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**Does Etravirine decrease central nervous system
(CNS)/neuropsychiatric (NPS) adverse events compared to
Efavirenz, in HIV positive patients?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Etravirine (ETR) decreases adverse reactions on the central nervous system (CNS) compared to Efavirenz (EFV) in Human Immunodeficiency Virus (HIV) positive patients.

STUDY DESIGN: Review of three, English language, primary randomized controlled trial studies published in 2011.

DATA SOURCES: Three randomized controlled trials studying the possible decrease of ADR's in HIV positive patients who are taking Efavirenz compared to study medication Etravirine.

OUTCOME(S) MEASURED: Outcomes measured were by surveys from patients that assess the development or cessation of CNS ADR's. The self reported questionnaire was grade on a scale of 0-4 rating where 4 was reported as life threatening. Another survey included the Depression Anxiety and Stress Scale (DASS). The CNS ADR's included, but was not limited to dizziness, depression, anxiety, headache, and somnolence.

RESULTS: In the article by Nelson et. al., there was a statistically significant benefit for etravirine over efavirenz for NPS adverse events, most of the adverse events were grade 1 (mild) or grade 2 (moderates) in intensity. There was no significant difference between the arms in the number. The other two article reviews showed that ETV was not superior to EFV regarding CNS ADR's.

CONCLUSIONS: Efavirenz is not superior to Etravirine, in regards to decreasing CNS ADR's in HIV positive patients.

KEY WORDS: HIV positive patients, Central Nervous System ADR's, AIDS

Introduction

The human immunodeficiency viruses (HIV), types I and II, causes cellular or humoral immune dysfunction possibly leading to acquired immune deficiency syndrome (AIDS). HIV infects all cells containing the T4 antigen, primarily the CD4 helper induced lymphocytes. The result is a dysfunction of the immune system leading to cell fusion or cell death. AIDS is defined as a CD4 count <200 cells/mcL or CD4 < 14%. The end result is the patient is at an increased risk for opportunistic infections, possibly leading to death.

The incidence of HIV affects more than 40 million people worldwide. The highest prevalence is in Central and East Sub-Saharan Africa. 1 million Americans are affected, and there are 50,000 new infections/year. 60% of the new cases are African American (AA) and AIDS is the number 1 cause of death in the AA community ages 25-34 in the US. The lifetime treatment cost of an HIV infection is estimated at \$379,668 (in 2010 US dollars).⁴ With such a large prevalence of this disease, as a physician assistant, there will be patients that we need to know how to treat and increase a patients quality of life and protect them from opportunistic infections. This number varies due to disease complications and the need for multiple specialty visits. Each, HIV positive patient should visit their primary care physician, at least 4 times per year. If a patient develops complications or has a rapidly increasing viral load, they may need to visit other physicians including, but not limited to, infectious disease, and pulmonologist. Poor compliance can cause the need for increased office visits per year.⁵

Through extensive research we know that transmission of HIV is via blood, semen, vaginal secretions, or IVDA. The virus uses macrophage as the reservoir. The

macrophages allow the virus to enter other organs, leading to organ damage. HIV causes immunodeficiency through viral replication after attaching to T4 (CD4) antigen. Once attached to the cell, the virus attaches to the DNA and through an enzyme produced by the virus, reverse transcriptase, the RNA is incorporated into the DNA, where it can be passed onto other cells, through DNA replication. Even though we know a great deal about HIV, we do not know exactly how to completely stop the replication of the virus, essentially leading to a cure. The treatments today have made great advances in science, allowing patients to live a manageable life with the disease.

The gold standard of treating HIV positive patients depends on if the patient is symptomatic or asymptomatic and their CD4 count. Serial viral load assessments and CD4 count guide therapy. Antiviral treatment should begin in all symptomatic patients. Asymptomatic patients should be started on antiviral treatment if CD4 lymphocytes < 350 (starting between 350-500 is controversial), rapid declining CD4 lymphocyte count or rapidly increasing HIV viral load, viral hepatitis co-infection, HIV related cancers, HIV neuropathy, and pregnancy.⁴

Patients must take 3 medications from at least 2 different categories including nucleoside reverse transcriptase inhibitors (NRTI), protease Inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as Efavirenz (EFV), entry inhibitors, and integrase inhibitors. Currently there is no cure for HIV positive patients, but the goal of treatment is to decrease the viral load, increase the quality of life, and prevent complications from opportunistic infections. EFV is apart of the standard treatment, but consequently causes central nervous system/neuropsychiatric side effects including, but not limited to, dizziness, insomnia, depression, anxiety, and impaired concentration.

