# Predictors of discontinuation of efavirenz as treatment for HIV, due to neuropsychiatric side effects, in a multi-ethnic sample in the UK

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**Running Head:** Predictor of discontinuation of efavirenz in the UK

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# ABSTRACT

**Background:** Efavirenz (EFV) is one of the most commonly prescribed antiretroviral (ART) medications for HIV-infected adults because of its favorable pharmacokinetic profile and well-documented efficacy. Nonetheless, neuropsychiatric adverse events (AE) occur in almost half of the EFV users and it is the main reason for treatment discontinuation. **Objective:** To identify the socio-demographic characteristics and reported neuropsychiatric side effects that placed EFV users at an increased risk of discontinuation in a multi-ethnic sample in the UK. **Methods:** A retrospective medical records analysis of patients prescribed EFV-containing ART in an outpatient sexual health clinic between 2010 and 2016. **Results:** One hundred and forty-nine medical records were reviewed. Fifty-five patients discontinued EFV within the study period. 55.7% of patients suffered from at least one neuropsychiatric AE, the most commonly recorded symptoms were depression, vivid dreams, dizziness and sleep disturbance. There was an inverse relationship between number of AE and EFV continuation (*Adjust OR* = 0.12; 95% CI = 0.03 – 0.44, *p* < .05). Furthermore, neuropsychiatric symptoms, including depression (*Adjust OR* = 3.01; 95% CI = 1.30 – 6.96, *p* < .05), sleep disturbance (*Adjust OR* = 3.00; 95% CI =1.10 – 8.19, *p* < .05) and vivid dreams (*Adjust OR* = 2.51; 95% CI = 1.05 – 6.00, *p* < .05), were independent predictors of EFV discontinuation. **Conclusion:** The findings revealed that patients who did not experience any neuropsychiatric side effects were 8 times more likely to stay on an EFV-containing regimen than those who suffered from more than 3 symptoms. Additionally, patients who experienced depression or sleep disturbance were at 3-fold elevated risk of discontinuing an EFV-based regimen. The implications for clinical practice are discussed.

# INTRODUCTION

According to the Joint United National Programme on HIV/AIDS, there were approximately 37 million people worldwide living with human immunodeficiency virus (HIV) whilst around 1 million people died from HIV-associated illnesses such as tuberculosis in 2017 [1]. Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor and globally one of the most commonly prescribed antiretroviral drugs [2]. In combination with a nucleoside reverse transcriptase inhibitor backbone, EFV is recommended by the World Health Organization (WHO) as preferred and the British HIV Associationas an alternative first-line antiretroviral therapy (ART) regimen for HIV-infected adults. EFV is no longer the preferred first-line ART in Europe and North America but is extremely widely used in these and in resource-limited settings [3,4]. While the use of EFV is waning in many high income settings the WHO project that by 2020 it will have an 88% ART market share globally. EFV has a favorable pharmacokinetic profile, few food restrictions and once daily dosing [5,6]. The availability of low cost, generic EFV makes it a cost effective option in many health care systems [7].

The benefits of EFV are clear, but it is also associated with central nervous system (CNS) toxicity such as depression, anxiety and insomnia. The underlying mechanism for such symptoms have not been fully elucidated, but may be due, in part, to CNS drug concentrations and genetic mediators of drug metabolism [7]. Long-term use of EFV has been shown to disrupt information processing, working memory and verbal fluency [8]. Furthermore, patients who were treated with EFV for more than 6 months reported higher levels of anxiety and severe stress [9]. Many of the symptoms associated with EFV-induced CNS toxicity are also found in depressionand HIV-associated neurocognitive disorder [10] making it difficult to disentangle the contribution of EFV to CNS symptoms in people with HIV.

Acute neuropsychiatric AEs have been described in almost 50% of patients treated with an EFV-based regimen in some studies [11,12]. The most common reported symptoms were abnormal dream, dizziness, insomnia and mood swings [2,13-15].

