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Tolerability of central nervous system symptoms among HIV-1 infected efavirenz users: analysis of patient electronic medical record data

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ABSTRACT

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor indicated for treatment of HIV-1 infection. Despite concern over EFV tolerability in clinical trials and practice, particularly related to central nervous system (CNS) adverse events, some observational studies have shown high rates of EFV continuation at one year and low rates of CNS-related EFV substitution. The objective of this study was to further examine the real-world rate of CNS-related EFV discontinuation in antiretroviral therapy naïve HIV-1 patients. This retrospective cohort study used a nationally representative electronic medical records database to identify HIV-1 patients ≥12 years old, treated with a 1st-line EFV-based regimen (single or combination antiretroviral tablet) from 1 January 2009 to 30 June 2013. Patients without prior record of EFV use during 6-month baseline (i.e., antiretroviral therapy naïve) were followed 12 months post-medication initiation. CNS-related EFV discontinuation was defined as evidence of a switch to a replacement antiretroviral coupled with record of a CNS symptom within 30 days prior, absent lab evidence of virologic failure. We identified 1742 1st-line EFV patients. Mean age was 48 years, 22.7% were female, and 8.1% had a prior report of CNS symptoms. The first year, overall discontinuation rate among new users of EFV was 16.2%. Ten percent of patients ($n = 174$) reported a CNS symptom and 1.1% ($n = 19$) discontinued EFV due to CNS symptoms: insomnia ($n = 12$), headache ($n = 5$), impaired concentration ($n = 1$), and somnolence ($n = 1$). The frequency of CNS symptoms was similar for patients who discontinued EFV compared to those who did not (10.3 vs. 9.9%; $P = .86$). Our study found that EFV discontinuation due to CNS symptoms was low, consistent with prior reports.

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Efavirenz (EFV); central nervous system (CNS); discontinuation; HIV-1

Introduction

In the US, approximately 1.2 million people were living with human immunodeficiency virus (HIV) at the end of 2011 (Centers for Disease Control and Prevention, 2014). About 50,000 new HIV infections occur each year, with the prevalence rate in adults estimated at approximately 0.45% (Centers for Disease Control and Prevention, 2012a, 2012b, n.d.). Treatment of HIV requires lifelong antiretroviral therapy (ART), adherence to which is crucial in preventing viral mutation, treatment resistance, poor health outcomes, and mortality (National Institutes of Health, 2013).

Efavirenz (EFV, Sustiva®; Bristol-Myers Squibb Company, Princeton, NJ, USA) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for the treatment of HIV Type 1 (HIV-1) infection. Approved in the US since 1998, EFV was first recommended in combination with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) as a regimen for initial therapy of HIV infection in the 2003 Department of Health and Human Services Guidelines (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2003, November 10). Atripla® (efavirenz/emtricitabine/TDF; Gilead Sciences, Inc. Foster City, CA, USA and Bristol-Myers Squibb, Princeton, NJ, USA), the co-formulation of EFV, FTC, and TDF as a single-tablet regimen, was approved in the US in 2006 for adults and adolescents 12 years of age and older (U.S. Food and Drug Administration, 2006).

The tolerability of EFV related to potential central nervous system (CNS) adverse events has generated interest in clinical trials and secondary research with mixed results. Clinical trial data show varied rates of CNS-related discontinuation, ranging from 2% to 11% (Kenedi & Goforth, 2011). Further, according to a systematic review of 37 clinical trials, overall EFV discontinuation was moderate as over 90% of patients remained on EFV-based 1st-line regimens for more than one year (Ford et al., 2015).

Findings from observational research also vary. A multi-center prospective study of EFV safety and

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tolerability in Spain determined a rate of EFV discontinuation due to CNS disturbances of 6% (Pérez-Molina, 2002). A Swiss study of longitudinal cohort data found that CNS-related EFV substitution occurred at a rate of under 4 substitutions per 100 person years (Elzi et al., 2010). However, a secondary data analysis in Denmark showed substantial rates of all-cause EFV discontinuation (26.2%) and of discontinuation due to neuropsychiatric disturbances, which includes both CNS and psychiatric symptoms, (16.1%) within the first year of use (Leutscher, Stecher, Storgaard, & Larsen, 2013).