Current research is hopeful that Etravirine (ETR) will prove to be a superior option to EFV, in efficacy and tolerability, decreasing CNS adverse events.

Objective

The objective of this selective EBM review is to determine whether or not “etravirine decreases central nervous system adverse events in HIV positive patients?”

Methods

The population studied were adults (>18 years of age) who are HIV positive. The main intervention was antiviral, ETR. The studies compared patients taking ETR and EFV. Outcomes were measured using self-reported surveys assessing the development or cessation of CNS ADR's. The questionnaires regarding CNS side effects were graded on a scale with a 0-4 rating where 0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = life threatening. The other survey was the Depression Anxiety and Stress Scale (DASS). The CNS ADR's included, but not limited to, dizziness, depression, anxiety, headache, and somnolence.

The 3 randomized control trials (RCTs) were found using the search engines OVID, Medline, and PubMed. The language used for the articles selected was English. The types of studies included 2 randomized, double blinded, controlled trials and 1 randomized, crossover controlled trial. All the articles fit the inclusion criteria of randomized, controlled, double blind, and from 1996 or later. Exclusion included systemic reviews and meta-analyses. Article focused on outcomes that were of importance to the patient (Patient Oriented Evidence that Matters or POEMS). All 3 of

the articles compared EFV and ETR. **Table 1** demonstrates the demographics of the studies included. The author, using the key words HIV positive patients, central nervous system adverse events, and AIDS treatments, did a detailed research. Statistics were reported using p-values, relative risk increase (RRI), absolute risk increase (ARI), and number needed to harm (NNH).

Outcomes Measured

Outcomes measured in all the studies assessed the decrease or development of CNS ADR's reported by patient questionnaire. All three of the studies used a graded scale 0 – 4 (previously discussed), and DASS. The severity of the symptoms being measured, are very important to the patient, thus qualifying the outcome as POEM.

The DASS is based on a dimensional rather than categorical, self reported survey that measures the negative emotional states of depression, anxiety, and stress. This scale contains 42 questions. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The Anxiety scale evaluates skeletal muscle effects, situational anxiety, and experiences of anxious affects. The Stress scale assesses the ability to relax, level of nervousness, and how easily someone is agitated/irritable. The scale uses a 4 – point severity scale (0 – 3, 0 = absent, 3 = applied to me very much, or most of the time) to rate the degree that the patient was experiencing symptoms of depression, anxiety, and stress in the past week. This scale was chosen for its high internal consistency, temporal stability, and stable factor structure applying to clinical and normal samples.²

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (Yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Nelson ¹ (2011)	RCT, double blind	157	Median age was 38 for both arms; Etravirine arm 18-63; Efavirenz arm 19-66	Antiretroviral treatment naive Individuals, with HIV- RNA levels above 5000 copies/ml	Genotypic or phenotypic resistance to antiretrovirals at the screening visit	18	Etravirine 400 mg tablet once a day or Efavirenz 600 mg tablet once a day
Nguyen ² (2011)	RCT, crossover	58	Median age was 47 (42- 55)	Patients aged 18 years or older, on stable HAART including EFV and with undetectable HIV-RNA (<50 copies), for at-least 3 months	Pregnant or patients with known or severe psychiatric illness	0	Etravirine 400 mg four times daily and placebo
Waters ³ (2011)	RCT, double blind	38	Median age was 43 (26- 64)	Undetectable plasma viral load (< 50 copies/ml) and CD4 cell count greater than 50 cells/ml at screening.	Exposure to etravirine, psychiatric condition, viral hepatitis, AIDS defining illness, significant laboratory abnormality, resolution of CNS toxicity between screening and baseline, disallowed concomitant medication, pregnant or breastfeeding	0	2 NRTI + Etravirine 400 mg four times a day + Efavirenz – placebo or 2 NRTI + Efavirenz 600 mg four times a day + Etravirine- placebo

Results

This EBM review was completed on three randomized controlled trials (RCTs). Two of them had a study period of 12 weeks, and one study was 24 weeks total. The studies were all double blind, and included one study that was crossover study, where the other two were the classic RCT. All three of the articles used dichotomous data to present the outcomes and answer the objective.