Women are more likely to report EFV-induced neuropsychiatric AEs possibly due to higher drug concentrations, mediated through differences in body composition, compared to men [16]. A cohort study showed that Blacks were at 1.5 times greater risk of discontinuing an EFV/nevirapine-containing regimen than non-Hispanic Whites [17]. Abah et al. [16] proposed that Whites experience faster hepatic clearance of EFV than Africans and Asians resulting in decreased EFV-induced neurotoxicity and treatment discontinuation.

Prosperi et al. [18] demonstrated that older patients were more likely to experience ART-associated side effects because of reductions in drug metabolism with aging, nonetheless, empirical evidence consistently illustrates that younger age is a risk factor for lower ART adherence [17,19-23].

Partner support is important in improving ART adherence [24], being married was a protective factor for ART adherence in 2 African samples [19,25]. In contrast, Spire et al. [26] found that patients with a stable partner were 70% more likely to discontinue an EFV-based regimen. A meta-analysis included 28 studies with 8,743 HIV-infected individuals reported that unemployment was an independent predictor of ART discontinuation [27]. This was seen in high income but not resource-limited countries suggesting employment per se is not the key factor but perhaps a marker of other socioeconomic influences [27].

Sexual orientation has been identified as a risk factor of ART discontinuation. Bi/homosexual patients were at twice at the risk of discontinuing ART, including EFV-based regimens [18,21].

Whilst some of the socio-demographic factors that determine EFV adherence are becoming clear, the role of neuropsychiatric AE is less well understood. No study to date has comprehensively explored which EFV-induced neuropsychiatric AE best predict treatment discontinuation. Therefore, the present study aimed to identify the socio-demographic risk factors for EFV discontinuation, the frequency of reported EFV-associated neuropsychiatric AE as well as the contribution of those symptoms in predicting treatment discontinuation.

# METHODS

## Study Design, Setting and Population

The study involved a retrospective exploratory analysis of medical records from an ethnically diverse, publicly-funded HIV clinic in Slough, UK offering sexual health services including continuity HIV care to a cohort of approximately 600 individuals. Patient-level data were reviewed and evaluated through the clinic’s electronic database to identify those who met inclusion criteria. All HIV-infected patients aged 18 years or above when initiating ART, and prescribed EFV between 2010 and 2016 were included.

The data source was medical and nursing records handwritten in patients’ medical records during routine clinical encounters. All medical records that met the inclusion criteria were reviewed and extracted data transferred into a secure, password-protected database. Ethical approval was granted from the School of Psychology and Clinical Language Sciences Ethics Committee, University of Reading (Study no: 2017-104-LB).

## Measurements and Procedure

Demographic characteristics including the patient’s age, sex, race/ethnicity, country of birth and employment status were accessed through a standardized form from the medical record. Relationship status and sexual orientation were identified from the medical record, the latter was determined either by the recorded sex of their partners or the patients’ risk factor for HIV, if sexual.

In order to establish pre-ART stressors medical records were reviewed from one month prior to their treatment initiation. Stressors included health-related issues, family or relationship problems, and academic or work-associated pressures. If the patient had recently moved to the UK before treatment commencement this was also classified as a stressful event based on the assumption that s/he had to face acculturative stresses [28] including cultural adaptation and fewer social supports in general. Data on comorbid conditions, HIV stage and CD4 count and viral load were not collected for this study. Race/ethnicity categorizations were limited to pre-specified patient-level categories of Black (Black African and Black Caribbean), White (Caucasian) and Asian (East/South Asian and Indian). Sex categories were binary (male/female) only.

Since EFV-induced neuropsychiatric AEs are most likely to appear in the first week of treatment commencement and resolve within a month [2] all neuropsychiatric symptoms and their total number recorded within the first month of treatment initiation were included in the analysis. Socio-demographic variables and the documented neuropsychiatric AE served as predictor variables; the outcome variable was EFV discontinuation. Discontinuation was defined as switching to an EFV-free regimen or failure to return to the clinic within the study period. If a symptom was not recorded in the medical record, it was considered absent.

