (ACTG) studies (A5035, A5141, A5175, A5155), identified an increased rate of suicidality with efavirenz-containing regimens compared to efavirenz-free regimens: 

Suicide incidence per 1000 person-years was 6.09 (97% CI 4.16–9.04) in the efavirenz group and 3.66 (15% CI 2.28–5.90% confidence interval [CI]) 1.27, 1.65, 1.006). 

This study has limitations: It was a retrospective analysis using pooled data, three of the studies were open label, some of the treatment regimens are no longer recommended and more included resistant psychiatric measures of suicidality or depression. 

To further explore the potential association of efavirenz and other antiretrovirals (ARVs) with suicidality, we performed a disproportionality analysis on the Food and Drug Administration Spontaneous Adverse Event Reporting System (FAERS) database.

BACKGROUND

FAERS is a public database developed to support postmarketing surveillance of medications by recording adverse events (AEs) reported by consumers and healthcare professionals to the Food and Drug Administration (FDA) or its foreign collaborators. 

Disproportionality analysis is used to identify increased reporting rates of AEs for a selected drug in AE reporting surveillance databases. 

– With this analysis, the reporting rate at which a selected AE occurs with a given drug is compared with the reported rate at which it occurs without the drug. 

This analysis can also identify increased reporting rates for low frequency events.

STUDY OBJECTIVE

To assess the potential association of ARVs drugs, including efavirenz, with suicidality using real world data in the FAERS database collected from 1998-up to August 2012

METHODS

Searching the FAERS Database

A disproportionality analysis was performed using the Multi-Hem-Garrera Poison Shriver (MIPS) method, a well-established technique that incorporates non-negative reporting rates. 

The drugs included in the analysis were efavirenz (Sustiva® and ATR IPLA ®), atazanavir (Reata®, Evolvea®, Evince®), darunavir (prevailing in the efavirenz-free group, heard via 1B: 2.86% [95% confidence interval [CI]] 1.27, 1.65, 1.006). 

Suicidality was defined using the Medical Dictionary for Regulatory Activities (MedDRA), suicide ideation, suicide attempt, and suicide attempt, representing AEs from different drug classes. 

Suicidality was defined using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 preferred terms which included suicidal ideation, suicide attempt, and suicide ideation. A combination of suicidality term was generalised that combined all terms for MedDRA preferred terms.

Two parallel analyses were performed to assess the validity of the methodology using: 

– Fluoxetine and sertraline, antidepressants known associated with suicidality. 

– Raltegravir, an antiretroviral with thymolism and memory listed as “uncommon” events in the US prescribing information, as a sensitivity analysis

Defined as <1% and <0.1% of expected for AEs, respectively. 

Available at: http://www.dcrs.com/pub/products/pt/informatica.pdf [p139]

RESULTS

Suicidality Ideation

A disproportionality analysis was performed for the selected drug and selected AE using the MIPS method.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>Number of reports</th>
<th>EB05</th>
<th>EB95</th>
<th>EBGM ± 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>2238</td>
<td>1579</td>
<td>0.36</td>
<td>0.65</td>
<td>0.48 [0.38, 0.59]</td>
</tr>
<tr>
<td>Other ARVs</td>
<td>934</td>
<td>387</td>
<td>0.37</td>
<td>0.65</td>
<td>0.44 [0.31, 0.64]</td>
</tr>
</tbody>
</table>

Suicide attempt was not disproportionately reported for efavirenz and other ARVs.

Fluoxetine and sertraline had EB05:2 for suicide ideation.

Suicide Attempt

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>Number of reports</th>
<th>EB05</th>
<th>EB95</th>
<th>EBGM ± 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>50</td>
<td>43</td>
<td>0.66</td>
<td>1.24</td>
<td>0.95 [0.63, 1.46]</td>
</tr>
<tr>
<td>Other ARVs</td>
<td>142</td>
<td>81</td>
<td>0.43</td>
<td>0.78</td>
<td>0.57 [0.41, 0.80]</td>
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</tbody>
</table>

Fluoxetine and sertraline had EB05:2 for suicide attempt.

Completed Suicide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>Number of reports</th>
<th>EB05</th>
<th>EB95</th>
<th>EBGM ± 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>3</td>
<td>0</td>
<td>0.37</td>
<td>0.73</td>
<td>0.50 [0.17, 1.47]</td>
</tr>
<tr>
<td>Other ARVs</td>
<td>13</td>
<td>3</td>
<td>0.27</td>
<td>0.56</td>
<td>0.36 [0.12, 0.99]</td>
</tr>
</tbody>
</table>

Fluoxetine and sertraline had EB05:2 for completed suicide.

Suicidality (Composite Term)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>Number of reports</th>
<th>EB05</th>
<th>EB95</th>
<th>EBGM ± 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>217</td>
<td>136</td>
<td>0.63</td>
<td>1.28</td>
<td>0.91 [0.64, 1.30]</td>
</tr>
<tr>
<td>Other ARVs</td>
<td>712</td>
<td>402</td>
<td>0.45</td>
<td>0.84</td>
<td>0.55 [0.44, 0.66]</td>
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</tbody>
</table>

Fluoxetine and sertraline had EB05:2 for composite suicidality.

Suicide Sensitivity Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>Number of reports</th>
<th>EB05</th>
<th>EB95</th>
<th>EBGM ± 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>10</td>
<td>7</td>
<td>0.49</td>
<td>0.96</td>
<td>0.67 [0.26, 1.66]</td>
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<tr>
<td>Other ARVs</td>
<td>136</td>
<td>55</td>
<td>0.35</td>
<td>0.69</td>
<td>0.44 [0.31, 0.63]</td>
</tr>
</tbody>
</table>

Fluoxetine and sertraline had EB05:1 for suicidal ideation.

CONCLUSIONS

No evident association between suicidality and antidepressants, including efavirenz, was observed.

DISCUSSION

These findings differ from a previously reported pooled analysis of clinical trials.

The association between efavirenz use and suicidality, as reflected in the product labeling warning, should be kept in mind when making treatment decisions.

As there is an increased risk of depression and suicidality among patients diagnosed with HIV infection, psychiatric screening and counseling are important aspects of clinical management, irrespective of ARV therapy choice.

Given the challenges of evaluating insufficient AEs, additional studies are needed to better evaluate the risk of serious psychiatric adverse events with efavirenz.

ACKNOWLEDGMENTS

The authors would like to acknowledge Derek Hluiton for the valuable advisory role he played in the interpretation of the data, Medical writing assistance was provided by Lorena Ralph of influence communications, Springer Healthcare, which was funded by Bristol-Myers Squibb.

REFERENCES


4. Personal communication with J. Daniel Seekins, Bristol-Myers Squibb, Hopewell, NJ, USA.