Treatment non-responsiveness in depression following Efavirenz administration

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Abstract
Depression is found as a comorbid condition in patients with human immunodeficiency virus (HIV) infection. Antiretroviral drugs used for the treatment of such infection may result in emergent depression. One such antiretroviral drug is efavirenz (EFV). Induction or exacerbation of depression with EFV has been reported in studies, which resolved after stopping EFV. We report a case of a 23-year-old male patient suffering from HIV for 5 years with treatment nonresponsive depressive symptoms due to EFV which improved after stopping it.

Key words: Depression, efavirenz, human immunodeficiency virus

INTRODUCTION
Worldwide, an estimated 0.8% of adults, aged 15–49 years, are living with human immunodeficiency virus (HIV), although the burden of the epidemic continues to vary considerably between countries and regions.[1] Sub-Saharan Africa remains the most severely affected, with nearly one in every twenty adults living with HIV and accounting for nearly 71% of the people living with HIV worldwide.[1] About 2.40 million Indians have HIV (1.93–3.04 million) with an adult prevalence of 0.31%.[2]

AIDS is an advanced HIV disease. A person with AIDS has an immune system weakened by HIV that results in one of several opportunistic infections or cancers such as pneumocystis carinii pneumonia (a type of pneumonia) or (Kaposi sarcoma, a type of cancer that affects the skin and internal organs in HIV), wasting syndrome (involuntary weight loss), memory impairment, or tuberculosis.[3]

Treatment for HIV infection usually involves using three or more antiretroviral medicines – sometimes referred to as an “anti-HIV cocktail.”[4] This treatment offers the best chance of preventing HIV from multiplying, which allows the immune system to stay healthy. Antiretroviral medicines that are often used to treat HIV include (a) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), also called nucleoside analogs, such as abacavir, emtricitabine, and tenofovir. These medicines are often combined for best results: (b) non-NRTIs (NNRTIs) such as efavirenz (EFV), etravirine, and nevirapine; (c) protease inhibitors (PIs) such as atazanavir, darunavir, and ritonavir; (d) entry inhibitors such as enfuvirtide and maraviroc; and (e) integrase inhibitors such as dolutegravir and raltegravir.[4]
Psychiatric comorbidities are common in HIV; depression and anxiety are often prevalent among those with HIV infection. Furthermore, there may be minor cognitive deficits as well as gross psychomotor retardation and dementia. Instances of frank psychosis are often reported too.

Treating comorbid depression is very essential as it significantly lowers morbidity and mortality from HIV disease. However, it is very challenging to treat depression in individuals with HIV infection as there may be interactions between disease processes and pharmacological agents used to treat them. Depression is also a recognized side effect of NRTIs, PIs, and NNRTIs.

EFV is a potent NNRTI of HIV-1 which is well-tolerated. About 50% of patients in open-label studies reported dizziness, headache, mild cognitive difficulty, fatigue, or sleep disturbance characterized by intense and sometimes disturbing dreams due to its use. EFV has been found to be associated with depression, but very few high-quality data exist that adequately address this issue. There are a few case reports that mention about exacerbation or even new onset of psychosis or mania attributed to EFV, with resolution of symptoms after discontinuation of therapy.

In an observational clinical trial, involving a consecutive series of 47 HIV-infected participants on long-term EFV treatment, it was found that neuropsychiatric symptoms were prevalent; depression, anxiety, stress, insufficiency in thinking, and paranoia were very common. The study goes on to add that after discontinuing EFV, these symptoms improved significantly and reached almost normal levels.

Here, we report a case of bipolar affective disorder, presenting with depression in an individual with HIV infection, where there was unresponsiveness to antidepressants following the use of EFV in a short time which resolved after the drug was discontinued.