## Data Analysis

All required information was captured and categorized using Microsoft Excel® between March and May 2017. Data were analyzed using Statistical Package for Social Sciences (SPSS), Version 22, and the statistical significant level was set as *P* = 0.05. All the missing data were grouped in the ‘not documented’ category.

Descriptive statistics were calculated for neuropsychiatric AE, socio-demographic characteristics and discontinuation rates. For univariate analyses, in order to access the associations of all predictor variables with EFV discontinuation, nonparametric hypothesis testing techniques including Pearson’s chi-squared or likelihood ratio tests (*χ*2) were used.

Multivariate logistic regression was selected to undertake an exploratory analysis into risk factors for EFV discontinuation. Adjusted odd ratios and 95% confidence intervals were computed to measure the predictive effect of each factor. Two logistic regression models were performed, the first consisted of all socio-demographic characteristics, whether or not the participant encountered a stressful event and the total number of neuropsychiatric AE experienced. The total number of neuropsychiatric AE was entered in the first regression model because there would be many overlaps with the recorded neuropsychiatric symptoms. The second model included all of the recorded neuropsychiatric symptoms that the patient reported. All factors or symptoms with P ≤ 0.05 were entered into the multivariate analyses.

# RESULTS

Data from 149 HIV-infected patients who were prescribed EFV-containing ART between 2010 and 2016 were analyzed. Participants’ ages ranged from 19 to 74 years (*M* = 40.77; *SD* = 10.22) and 68.4% were between 30 and 49 years. The majority of the participants were male (58.4%), heterosexual (79.2%), Black (64.4%), born in African countries (62.4%) and 60.4% were formally employed (Table 1). Equal proportions were living with and without partners (36.2%). 25.5% encountered ≥1 stressful event one month prior to ART initiation. As shown in Table 2, 55 (36.9%) participants had discontinued EFV-containing regimens during the study period, of which 40% (*n* = 22) had discontinued the said regimen within the first 3 months of treatment initiation.

In the univariate analyses, chi-squared tests of independent or likelihood ratio tests were calculated to explore the relationships between the measured risk factors and EFV discontinuation. EFV discontinuation was not associated (*p* > .05) with sex, age, sexual orientation, country of birth, relationship status or employment status.

EFV discontinuation was significantly associated with stressful events (*χ*2 (1) = 9.64, *p* < .01), number of neuropsychiatric side effects (*χ*2 (2) = 20.25, *p* < .001) and ethnicity (*χ*2 (2) = 7.40, *p* < .05) (see Table 3). Black and Asian participants who encountered a recent stressor, and who experienced more neuropsychiatric symptoms were more likely to discontinue EFV-based ART.

Overall, more than half of the participants (55.7%) experienced at least one neuropsychiatric AE within the first month of treatment initiation. The most frequently reported symptoms were depression (24.2%), vivid dreams (21.5%), dizziness (19.5%), sleep disturbance (16.1%) and fatigue (13.4%). The frequency distribution of the neuropsychiatric AE is summarized in Table 4.

Univariate analyses with the 7 most commonly recorded neuropsychiatric symptoms showed significant associations between EFV discontinuation and depression (*χ*2 (1) = 11.94, *p* < .01), sleep disturbance (*χ*2 (1) = 10.88, *p* < .01) and vivid dreams (*χ*2 (1) = 8.83, *p* < .01) (see Table 3). A marginally significant association was found between EFV discontinuation and lack of appetite (*χ*2 (1) = 3.82, *p* = .051). However, there was no evidence to suggest that dizziness, fatigue and nausea were associated with EFV discontinuation (*p* > .05).