Given the variation in findings on the extent to which EFV use leads to CNS effects and discontinuation, additional evidence is needed. The aim of our study was to further examine the topic of EFV tolerability as it relates to CNS symptoms using a real-world data source of electronic medical records (EMRs).

Methods

Data source

In this retrospective cohort analysis, we used 2008–2014 Cegedim® EMR data to determine the real-world tolerability of CNS symptoms related to efavirenz use in the treatment of HIV-1. The Cegedim Strategic Data Longitudinal Patient Database comprises a collection of longitudinal EMR data from a fixed panel of nationally representative providers in the US Individual patients were distinguished by unique identifiers in each information table of the EMR. The tables included patient-level demographic, clinical, laboratory (lab), and medication data, in addition to relevant provider information. Diagnostic information was included in the "Problems" table of the EMR in the form of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes and as searchable text in the corresponding text field. Physician reporting of patient symptoms was also included in the text field of the problem table. Medication information was described in the EMR "Medication" table in the form of searchable text or National Drug Codes.

Patients

We identified ART naïve HIV-1 patients (ICD-9-CM: 042, V08, 795.71) who were treated with EFV (in the form of Sustiva or Atripla) as a first-line ART regimen from 1 January 2009 to 30 June 2013. The first date of EFV use in that period, as indicated by the first date EFV appeared in the EMR medication table, was assigned as the index date. Patients were considered naïve and therefore new users if, based on the medication table, they did not use any HIV medication within six months prior to the index date (i.e., baseline period). The follow-up period began immediately after the index date and continued for a fixed period of 12 months. Based on prior research, we assumed the loss to follow-up due to mortality would be low during this period (Samji et al., 2013). Patients were removed from the analysis if they lacked evidence of services during the baseline or follow-up periods. We also excluded patients less than 12 years old and those with any indication of pregnancy at any point during the baseline or follow-up periods.

Study measures

The primary outcome was the frequency of EFV discontinuation due to CNS symptoms. This frequency was defined as the proportion of EFV initiators who subsequently discontinued the medication, who had an EMR notation of a CNS symptom of new onset within the prior 30 days, and who did not have virologic failure. It was assumed that if a symptom was severe enough to lead to discontinuation of a particular therapy that the physician would note this within 30 days of discontinuation. The 30 day window was selected for several reasons: expert physician opinion, an a priori hypothesis that discontinuation due to a CNS symptoms would occur soon after the reporting of CNS symptoms and a desire to prevent overestimation by allowing too wide of a time window. EFV discontinuation was defined as a switch from EFV to a replacement ART medication. The following medications were considered substitutes for EFV and their presence in the medication table was considered evidence of EFV (Sustiva) discontinuation: NNRTIs, integrase inhibitors (INSTIs), fusion inhibitors (FIs), or protease inhibitors (PIs). For Atripla, the presence of any new ART medication was considered a discontinuation of EFV. We did not consider as EFV discontinuation switching from a Sustiva-based regimen to Atripla, as might be done to simplify treatment.

The presence of a CNS symptom was defined as the report of any of the following symptoms in the EMR problem table by ICD-9-CM code or relevant keywords: abnormal dreams, dizziness, hallucinations, headache, impaired concentration, insomnia, or somnolence. New onset of a CNS symptom was defined as a symptom reported after initiation of EFV that either was not reported during baseline or, if present at baseline, was absent from at least one EMR during follow-up before being newly reported in a subsequent EMR. This was done to allow the inclusion of patients who had common symptoms before treatment, like headache, and still be

able to identify if these symptoms re-occurred after treatment initiation. Virologic failure, another possible cause of ART discontinuation, was defined as indication of viral load ≥200 copies/mL in the lab data. Viral load data were reported for 37.1% ($n = 647$) of patients during follow-up.