In Nelson et al. the study population included mainly white men with an average age of 36, had a baseline CD4 count of 302, and a total of 157 patients. The patients included in this study were treatment naïve individuals. Patients were randomized into two groups. One ETR group (n=79) with a dosage of 400 mg once daily, and the other group (n=78) was treated with EFV 600 mg once daily, and both medications were given by mouth. In the intent-to-treat analysis, 13 of 79 individuals (16.5%) in the ETR arm and 36 of 78 individuals (46.2%) in the EVF arm showed at least one grade 1-4 drug related treatment-emergent neuropsychiatric adverse event ($p < 0.001$).¹ **Table 2**

In this study, 5 individuals that were in the ETR arm experienced serious adverse events (SAEs) compared to the other where only 3 subjects reported SAEs with EFV. Four patients in each group did discontinue the study due to a grade 2 (moderate) and grade 3 (severe) rash; two patients had each type of severity in each group.

The Nguyen et al. RCT, which was crossover study at 6 weeks, had 55 patients complete the study. These patients had to have contained less than 50 copies/ml of HIV-RNA. This group had a median CD4 count of 589 cells/microliter. These patients

needed to be on EFV for a total of 3.9 years. The patients received dosages of ETR 400 mg four times a day and EFV-placebo in the ETR-first group, and then in the EFV-first group with EFV and ETR-placebo. Patients who continued EFV during the first phase of the trial preferred EFV (15/21, 71%), where as patients who started with ETR were more likely to prefer ETR (n=16/17, 94%).² This was shown by a strong significance with a $p < 0.0001$.² **Table 3**

At the end of the study the treatment preference was assessed at the final visit. The self reported desired treatment was assed at the first 6 weeks vs. the last 6 weeks of the 12-week trial. Sixteen patients preferred EFV and 22 preferred ETR, and 17 subjects did not express a preference. This seemed to also correspond to what medication you were started on. The people who were started on EFV preferred EFV and vs. versus ($P < 0.0001$).² Two SAE's were reported, but when investigated where concluded that they were not related to either of the study medications.

Table 2: ETR vs. EFV

Study	P value	CER	EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
Nelson ¹	$P < 0.0001$	0.462	0.165	-0.643	-0.297	3

Table 3: ETR vs. EFV, crossover study

Study	P value	CER	EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
Nguyen ²	$P < 0.0001$	0.71	0.94	0.32	0.23	4

Waters et. al., study included 38 men, where 20/18 were randomized to immediate switch/delayed switch; median CD4 count was 444/498 cells/microliter, respectively.³ The median age of the study was 43 years of age. Between the two groups that were treated and switched, at the 12-week mark, there was a major decline in CNS adverse events, such as insomnia and anxiety. The study lasted for a total of 24 weeks and contained two phases. The groups were treated with ETR 400 mg every day or EFV 600 mg every day. Immediate switch G2-4 CNS adverse events: 90% at baseline, 60% at week 12 (P=0.041).³ Delayed switch G2-4 CNS adverse event: 88.9% at baseline, 81.3% at week 12 (P=ns).³ In this study the CNS score that was graded using the interquartile ranges (IQRs) did not show a significant difference between the study medication and standard treatment (P=0.534).³

The CNS scores between the two groups were similar, with the exception of insomnia. Between the two arms of the study, at baseline there was a report of similar CNS adverse events. Ninety percent were found in the immediate switch arm, and 88.9% in the delayed switch had at least grade 2-4 CNS adverse events.

