

# Patient Reported Central Nervous System Adverse Events of Efavirenz-Based Antiretroviral Therapy in People Living with HIV in Northwest Ethiopia

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**Background:** Central nervous system (CNS) toxicities from regimens containing efavirenz are the main reasons for non-adherence, switch and discontinuation of antiretroviral therapy (ART). We aimed to assess prevalence of CNS adverse events and associated factors among HIV patients taking efavirenz-based regimens at the University of Gondar Comprehensive and Specialized Hospital (UoGCSH), Northwest Ethiopia.

**Methods:** A hospital-based cross-sectional study was conducted from March 15 to May 15, 2018 on 345 patients living with HIV who were taking efavirenz-based regimens. Information on sociodemographic and clinical characteristics was taken from medical records and patient interview. Binary logistic regression analysis was done to determine association. Statistical significance was declared at P value of  $\leq 0.05$ .

**Results:** About 52.8% of participants experienced CNS adverse events. Vivid dreams, confusion, insomnia and somnolence were the most frequently reported adverse events. Most of the CNS adverse events occurred in the first year of treatment initiation and resolved within 1–4 weeks. Age, economic status, CD4 count, disease stage, presence of comorbidities and concurrent use of other medication had a significant association with the occurrence of CNS adverse events.

**Conclusion:** More than half of HIV patients taking efavirenz-based regimens at UoGCSH experienced CNS adverse events. Health-care providers should give attention to patients on efavirenz therapy to monitor for CNS adverse events, especially for patients who have low CD4 count, advanced disease, comorbidities, low income and are older in age.

**Keywords:** CNS, adverse effect, efavirenz, antiretroviral therapy, low- and middle-income country

## Introduction

Antiretroviral therapy (ART) regimens have the capacity to reduce patients' human immunodeficiency virus (HIV) load to undetectable levels and decreasing HIV-related opportunistic infections by increasing their CD4 T-lymphocyte counts. In spite of the benefits, antiretroviral drugs might cause adverse reactions which may be the main reason for drug discontinuation, switching and non-adherence. As a result, intended benefits from antiretroviral drug therapy may not be achieved or treatment failure may occur.<sup>1–3</sup> Antiretroviral therapy comprising of two nucleoside reverse transcriptase inhibitors (NRTIs) as a backbone and one non-nucleoside reverse transcriptase inhibitor (NNRTI) is maintained as the preferred first-line treatment regimen in adults because of its high viral suppression capacity.<sup>4</sup> First-line antiretroviral regimens

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recommended by the Ethiopian HIV treatment guidelines for treatment-naive individuals are: tenofovir + lamivudine + efavirenz/nevirapine (TDF+3TC+EFV/NVP) or zidovudine + lamivudine + nevirapine/efavirenz (AZT+3TC+NVP/EFV).<sup>5</sup>

Efavirenz (EFV), one of the NNRTIs, has high antiretroviral efficacy and prolonged half-life allowing once-daily dosing.<sup>6</sup> However, it crosses the blood–brain barrier (BBB) and can cause CNS adverse effects.<sup>7</sup> As compared with structurally similar agents such as nevirapine, neuropsychiatric effects from EFV occur more frequently and with greater severity.<sup>8</sup> A systematic review and meta-analysis study conducted by Shubber et al. reported that patients receiving EFV were more likely to experience severe central nervous system events than people receiving nevirapine-based regimens.<sup>9</sup> A study conducted on Chinese HIV patients receiving tenofovir + lamivudine + efavirenz (TDF+3TC+EFV) as their first-line ART regimen reported that the most commonly reported adverse events (95.6%) were related to the CNS.<sup>10</sup>