**CASE REPORT**

A 23-year-old male patient (whose verbal consent was taken for reporting this case) presented in our outpatient department (OPD) with a history of decreased sleep, odd behavior, wandering about, frequent irrelevant talks, fearfulness, referential thinking, and persecutory ideas for 2 days with a history of being HIV positive for 5 years. This was the first episode. He was treated with tablet olanzapine 5 mg, which was increased up to 10 mg. He improved in a month. After 2 months, he presented with sadness, decreased interaction, crying spells, and hopelessness. Hence, along with tablet olanzapine, antidepressant tablet escitalopram 5 mg was started which was gradually increased to 10 mg. He improved in about 2 months and maintained well for about 11 months. He was compliant to the treatment and was followed up once a month in the OPD. After 11 months, he presented with a history of decreased sleep, increased talk, irritability, and cheerfulness. Hence, escitalopram was stopped, and he was continued with tablet olanzapine 10 mg. He recovered in 15 days and maintained well for further 8 months, and tablet olanzapine was gradually reduced to 5 mg. A diagnosis of “bipolar affective disorder, current episode mania without psychotic symptoms” was made.

In the meantime, he was tried with various antiretroviral drugs in combinations, i.e. lamivudine 150–300 mg, zidovudine 300 mg, nevirapine 600 mg, stavudine 20 mg, and tenofovir 300 mg. In 2014–2015, he was prescribed with EFV 600 mg in combination with nevirapine up to 600 mg and lamivudine up to 300 mg at different times. Around this time, the patient presented with decreased sleep, sadness, weeping spells, decreased interaction, decreased appetite, odd behavior, and irrelevant and inappropriate talk at times and had socio-occupational dysfunction. A diagnosis of “bipolar affective disorder, current episode severe depression with psychotic symptoms” was made, and the treatment was started with antidepressant tablet escitalopram 10 mg, which was increased to 20 mg, and antipsychotic olanzapine 5 mg tablet was added to it. This time, he did not improve with the treatment even after 3 months. Hence, olanzapine was discontinued, and tablet quetiapine 50 mg was started which was gradually increased to 300 mg. Electrocardiogram was done periodically while quetiapine was increased and it was found to be normal; no QTc (corrected QT interval of ECG) prolongation was there. As there was no improvement in depression, the antidepressant was changed to another selective serotonin reuptake inhibitor, i.e., fluoxetine capsule at a dosage of 20 mg. Still, the patient did not improve at the end of 3 months, and the score on the Beck Depression Inventory was 55 which corresponded to severe depression. The status about lack of any improvement in depression was communicated to the physician who was aware that antiretroviral drugs may cause depression. Hence, he discontinued EFV and started nevirapine. After discontinuing EFV, the patient started to improve in a month and recovered completely in 3 months with good socio-occupational functioning. Quetiapine in the meantime was reduced and stopped (as he complained of increased sedation and found the drug to be costly), and he was continued on fluoxetine 20 mg and aripiprazole 2.5 mg. The score on the Beck Depression Inventory at the end of 3 months was 6 which corresponded to minimal depression.


DISCUSSION

Different studies on EFV-induced depression or improvement in depression after discontinuing EFV have given inconclusive results.[8] Studies have reported about EFV-induced depression or exacerbation in depressive symptoms with EFV. Previous studies have found that depression is the most common comorbid condition in HIV-positive patients, most common symptoms being anhedonia and suicidal ideas,[7] but these were not prominent in the present case.

Like the observational clinical trial,[7] our case too showed improvement in depression after discontinuing EFV. However, what is interesting in our case is that depression may not have emerged because of EFV but could have been a part of a preexisting illness, and due to the use of EFV, there was nonresponsiveness to antidepressants. This can be judged from change in the Beck Depression Inventory scores from 55 to 6 over a span of 3 months following discontinuation of EFV. Although the patient was initially on tablet escitalopram 20 mg and later on capsule fluoxetine 20 mg all throughout, the improvement in depression had a robust temporal relation to discontinuation of EFV than to the use of fluoxetine. This is further clear from the fact that while applying “Naranjo Adverse Drug Reaction Probability Scale,”[10] the score was 4, which corresponds to possible association of EFV in causing depression and the lack of response to antidepressants.

Considering all these, it can be said that EFV not only induces or exacerbates depressive symptoms but also is responsible for making a person nonresponsive to treatment with antidepressants.

Hence, whenever a case of treatment nonresponsive depressive symptoms with HIV-positive status presents, it would be worthwhile to review the antiretroviral therapies (ARTs) being used. Furthermore, one should keep in mind the possibility of comorbid depression in patients with HIV infection, and choice of ARTs should be based on the presence or absence of this prevalent comorbidity.

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Conflicts of interest

There are no conflicts of interest.

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