

Late Onset and Long Term Recovery of Neuropsychiatric Side-Effects of Efavirenz in HIV Infected Adult: A Case Report

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Abstract: Efavirenz (EFV) is an Anti Retroviral (ARV) as one of the class Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), which most frequently used to treat Human Immunodeficiency Virus (HIV) infection in the multidrug regimens as a Highly Active Anti Retroviral Therapy (HAART). It has demonstrated high anti retroviral efficacy and is currently a first-line drug. Although its reported has high efficacy and wide acceptance, EFV use has been associated with some of the side-effects. Neuropsychiatric Side-Effects (NPSEs) of EFV based regimens might be as the main reasons for non-adherence, switch and discontinuation of HAART that may lead to the treatment failure. Therefore to distinguish, all the doctors in the primary health care have to be aware, to work carefully and continuously monitor the clients.

Keywords: Adult, HIV infection, Efavirenz, Neuropsychiatric Side-Effects, Long term

1. Introduction

EFV is one of the medications used in combined Anti Retroviral Therapy (ART) for the HIV infection management. The predominant metabolism in the liver by the CYP450 enzyme system and it has a long half-life (40-55 hours).¹⁻³ The anti retroviral activity by binding directly to the enzyme reverse transcriptase, inhibit the viral replication. Almost a half of patients on EFV experiencing the NPSEs, and tend to occur within the first few days after initiation of therapy and then resolve spontaneously within the first 4-6 weeks.^{2,4} The most commonly manifestation of NPSEs have been reported in patients on EFV based regimen ART such as nightmares (bad/abnormal dream), dizziness, confusion and insomnia/difficulty sleeping, impaired/inability to concentrate.^{2,5,6} Its tend to occur within the first few days after initiation of therapy then resolve spontaneously within the first 4-6 weeks but in some cases can occurred late with long term recovery.^{1,2,5,7,8}

We reported a case with NPSEs of EFV with late onset (after almost a year starting EFV based regimen) and long term recovery (after more then three months).

2. Case Presentation

Case details and demographic information

The patient first presented as the outpatient at Merpati Clinic, Wangaya hospital in Denpasar, Bali, Indonesia on the fourteen of april two thousand fourteen (14/04/2014). The patient is male aged 68-years-old, born on the ten of april nine teen fifty two (10/04/1952). Based on clinical manifestation and support by serologic test (rapid test) result reactive, with CD4⁺ count 59 (410-1590) cells/UI confirmed that he was human immunodeficiency virus (HIV) positive. He was started on ART, TDF/3TC/EFV (FDC=Fixed Dose Combination) on the Three teen of May two thousand fourteen (13/05/2014). He had been stable (without any

complains) there after till he developed NPSEs induce by EFV on the four of May two thousand fifteen (04/05/2015).

Symptoms and Laboratory test outcomes

On the four of May two thousand fifteen (04/05/2015), due to routinely visit, patient presented to the clinic with complain nightmares (bad/abnormal dream), confusion and insomnia / difficulty sleeping. Patient's father reported that the symptoms started six days before he presented to the clinic. EFV was stopped and patient was placed on NVP containing regimen. He came back to the clinic four weeks after and the patient condition still status quo ante. Three months after, patient has been improved with TDF/3TC/ NVP. Father claims that the patient has been a good adherence to ART.

3. Discussion Perspectives on Efavirenz Therapy in HIV-Infected Patients

The NPSEs have been commonly associated with EFV base regimen ART. Almost 50% of patients on EFV based regimen ART experience at least one NPSEs.^{9,10} Its tend to occur within in the first few days after initiation therapy and will be resolve spontaneously within the first 4-6 weeks, but in some cases its may occur with late onset after initiation therapy EFV based regimen ART and long term recovery after EFV discontinuous (a few months or years).⁹ The mechanisms responsible for EFV induced neurotoxicity are unclear, although growing evidence points to disturbances in brain mitochondrial function and bioenergetics.¹¹ The most frequently reported NPSEs are headache, dizziness, insomnia, nightmares (bad/abnormal dream), and impaired concentration.^{10,12-14}

The other reports exist on long term efavirenz associated various NPSEs; **Ruiz et al (1999)**, found in their clinical trials, 54% of patients consuming EFV reported adverse reactions compared with 27% of patients not consuming

EFV. Among their study participants, 2.6% reportedly discontinued treatment due to NPSEs. The most frequent NPSEs were nightmares (bad dream), confusion and insomnia / difficulty sleeping, inability to concentrate and headache.¹⁵

Isaac Okoh Abah et al, 2015; in their clinical cohort study found that neuropsychiatric adverse drug events associated with EFV-Based ART had both early and late onset. Neuropsychiatric disorders are the most frequent and substantial adverse effects associated with EFV based regimen ART.⁴

The French Adverse Event Reporting System database had been notified of 15 cases of sleeping disorders possibly related to EFV-based ART in 5 of the 15 cases.⁶ **Esileman Abdela Muche, 2020;** more than half of HIV patients taking EFV based regimen ART experienced neuropsychiatric adverse events. Health care providers should give attention to patients EFV based regimen ART to monitor for neuropsychiatric effects, especially for patients who have low CD4 levels, advanced disease, comorbidities, and the older patients.⁷

We reported an elderly case, male aged 68-years-old, with low levels of CD4 count (59 cells/UI), with the experienced nightmares (bad/abnormal dream), confusion and insomnia/difficulty sleeping. The symptoms started six days before he presented to the clinic, after took EFV based regimen ART for more than a year. EFV was stopped and patient was placed on NVP containing regimen. He came back to the clinic four weeks after and the patient condition still status quo ante. Three months after, patient has been improved with TDF/3TC/ NVP. Father claims that the patient has been a good adherence to ART.

4. Conclusion

Although efavirenz is potent, it has a long half-life, relatively simple addition to HAART; however, its administration may be limited by serious NPSEs that require discontinuation of the drug, and reduce the dose might be not as an alternative approach. Mostly the NPSEs tend to occur within the first few days after initiation of EFV based regimen ART, but in this case report the NPSEs occurring after more than a year on EFV based ART. Therefore the clinicians should be aware that the NPSEs can occur on more than few months on EFV based regimen ART.

5. Declarations

Ethics approval and consent to participate. Ethical approval was obtained from the Ethical Committee of Wangaya hospital in Denpasar, Bali, Indonesia, and the study complied with the principles of the *Declaration of Helsinki*. The patient received detailed information and the written informed consents was signed.

6. Consent for publication

Written informed consent was obtained from the patient for publication of this case report

7. Competing Interests

The authors declare no conflict of interest.

8. Funding

The author(s) received no specific funding for this work.

9. Acknowledgements

The author appreciates to Wangaya HIV Study Group (WHSG) Merpati Clinic at Wangaya Hospital in Denpasar, Bali for a good team work. The author would also like to thank to the patients and their family, Director Wangaya Hospital for all of the supports.

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