CNS adverse effects reduce the patient's quality of life which leads to loss of confidence in the health care and the drug, which in turn makes the patient non-adherent to the medication. A prospective observational study showed that adverse effects of highly active antiretroviral therapy (HAART) was a reason for discontinuation of medications for about a quarter of HIV patients.<sup>11</sup> Scourfield et al. reported that of 89 patients who switched from an EFV-based ART regimen, 71% was due to CNS toxicity.<sup>12</sup> According to Fumaz et al. the risk of discontinuation of treatment as a result of experiencing symptoms was higher in EFV-treated patients compared with non-EFV-based regimens.<sup>13</sup>

Sub-Saharan Africa is a region of high HIV burden, increased ART need and limited treatment options. As a result, the impact of ART-related adverse effects in the region is serious. In addition, the risk of developing CNS adverse events from EFV for people in sub-Saharan Africa is high due to single nucleotide polymorphism in many patients living in this region, which exposes them to increased EFV plasma concentration. Nyakutira et al. estimated that about one-fifth of the population in sub-Saharan Africa are genetically slow metabolizers which may increase the risk of adverse events from EFV.<sup>14</sup> In such resource-limited settings information regarding the magnitude of adverse drug effects and associated factors is very important for monitoring risks. In addition, investigating

treatment adverse events is crucial because of their direct impact on treatment adherence and patients' quality of life.

To the authors' knowledge, no detailed data exist in Ethiopia on the prevalence of EFV-related CNS adverse effects. The aim of this study is to determine the prevalence of CNS adverse events and to identify the possible contributing factors in adult patients taking EFV-based regimens at the University of Gondar Comprehensive and Specialized Hospital (UoGCSH), Northwest Ethiopia.

## Methods

### Study Area and Period

This study was conducted at UoGCSH, Gondar, Northwest Ethiopia. Gondar has a latitude and longitude of 12°36'N 37°28'E. It is located 737 kilometers away from Addis Ababa, the capital city of Ethiopia. The hospital is one of the biggest tertiary level referral and teaching hospitals in the region. It provides a service for an estimated 7 million people. The hospital has an ART clinic and a special pharmacy dedicated to serving people living with HIV. The study was conducted from March 15 to May 15, 2018.

### Study Design

A hospital-based cross-sectional study design was employed.

### Inclusion and Exclusion Criteria

#### Inclusion Criteria

HIV patients who were taking an EFV-based regimen.

#### Exclusion Criteria

Patients under the age of 15, pregnant women, patients with documented CNS illness prior to starting EFV and those who did not give consent to participate.

### Sample Size and Sampling Methods

About 1900 patients were taking an EFV-based regimen at the clinic. The sample size was calculated using the following single population proportion formula.  $N = ((Z_{\alpha/2})^2 (p)(1-p))/d^2$   $Z_{\alpha/2}$  (95% confidence interval) = 1.96;  $d$  (margin of error) = 5%,  $p$  (proportion of people developing an EFV-related adverse drug event (ADE)) = 50% (no previous study at the study area). Since the total population is <10,000 the sample was recalculated using the following corrective formula.  $N_f = n/(1+(n/N))$ ;  $n$  = sample size calculated by single population proportion formula,  $N_f$  = actual sample size,  $N$  = total number of

patients taking an EFV-based regimen in the study area (1900). Therefore, the sample size was:  $N_f = 384 / (1 + (384/1900)) = 319$ . By adding 8% contingency, a total of 345 patients were sampled. Participants were selected using a simple random sampling technique from eligible patients available at the hospital on each day of the study period.

### Data Collection Procedure

Data were collected by interviewing the patient using a well-structured questionnaire and reviewing paper-based medical records. The data collection tool was pre-tested on 17 patients (5% of calculated sample size), after which some language-related modifications were made to clarify some of the questions. Data were collected by two graduating pharmacy students. The collected data were revised and double-checked during data entry by two of the authors.

### Data Processing and Analysis

The collected data were cleaned, checked for completeness, categorized, coded, and entered in to SPSS version 20. Descriptive statistics was used to summarize demographic and clinical characteristics. Both univariate and multivariate binary logistic regression analysis were done to identify factors associated with the occurrence of CNS adverse events. Statistical significance was declared at  $p\text{-value} \leq 0.05$ .