The secondary outcomes included time to EFV discontinuation; time from first report of a new onset CNS symptom to EFV discontinuation; and frequency of new onset CNS symptoms.

The following baseline measures were examined: age, gender, geographic region, race, or ethnicity, most recent CD4 cell count, most recent viral load, history of an AIDS-defining illness (Centers for Disease Control and Prevention, 2008), history of psychiatric symptoms, and history of CNS symptoms. The most recent CD4 count and viral load values were collected from the EMR lab table. History of an AIDS-defining illness was determined by searching the EMR problem table for an ICD-9-CM code or relevant keyword indicating an illness on the Centers for Disease Control and Prevention list of AIDS-Defining Conditions (Centers for Disease Control and Prevention, 2008). Using a similar method, the presence of comorbid psychiatric symptoms was determined by examining the EMR problem table for any of the following symptoms: dementia, schizophrenic disorders, episodic mood disorders, anxiety, dissociative and somatoform disorders, depressive disorders, suicidal ideation, and other miscellaneous mental health conditions.

Analysis

Descriptive statistics, including means, medians, standard deviations, and percentages, were reported for all study measures. Chi-square tests were used to test selected bivariate comparisons. The results were reported for all EFV new users and stratified by Atripla vs. Sustiva treatment groups. All data transformations and statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics

Baseline patient characteristics are presented in Table 1. Our cohort comprised 1742 HIV-1 treatment naïve patients who initiated EFV. Most patients ($n = 1409$) initiated EFV-based ART with Atripla, while 333 patients used EFV – along with other ARVs – in the form of Sustiva. The overall mean patient age was 48 years, and about 23% of patients were female. Most patients were from the South and Northeast, followed by the Midwest and West region of the US. The

Table 1. Baseline characteristics.

	Atripla $N = 1409$	Sustiva $N = 333$	All EFV users $N = 1742$
Age, mean (SD), y	47.0 (11.5)	52.1 (11.3)	48.0 (11.6)
Female, *n* (%)	321 (22.8)	75 (22.5)	396 (22.7)
Region, *n* (%)[a]			
Midwest	293 (20.8)	52 (15.6)	345 (19.8)
Northeast	466 (33.1)	105 (31.5)	571 (32.8)
South	501 (35.6)	126 (37.8)	627 (36.0)
West	146 (10.4)	50 (15.0)	196 (11.3)
Race, *n* (%)			
White	621 (44.1)	132 (39.6)	753 (43.2)
Black or African American	406 (28.8)	91 (27.3)	497 (28.5)
Hispanic or Latino	39 (2.8)	11 (3.3)	50 (2.9)
Asian	6 (0.4)	3 (0.9)	9 (0.5)
Other/unknown	337 (23.9)	96 (28.8)	433 (24.9)
CD4 count and viral load			
Patients with CD4 count data, *n* (%)	106 (7.5)	29 (8.7)	135 (7.7)
CD4 count (cells/μL) for patient data, mean (SD)	399.5 (224.6)	616.1 (342.5)	446.1 (268.4)
Patients with viral load data, *n* (%)	252 (17.9)	46 (13.8)	298 (17.1)
Viral load (copies/mL) for patient with data, mean (SD)	35,604.8 (123,322.4)	17,346.5 (92,734.6)	32,786.4 (119,161.9)
History of AIDS-defining illness, *n* (%)	85 (6.0)	17 (5.1)	102 (5.9)
History of psychiatric symptoms, *n* (%)	263 (18.7)	62 (18.6)	325 (18.7)
History of CNS symptoms, *n* (%)	113 (8.0)	28 (8.4)	141 (8.1)
Abnormal dreams, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	10 (0.7)	1 (0.3)	11 (0.6)
Hallucinations	0 (0.0)	0 (0.0)	0 (0.0)
Headache	38 (2.7)	11 (3.3)	49 (2.8)
Impaired concentration	14 (1.0)	3 (0.9)	17 (1.0)
Insomnia	63 (4.5)	17 (5.1)	80 (4.6)
Somnolence	1 (0.1)	0 (0.0)	1 (0.1)

[a]Geographic region unknown for 0.2% of EFV users.

demographic characteristics were similar between the Atripla and Sustiva groups.