Table 4: ETV vs. EFV

Study	P value	CER	EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
Waters ³	P=0.534	0.060	0.813	12.55	0.753	2

There were very few patients that withdrew from the studies due to serious adverse events (SAE). In Nelson et. al, only 18 patients withdrew from the study, and in the others no one withdrew. Four patients in the etravirine arm and eight in the efavirenz withdrew due to ADR's, and more specifically, one patient in the

etravirine arm and five in efavirenz arm discontinued study medication due to NPS ADR's.¹ All the patients discontinued the study due to a grade 2 and 3 rash. Regardless, if the study medication decreased the CNS adverse events, it was considered safe and tolerable. In the studies the NNH seemed very high. NNH is defined as the number of patients who, if received the experimental treatment, would result in one additional patient being harmed.⁶ For example, in the Neslon et al. study, the NNH was 3, which means that for every 3 people that take the study medication, one will experience an ADR. This information can be used by the healthcare provider to assess how many people could potentially be harmed by the study medication, and if this medication is a good idea to use.

Discussion

EFV is a second generation NNRTI, and a common treatment in the HIV positive population. A large number of patients suffer from CNS adverse events from EFV. Regardless of the adverse effects, it is still the preferred medication, along with a combination of medications. These three studies were to possibly find the cure for the CNS adverse events while still trying to repress the viral infection of this population, by switching patients from EFV to ETR. At the end of the studies, there were mixed reviews on if one medication was better than the other. The improved NPS adverse event profile of etravirine is consistent with other studies that show there are more adverse events with efavirenz.¹ Patients on long-term EFV do not as a rule, prefer ETR, nor do those on a stable and extended EFV treatment sense any more CNS adverse events after switching to ETR.² This study demonstrates an

improvement in several measures of CNS toxicity when switching from EFV to ETR in patients stable on an EFV-based regimen.³ There need to be more studies in order to better asses the ability to see if there is truly a decrease in adverse events when switching from EFV to ETR.

Longer-term follow-up is required to determine whether the safety benefits of etravirine are sustained, and if there is also durable HIV-RNA suppression.¹ As the study of ETR continues to move forward I think that it needs to include a larger population regarding gender and sexuality. The study populations, in all the articles, were white men, and reported to be MSM. This medication could possibly not have the same positive effects on different races, and should be studied. The fact that the one study was a crossover study was impressive to me, to see if the medication really made a great impact on the patient compared to the other. This allowed researchers to address the effects of two different medications on one person.

In one of the studies, the patients had to be on a stable dose of EFV, to be included in the study, whereas the other two studies required you to be treatment naïve. Those that were on a stable treatment with EFV for at least 3 years could have possibly been bias.² More significant clinical data could have been collected if all the patients had not experienced this treatment before.

Etravrine could also have different results if patients were not as healthy as those individuals in the study. Since their viral load was low and CD4 count was of good measure, the medication possibly could not have worked as well or could cause harm to the patients in this setting. This is an area that could come along with

more knowledge as more testing is done on medications to help decrease CNS adverse events.

Conclusion

The studies reviewed had conflicting data regarding if etravirine decreases CNS side effects compared to efavirenz in HIV positive patients. ETR might be a tolerable and effective medication in combo with a 2 other medications from at least two different categories, but there seems to be the need for more testing and analysis to be done. The study by Nelson et. al. did show promising results, where CNS adverse events were decreased with patients who took ETR. The other two studies did not show any more benefit than the traditional NNRTI, EFV.

Future studies should evaluate the study population to mimic society a bit better, which will allow the true assessment of the medication across different backgrounds. HIV is a chronic disease that affects any person regardless of race, gender, and sexuality. Longer and more thorough studies need to be completed in order to truly assess the efficacy and tolerability of ETR versus EFV.

The study medication needs to be more consistent amongst the study population. Some patients, were on a combo medication, mimicking the normal HIV medication regimen, whereas the other two studies, just treated the study population with ETR or EFV. This can cause inconsistent results because we are not sure if the study medication is interacting with the other drugs, or actually causing ADR's. A more consistent drug treatment is warranted.

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