### Ethics Approval

Letter of ethical clearance was obtained from an ethical review committee of School of Pharmacy of the University of Gondar (reference number SoPs 254/2018). Letter of cooperation was obtained from the medical director of UoGCSH. The study was conducted in accordance with the Declaration of Helsinki. Participants and parents/legal guardians of participants under the age of 18 years were informed about the purpose of the study. Written consent was taken from participants aged 18 years or above. For participants under the age of 18 years, in addition to their assent, parental/legal guardian informed consent was obtained. Privacy and confidentiality were ensured during patient interview and review of patients' medical records. Thus, the name and address of participants were not recorded in the data collection tool.

## Results

### Sociodemographic Characteristics

From the total of 345 patients included in the current study more than half (59.7%) were males, nearly a quarter (23.5%) had no formal education and the majority (58.0%) were 25–44 years old. The age range of participants was 15–70 years with a mean of  $37.7 \pm 10.7$  years. Most (71.7%) of the participants had a low economic status. A large proportion (36.5%) of the study participants were single and 35.1% were unemployed. Forty percent of participants had an alcohol use history while only 8.1% were smokers. [Table 1](#) shows the detail of sociodemographic characteristics of study participants.

### Clinical Characteristics

Regarding clinical characteristics of participants, about half (50.7%) had a CD4 count of  $<200$  cells/mm<sup>3</sup> and 42.0% had stage 3 disease. Most (78.8%) of the participants were on a tenofovir + lamivudine + efavirenz (TDF + 3TC + EFV) regimen and nearly three-quarters (73.0%) were taking the medication at night. Some of the participants (12.5%) had other concomitant chronic illnesses and more than a quarter (26.1%) were taking other medications in addition to their ART regimen. [Table 2](#) illustrates the clinical characteristics of participants.

### CNS Adverse Events

As indicated in [Figure 1](#), more than half (52.8%) of the study participants reported at least one type of CNS adverse event. Vivid dreams (29.9%), confusion (27.5%), insomnia (24.1%) and somnolence (20.9%) were the most frequently reported adverse events. The majority (89.0%) of participants who reported an ADE experienced the event within a year of starting the EFV-based regimen and in 68.7% of participants ADEs were resolved within 1–4 weeks.

### Sociodemographic Factors Associated with Reported CNS Adverse Events

As indicated in [Table 3](#), the result of multivariate binary logistic regression analysis showed that age and economic status had a significant association with the occurrence of CNS adverse events. Accordingly, patients who are 45 years old or above are three times more likely to have an ADE than patients who are less than 25 years old (AOR = 3.183 (1.302–7.782),  $P=0.011$ ). Patients with good (monthly income of  $>5000$  Ethiopian birr) and moderate

**Table 1** Sociodemographic Characteristics of Participants

Characteristics	Category	Frequency (%)
Sex	Male	206(59.7)
	Female	139 (40.3)
Age	<25	46(13.3)
	25–44	200(58.0)
	≥45	99(28.7)
Weight	≤50kg	133 (38.6)
	51–69kg	189 (54.8)
	≥70kg	23 (6.7)
Body mass index (BMI)	<18.50 (underweight)	61(17.7)
	18.50–24.99 (normal)	251(72.8)
	≥25.00 (overweight)	33(9.6)
Education status	No formal education	81(23.5)
	Primacy school	105(30.4)
	Secondary school	115(33.3)
	Higher education	44(12.8)
Religion	Orthodox	281(81.4)
	Muslim	49(14.2)
	Others	15(4.3)
Economic status	Low	247(71.6)
	Moderate	77(22.3)
	Good	21(6.1)
Marital status	Married	125(36.2)
	Single	126(36.5)
	Divorced	49(14.2)
	Widowed	45(13.0)
Employment status	Employed by Government or private organization	105(30.4)
	Self-employed	119(34.5)
	Unemployed	121(35.1)
Alcohol use	Yes	138(40.0)
	No	207(60.0)
Smoking status	Yes	28(8.1)
	No	317(91.9)

(monthly income of 2000–5000 Ethiopian birr) economic status are less likely to have CNS adverse events as compared with those with low economic status (monthly income of less than 2000 Ethiopian birr).