The mean CD4 count at baseline among patients with available data ($n = 135$, 7.7%) was 446.1 cells/μL as shown in Table 1. For patients with baseline virologic data ($n = 298$, 17.1%), the mean viral load was 32,786.4 copies/mL. About 6% of EFV patients had a history of an AIDS-defining illness at the time of treatment. The percentage of patients having a history of psychiatric symptoms was 18.7%, of which depressive disorders (10.6%) and anxiety (7.2%) were most common (results not shown). Approximately 8% of patients starting EFV had a prior report of a CNS symptom. The most prevalent CNS symptoms reported during baseline were insomnia (4.6%), headache (2.8%), and impaired concentration (1.0%).

First-year efavirenz discontinuation

As shown in Table 2, in the first year, 1.1% ($n = 19$) of all patients discontinued EFV within 30 days of reporting a new onset CNS symptom: insomnia ($n = 12$), headache ($n = 5$), impaired concentration ($n = 1$), and somnolence ($n = 1$). The discontinuation rate of EFV due to any cause was 16.2% and was more common among Sustiva users compared to Atripla users (30.0% [$n = 100$] vs. 12.9% [$n = 182$]; $P < .001$). Multiple probable causes for discontinuation were identified. Among the subset of patients who discontinued EFV, 6.7% ($n = 19$) switched from EFV to a replacement medication likely due to CNS symptoms, 5.7% due to virologic failure, 30.5% because of other possible adverse events, and 57.1% for reasons that could not be identified.

Table 2. Frequency and probable cause of EFV discontinuation.

	Atripla $N = 1409$	Sustiva $N = 333$	All EFV users $N = 1742$
Discontinue EFV in one year, *n* (%)	182 (12.9)[a]	100 (30.0)[a]	282 (16.2)
Frequency of discontinuation by probable cause, among all patients, *n* (%)			
Virologic failure	12 (0.9)	4 (1.2)	16 (0.9)
CNS symptom[b]	14 (1.0)	5 (1.5)	19 (1.1)
Other possible adverse event	54 (3.8)	32 (9.6)	86 (4.9)
Unknown	102 (7.2)	59 (17.7)	161 (9.2)
Frequency of discontinuation by probable cause, among patients who discontinued, *n* (%)			
Virologic failure	12 (6.6)	4 (4.0)	16 (5.7)
CNS symptom[b]	14 (7.7)	5 (5.0)	19 (6.7)
Other possible adverse event	54 (29.7)	32 (32.0)	86 (30.5)
Unknown	102 (56.0)	59 (59.0)	161 (57.1)
Frequency of discontinuation by symptom-specific cause, among patients who discontinued due to a CNS symptom[b], *n* (%)			
Headache	3 (21.4)	2 (40.0)	5 (26.3)
Impaired concentration	1 (7.1)	0 (0.0)	1 (5.3)
Insomnia	9 (64.3)	3 (60.0)	12 (63.2)
Somnolence	1 (7.1)	0 (0.0)	1 (5.3)

[a]$P < .001$.
[b]Symptom is newly onset after EFV initiation.

Table 3. Time from EFV initiation and from first CNS symptom to discontinuation among patients who discontinued EFV due to CNS symptom.