In order to conduct a predictive model of the risk factors for treatment discontinuation, significant and marginally significant variables were entered simultaneously into 2 multivariate logistic regression analyses. In the first model (see Table 5), Nagelkerke pseudo R2 indicated that 3 predictor variables explained 21.1% of variability of EFV discontinuation. Table 5 shows that the number of neuropsychiatric AE experienced was an independent predictor of EFV discontinuation. Patients who experienced less than 3 neuropsychiatric AE were almost 4 times more likely to stay on an EFV-containing regimen than those experiencing ≥3 (*Adjust OR* = 0.24; 95% CI = 0.07 – 0.86, *p* < .05). Meanwhile, those who did not experience any neuropsychiatric AE were 8 times more likely to continue an EFV-containing regimen (Adjust OR = 0.12; 95% CI = 0.03 – 0.44, p < .05). However, participant race/ethnicity and whether or not they encountered a stressful event in the month prior to treatment initiation did not significantly predict treatment discontinuation (*p* > .05).

The results for the second multiple logistic regression analysis is presented in Table 6. Nagelkerke pseudo R2 illustrated that 4 symptoms explained 21.4% of variability of EFV discontinuation. Depression (*Adjust OR* = 3.01; 95% CI = 1.30 – 6.96, *p* < .05), sleep disturbance (*Adjust OR* = 3.00; 95% CI =1.10 – 8.19, *p* < .05) and vivid dreams (*Adjust OR* = 2.51; 95% CI = 1.05 – 6.00, *p* < .05) remained independent predictors of EFV discontinuation whilst lack of appetite did not (Adjust OR = 2.59; 95% CI = 0.79 – 8.53, p = .118). Compared to those who did not experience these symptoms, participants who experienced depression or sleep disturbance, and vivid dreams were at 3- and 2.5-fold elevated risk of discontinuing EFV-containing ART.

In sum, this analysis found an overall EFV discontinuation rate of 36.9%. Acute neuropsychiatric AE were reported and documented in 83 out of 149 (55.7%), the most commonly recorded were depression, followed by vivid dreams, dizziness and sleep disturbance.

There were significant relationships between EFV discontinuation and patient’s race/ethnicity, recent stressful life events and the number of neuropsychiatric side effects. White participants were less likely to discontinue an EFV-containing regimen compared with Blacks and Asians. Moreover, patients who experienced more neuropsychiatric AE and a stressor 1 month prior to treatment initiation were more likely to discontinue. The adjusted odd ratios demonstrated an inverse relationship between number of neuropsychiatric AEs and EFV continuation, the fewer neuropsychiatric symptoms patients experienced, the more likely they continued EFV. Those who reported depression, sleep disturbance or vivid dreams were more likely to discontinue EFV compared to those who did not. Also, the regression model illustrated that these 3 neuropsychiatric symptoms were independent predictors of EFV discontinuation; those reporting depression or sleep disturbance were at 3-fold risk of discontinuation.

# DISCUSSION

A total of 36.9% participants discontinued EFV-based regimen between 2010 and 2017, 34 (22.8%) discontinued within 1 year of treatment commencement, which is slightly lower than another European study where 26.2% discontinued EFV within 1 year [13]. Leutschers et al. [13] found31.5% of patients discontinued an EFV-containing regimen within 4 years of treatment initiation, similar to an Italian sample who reported a rate of 29.1% over the same time span [29]. Therefore, the results of the current study provide further evidence that EFV-induced neuropsychiatric AE will occur in around half of the users [2,7].These data confirm the expected association between symptom ‘burden’ and continuation of EFV; the more neuropsychiatric symptoms experienced, the higher likelihood of discontinuation.