## Clinical Factors Associated with Reported CNS Adverse Events

CD4 count, World Health Organization (WHO) disease stage, concomitant medical condition and concurrent use of other medication were found to have

**Table 2** Clinical Characteristics of Participants

Characteristics	Category	Frequency (%)
CD4 count	<200 cells/mm <sup>3</sup>	175 (50.7)
	≥200 cells/mm <sup>3</sup>	170 (49.3)
Viral load	Undetectable	138 (40.0)
	≤1000 copies	97 (28.1%)
	>1000 copies	47 (13.6)
	Not reported	63 (18.3)
Disease stage	Stage 1	80(23.2)
	Stage 2	75(21.7)
	Stage 3	145(42.0)
	Stage 4	45(13.0)
Efavirenz-based regimen	TDF+3TC+EFV	272(78.8)
	AZT+3TC+EFV	73(21.2)
Duration since the start of efavirenz	<1 years	60(17.4)
	1–3 years	119(34.5)
	4–6 years	85(24.6)
	7–10 years	36(10.4)
	>10 years	45(13.0)
Time of the day medication is taken	Morning	10(2.9)
	Night	252(73.0)
	Both	83(24.1)
Medication taking in relation to meal	Before meal	34(9.9)
	After meal	233(67.5)
	Both	78(22.6)
Any concomitant medical condition	Yes	43(12.5)
	No	302(87.5)
Concurrent use of other medication	Yes	90(26.1)
	No	255(73.9)

**Abbreviations:** TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; AZT, zidovudine.

a significant association with occurrence of EFV-related CNS adverse events. Patients with a CD4 count of 200 or above are 88% less likely to have CNS adverse events than those with a CD4 count of below 200 (AOR=0.120 (0.038–0.383),  $P<0.0001$ ). As indicated by the larger odds ratio in Table 4, patients who had advanced WHO stage disease (stages 3 or 4) were very much more likely to develop CNS adverse events than patients with WHO stage 1 disease. The absence of a concomitant medical condition is associated with a lower rate of CNS adverse events (AOR=0.107 (0.016–0.714),  $P=0.021$ ). However, patients who were not taking other medications concurrently were five times more likely to report having CNS adverse events (AOR=5.466 (1.545–19.336),  $p=0.008$ ).