	Atripla $N = 14$	Sustiva $N = 5$	EFV users who discontinued EFV due to CNS symptom $N = 19$
Days from EFV initiation to discontinuation, mean (SD) [median]	108.5 (59.1) [111]	190.0 (125.9) [210]	129.9 (86.0) [128]
Days from first CNS symptom[a] to discontinuation, mean (SD) [median]	11.6 (25.5) [0]	3.8 (8.5) [0]	9.6 (22.3) [0]

[a]Symptom is newly onset after EFV initiation.

Patients who discontinued EFV in association with reported CNS symptoms did so at a mean of 129.9 days (SD = 86) after starting therapy and 9.6 days (SD = 22.3) after first reporting the symptom (Table 3). The mean time to discontinuation for all patients who discontinued EFV, irrespective of probable reason, was similar at 128.4 days (SD = 103.4; results not shown).

First-year reporting of CNS symptoms

Ten percent of patients ($n = 174$) had a report of a new onset CNS symptom after initiating the medication (Table 4). Reports of insomnia symptoms (5.3%) and headache (3.3%) were most prevalent, followed by dizziness (1.0%), impaired concentration (0.7%), somnolence (0.2%), and hallucinations (0.1%). The 2% difference in CNS symptom reporting from before to after EFV initiation was statistically significant (8.1% vs. 10.0%, $P = .035$). New onset CNS symptoms were reported at similar rates among patients who discontinued EFV compared to those who stayed on the medication (10.3% [$n = 29$] vs. 9.9% [$n = 145$], $P = .857$; results not shown). New onset CNS symptoms in a subset with no prior history of CNS symptoms were also reported at similar rates among patients who discontinued EFV compared to those who stayed on the medication (10.2% [$n = 26$] vs. 8.4% [$n = 113$]; results not shown).

Table 4. Report of new onset CNS symptoms after EFV initiation.[a]

	Atripla $N = 1409$	Sustiva $N = 333$	All EFV users $N = 1742$
Any CNS symptom while on EFV,[b] *n* (%)	150 (10.6)	24 (7.2)	174 (10.0)
Abnormal dreams, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	14 (1.0)	3 (0.9)	17 (1.0)
Hallucinations	1 (0.1)	1 (0.3)	2 (0.1)
Headache	48 (3.4)	9 (2.7)	57 (3.3)
Impaired concentration	11 (0.8)	1 (0.3)	12 (0.7)
Insomnia	83 (5.9)	10 (3.0)	93 (5.3)
Somnolence	3 (0.2)	1 (0.3)	4 (0.2)

[a]Occurred while patients still had evidence of EFV up to 1 year after initiation.
[b]Patients might have more than one type of CNS symptom.

Discussion

Our analysis of EMR revealed that the discontinuation rate of EFV due to CNS symptoms is low. In a sample of 1742 HIV-1 antiretroviral-naïve patients, about 1% of EFV initiators discontinued the drug in the 30 days following the identification of a new CNS symptom. This finding is consistent with observational and clinical trial data showing CNS-related EFV discontinuation rates of less than 4 patients per 100 person years and 2.1%, respectively (Bristol-Myers Squibb, 2016; Elzi et al., 2010). CNS symptoms are reported more often after than before initiation of EFV-based treatment, yet only to a small degree. Further, CNS symptom reporting was similar between patients who discontinued EFV and those who stayed on the medication, pointing to other (non-CNS) probable causes of discontinuation. Despite concerns raised over EFV tolerability, our study suggests that CNS symptoms associated with EFV use largely do not interrupt therapy.

Eighty-four percent of patients stay on EFV in the first year of use according to our investigation, which compares well with other real-world studies in which 74–90% of patients remained on EFV-based first-line regimens for more than one year (Elzi et al., 2010; Ford et al., 2015; Leutscher et al., 2013). For patients who stop taking EFV, multiple probable reasons may be determined. We found that virologic failure and CNS symptoms were each identified in about 6% of discontinuations. The remaining patients who substituted EFV with a replacement antiretroviral agent did so following report of other possible adverse events or for reasons that could not be identified.

