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

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BACKGROUND

- More than 1.2 million people in the United States are living with human immunodeficiency virus (HIV).[1]
- Adherence to antiretroviral therapy (ART) is vital in preventing morbidity and mortality.[2]
- Efavirenz (EFV, Sustiva) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated for the treatment of HIV type 1 (HIV-1).
  - Approved in the U.S. in 1998, EFV was first recommended 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 (DHHS) Guidelines.[3]
  - Atripla, the co-formulation of EFV/FTC/TDF as a single tablet regimen, was approved in the U.S. in 2006.
  - Concerns exist over EFV tolerability in clinical trials and practice, particularly related to central nervous system (CNS) adverse events.
    - 53% of patients on EFV in controlled trials reported CNS symptoms. 2.1% of patients discontinued therapy as a result.[4,5]

OBJECTIVE

- To assess the real world tolerability of CNS-related symptoms due to EFV use.

METHODS

Study design & data source

- Retrospective cohort study using a large electronic medical records (EMR) database from 7/1/2008 to 6/30/2014.

Selection criteria & timeline

- Inclusion criteria:
  - Previously untreated HIV-1 infected patients
  - Treated with 1st-line regimen including Sustiva or Atripla (first day of treatment initiation is the index date)
- Exclusion criteria:
  - Age <12 years
  - Any enrollment gap in the period from 6 months pre-index to 12 months post index

Primary outcome

- Frequency of EFV discontinuation due to CNS-related symptoms
  - Defined as percentage of EFV initiators who switched to replacement ART within 30 days of a new onset CNS-related symptom (in the absence of virologic failure).

RESULTS

New onset CNS-related symptoms after EFV initiation

- 10% of patients on EFV (n=174) reported at least one CNS-related symptom during the one year follow-up period (Figure 1). Of these, 19 discontinued therapy due to CNS-related symptoms.

EFV discontinuation

- 16.2% (282/1,742) of new users discontinued EFV over one year of follow-up (Table 2).
  - Discontinuation was 30.0% (100/333) among Sustiva users and 12.9% (182/1,409) among Atripla users.
  - 57.1% (161/282) of new users who discontinued EFV had no CNS-related symptoms recorded in the 30 days prior to their discontinuation of EFV.

Table 1. Baseline characteristics

Characteristic	EFV New Users (N=1,742)
Age, mean (SD), y	48 (11.6)
Male, %	77.3
Race/Ethnicity, %	
White	43.2
Black or Hispanic	31.4
Other or Unknown	25.4
Region, %	
Midwest	19.8
Northeast	32.8
South	36.0
West	11.3
History of AIDS defining illness, %	5.9
History of psychiatric symptom*, %	18.7
Depressive disorders	10.6
Anxiety	7.2
History of CNS symptom†, %	8.1

*Psychiatric symptoms include: 1) depressive disorders, 2) anxiety, dissociative and somatoform disorders, 3) dementias, 4) schizophrenic disorders, 5) episodic mood disorders 6) suicide ideation, and 7) other miscellaneous mental health disorders
†CNS symptoms include: 1) abnormal dreams, 2) dizziness, 3) hallucinations, 4) headache, 5) impaired concentration, 6) insomnia and 7) somnolence

Figure 1. Report of new onset CNS-related symptoms: Before and after EFV initiation among EFV new users

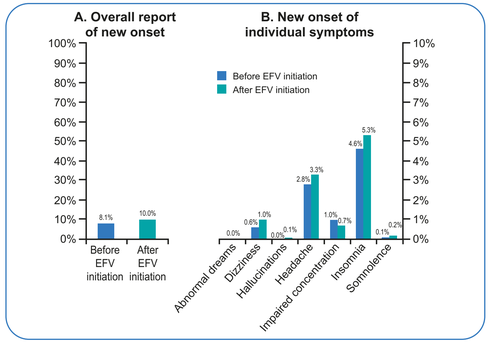

Table 2. Frequency and probable cause of EFV discontinuation

	Atripla N=1,409 (80.9%)	Sustiva N=333 (19.1%)	EFV New Users N=1,742 (100%)
Discontinue EFV over one year of follow-up, % (n)	12.9 (182)	30.0 (100)	16.2 (282)
Frequency of discontinuation by probable cause, all EFV New Users, % (n)			
Virologic failure	0.9 (12)	1.2 (4)	0.9 (16)
CNS-related symptom*	1.0 (14)	1.5 (5)	1.1 (19)
Other possible AEs	3.8 (54)	9.6 (32)	4.9 (86)
Unknown	7.2 (102)	17.7 (59)	9.2 (161)

*Insomnia (n=12), headache (n=5), impaired concentration (n=1), somnolence (n=1).

- Overall, 1.1% (19/1,742) of new users discontinued EFV due to reported CNS-related symptoms.
- Mean time to EFV discontinuation due to reported CNS-related symptoms was 129.9 days, on average 9.6 days following the report of symptoms.
- Frequency of CNS symptoms was 10.3% in EFV discontinuers vs. 9.9% in those who remained on EFV.

DISCUSSION

- We found that reports of CNS symptoms and discontinuation occurred about 4 months after EFV initiation.
- Consistent with a large prospective cohort analysis (N=1318),[6] we observed a low rate of EFV discontinuation due to CNS-related symptoms.
- Many discontinuations occurred for unknown reasons or were thought to be unrelated to EFV use.
- A limitation of analyzing EMR data is that reports of symptoms and medication use are not verified and are unlikely to be fully reported.
- Consistency was found in the frequency of CNS symptoms prior to and following EFV initiation, as well as between EFV discontinuers and continuers.

CONCLUSIONS

- EFV appears to be well tolerated in this analysis of real world EMR data. EFV discontinuation due to CNS-related symptoms was uncommon.
- CNS-related symptoms are common prior to EFV use and occur similarly after patients initiate EFV.
- Improvements in EMR data entry and collection may help to better define reasons for discontinuation of antiretroviral therapy.

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