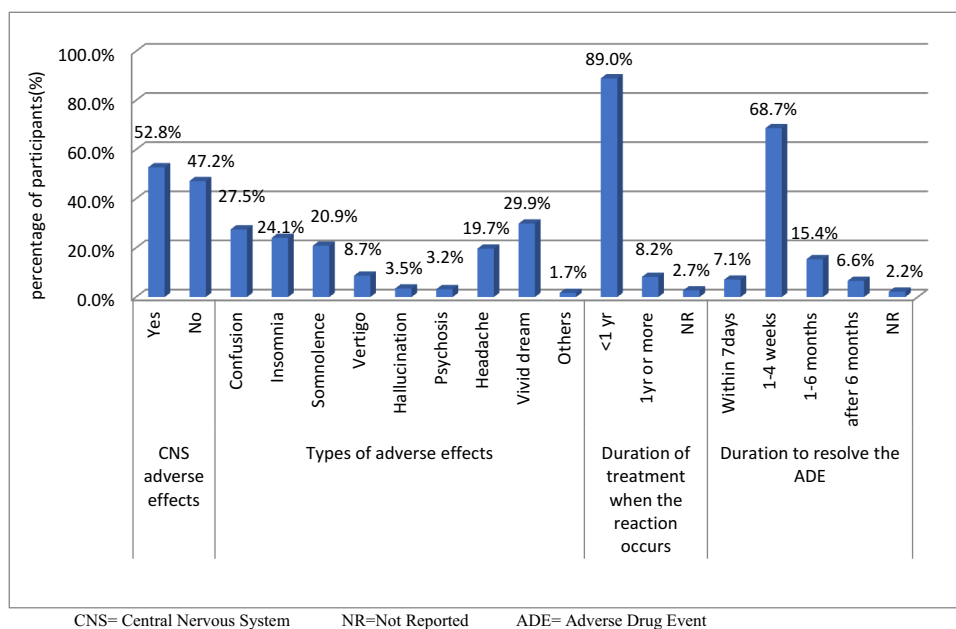


Figure 1 CNS adverse events.

## Discussion

The prevalence of CNS adverse events in the current study was 52.8%. Similarly, a study conducted in Kenya reported a prevalence of 48.6%,<sup>15</sup> a study in Spain reported 54%,<sup>13</sup> a study in the USA and one systematic review showed a prevalence of 50%.<sup>16,17</sup> However, the prevalence rate reported in this study is higher than the report from Ambo referral hospital, Ethiopia, which is 35.7%.<sup>8</sup> This difference might be because the study in Ambo referral hospital included patients who took ART for more than 6 months, obtained data from patient charts only and included patients on non-EFV-based ART regimens.

The most commonly reported CNS adverse events in our study were vivid dreams (29.9%), confusion (27.5%), insomnia (24.1%) and somnolence/drowsiness (20.9%). A study conducted in Ghana reported that insomnia, headaches, abnormal dreams and drowsiness were significantly more common among patients on EFV-based ART.<sup>18</sup> A study conducted by Shikuma et al. on HIV-positive subjects taking EFV-based therapy found that the rate of sleep disordered breathing (SDB) was substantially higher in study subjects compared with published age-matched norms.<sup>19</sup> The majority (89.0%) of participants who reported CNS adverse events experienced the event within a year of starting an EFV-based regimen and in 68.7% of participants the adverse events were resolved within 1–4

weeks. The Ghanaian study indicated that most neuropsychiatric toxicities were reported in the first year of therapy after which the occurrence of events declined.<sup>18</sup> A review article by Apostolova et al. reported that patients treated with EFV revealed neuropsychological symptoms during the first 4 weeks of treatment and that these resolved later on.<sup>7</sup>

Age and economic status had a significant association with the occurrence of CNS adverse events. Patients who are 45 years old or above are three times more likely to develop the adverse events than patients who are less than 25 years old. Likewise, many other African studies reported that occurrence of ART-related adverse events were significantly higher in older patients compared with younger ones.<sup>1,20–22</sup> Patients with good and moderate economic status are less likely to have CNS adverse events as compared with those with low economic status. This could be because people with better economic status could have improved living standards and better health-care access.

Patients who had severe disease (WHO stages 3 or 4 disease or low CD4 count) have higher risk of CNS adverse events from EFV-based ART regimens. In the current study patients with a CD4 count of below 200 are more likely to have CNS adverse events than those with a CD4 count of 200 or above. Patients who had advanced stage disease (WHO stages 3 or 4) were very much more likely to develop CNS adverse events than patients with stage 1 disease. This may be explained by



