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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[1]
- Recently, a pooled analysis of four AIDS Clinical Trials Group (ACTG) studies (A5095, A5142, A5175, A5202), identified an increased rate of suicidality with efavirenz-containing regimens compared to efavirenz-free regimens:
  - Suicidality incidence per 1000 person-years was 8.08 (47 events) in the efavirenz group and 3.66 (15 events) in the efavirenz-free group, hazard ratio (HR): 2.28 (95% confidence interval [CI]: 1.27,4.10, p=0.006)[2]
  - 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 none included recognized psychiatric measures of suicidality or depression
- To further explore the potential association of efavirenz and other selected 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 manufacturers
- 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 ARV drugs, including efavirenz, with suicidality using real world data in the FAERS database collected from 1968 up to August 2012

METHODS

Searching the FAERS Database

- A disproportionality analysis was performed using the Multi-Item Gamma Poisson Shrinker (MGPS) method; a well-established technique that minimizes false-positive reporting rates[3]
- The drugs included in the analysis were efavirenz (including Sustiva® and ATRIPLA®), etravirine, nevirapine, atazanavir, darunavir and raltegravir, representing ARVs from different drug classes
- Suicidality was defined using the Medical Dictionary for Regulatory Activities (MedDRA) (version 15.0) preferred terms which included, “suicidal ideation”, “suicide attempt”, and “completed suicide”. In addition, a composite suicidality term was generated that combined all three MedDRA preferred terms
- Two parallel analyses were performed to assess the validity of the methodology using:
  - Fluoxetine and sertraline, antidepressants with a known association with suicidality
  - Raltegravir, an antiretroviral with rhabdomyolysis and myopathy listed as “uncommon” events* in the US prescribing information, as a sensitivity analysis

*Defined as between 1% and 0.1% (1/100 to 1/1000).
Available at: http://www.cioms.ch/publications/g4-benefit-risk.pdf (p136)

Statistical Analysis

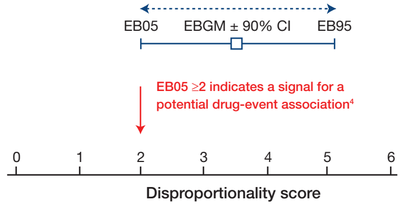
- A disproportionality analysis was performed for the selected drug and selected AE using the MGPS method
- The disproportionality measure, Empirical Bayesian Geometric Mean (EBGM), and the corresponding 90% CI (EB05, EB95) were estimated
- The threshold score above which a drug-event disproportionality signal is likely to be present is an EB05 ≥2[4]
- The measure of disproportionality was defined in terms of the relative reporting ratio (RRR) of observed to expected frequencies of reports mentioning both the selected drug (Y) and the selected AE (X), where:

$$\textit{Observed count} = \textit{Number of reports for event X with drug Y}$$

$$\textit{Expected count} = \frac{(\textit{Number of reports for event X}) * (\textit{Number of reports for drug Y})}{\textit{Total number of reports}}$$

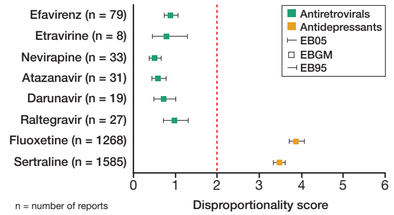
$$\textit{Relative reporting ratio} = \frac{\textit{Observed count}}{\textit{Expected count}}$$

- Using the MGPS method, the EBGM is derived from the RRR



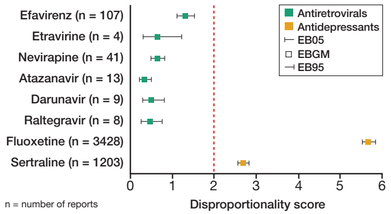
RESULTS

Suicidal Ideation



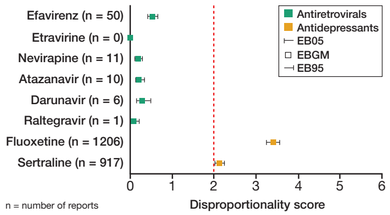
- Suicidal ideation was not disproportionately reported for efavirenz and other ARVs
- Fluoxetine and sertraline had EB05 ≥2 for suicidal ideation

Suicide Attempt



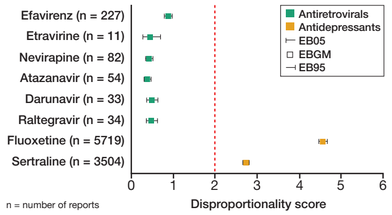
- Suicide attempt was not disproportionately reported for efavirenz and other ARVs
- Fluoxetine and sertraline had EB05 ≥2 for suicide attempt

Completed Suicide



- Completed suicide was not disproportionately reported for efavirenz and other ARVs
- Fluoxetine and sertraline had EB05 ≥2 for completed suicide

Suicidality (Composite Term)



- The composite term for suicide was not disproportionately reported for efavirenz and other ARVs
- Fluoxetine and sertraline had EB05 ≥2 for composite suicidality

Sensitivity Analysis

- Raltegravir had an EB05 of 2.334 for rhabdomyolysis and 2.333 for myopathy

CONSIDERATIONS

Strengths

- FAERS is a large, independent, public dataset containing real-world data that can enable identification of potential signals for rare AEs
  - The FAERS database and the tools used for its interpretation are overseen by the FDA

Limitations

- The quality of FAERS database records can vary and are typically reported with limited information
- Previously documented AE associations can lead to either underreporting or overreporting in the FAERS dataset
- Channeling bias can occur due to the warnings of suicide risk identified in the efavirenz label since 1998. This may lead providers to avoid using prescriptions of efavirenz in patients with a known history of mental health problems
- Observational data can never establish causality

CONCLUSIONS

- No evident association between suicidality and antiretrovirals, including efavirenz, was observed

DISCUSSION

- These findings differ from a previously reported pooled analysis of clinical trials[2]
- 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 persons diagnosed with HIV infection, psychiatric screening and counseling are important aspects of clinical management, irrespective of ARV therapy choice[5]
- Given the challenges of evaluating infrequent AEs, additional studies are needed to better evaluate the risk of serious psychiatric adverse events with efavirenz

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REFERENCES

1. Sustiva® (efavirenz) US prescribing information. Available at http://packageinserts.bms.com/pi/pi_sustiva.pdf
2. Mollan et al. 2013 *ID Week October 4th 2013*. San Francisco, CA
3. Suling et al. 2012 *Pharmaceutics* 4(4):607–640
4. Szarfman et al. 2004 *Pharmacotherapy* 24(9):1099–1104
5. Chippindale and French. 2001 *BMJ* 322:1533–5