Patients who switched therapy appeared to tolerate EFV for several months before discontinuation, which was contrary to our hypothesis that discontinuation would occur soon after initiation. On average, patients who discontinued EFV did so after approximately four months of therapy. EFV discontinuation due to CNS symptoms occurred in a similar period of time after the first EMR report of a symptom. A Danish observational study of medical records found a lag in EFV discontinuation of up to 12 months for one-third of patients who stopped use (Leutscher et al., 2013). We believe the time to discontinuation may be driven by the timing of the doctor visit, which – whether deferred due to provider or patient factors – could delay the discussion of problems with a medication or, simply, the opportunity to record (and for us to observe) an earlier discontinuation.

Treatments following EFV discontinuation varied greatly and were difficult to interpret. For example, discontinuation of EFV was more than twice as common for Sustiva compared to Atripla patients. The reason for this difference is unclear, but may be related to treatment simplification through switching to a single-tablet regimen other than Atripla. In addition, many patients switched from EFV to a protease inhibitor or to the integrase inhibitor raltegravir, the reasons for which we could not discern. Findings from comparative studies, suggest patients who switched from Atripla to other single-tablet regimens (e.g., Complera® [emtricitabine, rilpivirine, TDF; Gilead Sciences, Inc. Foster City, CA, USA] or, less commonly, Stribild® [elvitegravir, cobicistat, emtricitabine, TDF; Gilead Sciences, Inc. Foster City, CA, USA]) likely did so for reasons of tolerability (Cohen et al., 2010; Gallant et al., 2013; Shalit et al., 2013; Wohl et al., 2013).

This study has several limitations. First, EMR data are derived from physician reporting rather than from verified health service utilization (i.e., administrative claims). Completeness of physician record-keeping is affected by many things, and not all symptoms or treatments are recorded. If CNS symptoms were systematically underreported, we would have underestimated the rate of discontinuation due to these symptoms. Second, actual reasons for discontinuing medication were not directly reported. We imputed them by identifying symptoms in conjunction with discontinuation. If symptoms were present at the time of discontinuation, but were not the reason for the discontinuation, we would have overestimated the rate. In addition, we have likely underestimated the rates of reason-specific discontinuations due to missing probable cause data for more than half of discontinuations. However, overall discontinuation rate was low, and it is unlikely that all discontinuations due to unknown causes were actually due to CNS symptoms. Third, our measures of virologic failure and of CD4 counts relied on the availability of related lab data, which were reported by physicians for some but not all patients. Fourth, the data used were derived from a non-random subset of all practices and may not be representative of typical patients. The mean age of 48 years in our sample was higher than the peak age range for HIV incidence in the US (25–34 years) (Centers for Disease Control and Prevention, 2015), possibly because our sample reflects only insured patients who tend to be older than the uninsured population. Our sample was also composed of more white than black or African-American patients, although national estimates of HIV infection show the reverse of this pattern (Centers for Disease Control and Prevention, 2015). Nonetheless, the distributions of gender and geographic region in our study were similar to published estimates (Centers for Disease Control and Prevention, 2015).

Conclusion

The rate of discontinuation of EFV as a result of CNS adverse events is low. EFV discontinuation due to CNS

symptoms occurred in one percent of our sample during the first year of use, consistent with prior reports. Patients who experience CNS symptoms after starting first-line ART with EFV seem to tolerate it as evidenced by their continued use of the medication. Future work should focus on two things: first, improving EMR data entry and collection to better define reasons for discontinuation of therapy and second, validating physician reporting of medication use in EMR data against a gold standard of pharmacy dispensing data.

Disclosure statement

In accordance with Taylor & Francis policy and our ethical obligations as researchers, we are reporting that LR and JM are salaried employees and shareholders at Bristol-Myers Squibb. MB, TB, EC, SR and EP are employees of Partnership for Health Analytic Research, LLC, a health services research company paid by Bristol-Myers Squibb to conduct this research.

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