The current analysis provided support for the hypotheses that EFV-associated depression, sleep disturbance and vivid dreams were limiting factors of EFV continuation. Patient race/ethnicity and recent stressful events were associated with discontinuation of ART, but neither could predict EFV discontinuation in this sample with a high degree of certainty. Consistent with previous findings, Whites had a lower discontinuation rate when compared to Black or Asian patients [17,30]. The population in these analyses were multinational; it is possible that associations with race/ethnicity observed might be explained by ethnic/racial differences in EFV metabolism resulting in more pronounced neuropsychiatric symptoms hence to discontinuation [16]. The pharmacogenetic basis of such racial/ethnic differences in EFV metabolism is, in part, mediated through genetic differences in cytochrome P450 (CYP) hepatic metabolism; as well as differences in CYP2B6 and CYP2A6, and through phase II metabolism via conjugation by UDP-glucuronosyltransferase (UGT). Of note, 7 out of 9 (78%) Asian patients discontinued EFV-containing regimen within the study period. Therefore, more studies in Asian populations are needed and HIV healthcare providers may need to pay careful attention to the Asian EFV-users. The number of neuropsychiatric AE was significantly associated with recent stressful events (*χ*2 (2) = 17.53, *p* < .001) and participant’s sex (*χ*2 (2) = 6.14, *p* < .05) in this analysis. 31.6% of patients who encountered a recent stressor experienced ≥4 neuropsychiatric symptoms after initiating EFV compared to 6.3% of patients who did not. 14.9% of males reported experiencing ≥4 neuropsychiatric symptoms compared to 9.7% of women. These data demonstrate the association between recent life stressors and number of neuropsychiatric symptoms, as well as the association between higher number of symptoms and male sex. This finding is consistent with Prosperi et al. finding that suggested males are more likely to experience EFV-related neuropsychiatric AEs [18].

This analysis has several key strengths; it evaluated neuropsychiatric symptoms in an inner city, publicly-funded HIV service. The population were ethnically diverse and predominantly heterosexual African which is in contrast to much previous data in high income countries which has historically focused on Caucasian men who have sex with men (MSM). It also examines not only the individual symptoms associated with EFV discontinuation but their number.

Several limitations of this study must be acknowledged. There were many missing data, around a quarter of patient’s employment status and relationship status were not recorded. There were no clinical data on disease stage or medical comorbidities which may have influenced both ART choice and neuropsychiatric symptoms. Race/ethnicity and sex/gender data lacked granularity and may have affected outcomes. These limitations mean that a more nuanced analysis of associations was not possible. The retrospective nature of the analysis and lack of an EFV-free control groups will have resulted in numerous biases including selection, reporting, mislabelling and anchoring biases. The use of multiple statistical tests do raise the risk of type 1 error. The intention was to keep the number of individual tests to a minimum, however we did not include a correction for multiple analyses (i.e. reducing the nominal alpha level for each test as a function of the number of tests included) because we were conducting an exploratory study to identify possible predictor variables. The analysis is limited by the self-reported nature of symptoms and the lack of firm diagnostic categorization of neuropsychiatric symptoms by clinicians. For instance a patient may complain of ‘depression’ but have an underlying cognitive disorder such as HIV encephalopathy. The sample did not contain information on formal tests for affective disorders or establish if a patient had a pre-existing neuropsychiatric diagnosis.

This analysis omitted other important factors that may influence EFV-discontinuation. First, the duration of EFV-induced neuropsychiatric AE. Given that some neuropsychiatric AE may last longer and eventually cause discontinuation, the predictive effects of neuropsychiatric AEs would be more accurate if the duration of each side effect is considered. Second, the co-administration of others prescribed medication e.g. antidepressants and the use of drugs and alcohol. Third, there were no data on EFV concentrations, weight and body composition, which may have influenced neuropsychiatric symptoms. Fourth, the pre-ART initiation window of 4 weeks may have been insufficient to capture the full effects of stressful life events. It is possible that those with different ages, race/ethnicities and those with limited fluency in English and cognitive abilities experience such symptoms differently and use discrepant language to describe them. These factors may influence the effectiveness of pre-ART AE discussions and clinicians’ ability to enquire into the presence or absence of AE.

While EFV has been replaced as first line ART in high-income country guidelines it is likely to be widely used in these as well as in resource limited settings. The global use of EFV and changing epidemiology of mental health requires more studies that focus on EFV discontinuation so clinicians can tailor ART and promote tolerability [18,31].Additionally, research designed to assess the neuropsychiatric effects of different ART regimens and algorithms that predict likelihood of ART discontinuation are required [32]. This study indicates that pre-ART screening for psychological risk factors might be valuable particularly when EFV is being considered given that EFV-free options that induce fewer neuropsychiatric AE are available even in resource-limited settings.

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