**Table 3** Sociodemographic Factors Associated with Reported CNS Adverse Effects of Efavirenz

Variables	Category	CNS Adverse Event		COR (95% CI)	AOR (95% CI)	p-value
		No (%)	Yes (%)			
Sex	Male	93 (45.1)	113 (54.9)	1.00	1.00	0.754
	Female	70 (50.4)	69 (49.6)	0.811 (0.527–1.248)	0.926 (0.572–1.498)	
Age	<25 years	29 (63.0)	17 (37.0)	1.00	1.00	0.101
	25–44 years	94 (47.0)	106 (53.0)	1.924 (0.994–3.722)	1.955 (0.877–4.356)	
	45 years and above	40 (40.4)	59 (59.6)	2.516 (1.224–5.174)	3.183 (1.302–7.782)	
Weight	50 kg or less	72 (54.1)	61 (45.9)	1.00	1.00	0.098
	51–69kg	80 (42.3)	109 (57.7)	1.608 (1.029–2.514)	1.615 (0.915–2.848)	
	70 kg and above	11 (47.8)	12 (52.2)	1.288 (0.531–3.124)	1.281 (0.390–4.212)	
BMI	<18.5 (underweight)	28 (45.9)	33 (54.1)	1.00	1.00	0.191
	18.5–24.99 (normal)	120 (47.8)	131 (52.2)	0.926 (0.528–1.624)	0.626 (0.310–1.264)	
	≥25.0 (overweight)	15 (45.5)	18 (54.5)	1.018 (0.435–2.383)	0.538 (0.166–1.748)	
Education	No formal education	43 (53.1)	38 (46.9)	1.00	1.00	0.479
	Primary school	48 (45.7)	57 (54.3)	1.344 (0.751–2.403)	1.267 (0.658–2.440)	
	Secondary school	55 (47.8)	60 (52.2)	1.234 (0.698–2.182)	1.214 (0.647–2.277)	
	Higher education	17 (38.6)	27 (61.4)	1.797 (0.851–3.795)	1.696 (0.724–3.969)	
Religion	Orthodox Christian	130 (46.3)	151 (53.7)	1.00	1.00	0.989
	Muslim	24 (49.0)	25 (51.0)	0.897 (0.489–1.646)	0.995 (0.511–1.940)	
	Others	9 (60.0)	6 (40.0)	0.574 (0.199–1.655)	0.465 (0.143–1.513)	
Economic status	Low	99 (40.1)	148 (59.9)	1.00	1.00	<0.0001*
	Moderate	50 (64.9)	27 (35.1)	0.361 (0.212–0.615)	0.303 (0.169–0.545)	
	Good	14 (66.7)	7 (33.3)	0.334 (0.130–0.858)	0.273 (0.098–0.760)	
Marital status	Married	54 (43.2)	71 (56.8)	1.00	1.00	0.459
	Single	63 (50.0)	63 (50.0)	0.761 (0.463–1.250)	0.802 (0.447–1.439)	
	Divorced	23 (46.9)	26 (53.1)	0.860 (0.443–1.669)	0.779 (0.373–1.628)	
	Widowed	23 (51.1)	22 (48.9)	0.727 (0.367–1.441)	0.746 (0.355–1.564)	
Employment status	Employed by Government or private organization	47 (44.8)	58 (55.2)	1.00	1.00	0.990
	Self employed	56 (47.1)	63 (52.9)	0.912 (0.538–1.544)	0.996 (0.548–1.810)	
	Unemployed	60 (49.6)	61 (50.4)	0.824 (0.488–1.392)	1.083 (0.583–2.013)	
History of alcohol use	Yes	57 (41.3)	81 (58.7)	1.00	1.00	0.055
	No	106 (51.2)	101 (48.8)	0.671 (0.434–1.036)	0.611 (0.369–1.011)	
Smoking history	Yes	11 (39.3)	17 (60.7)	1.00	1.00	0.465
	No	152 (47.9)	165 (52.1)	0.702 (0.319–1.547)	0.716 (0.292–1.755)	

Note: \*Significant association.

Abbreviations: CNS, central nervous system; COR, crude odds ratio; AOR, adjusted odds ratio; BMI, body mass index.

the fact that patients with WHO stages 3 or 4 disease or a CD4 count of below 200 have deteriorated medically and may not cope with the drug effect, or may have multiple comorbidities and opportunistic infections which they may consider and report as ADEs.

The presence of a concomitant medical condition is one of the clinical factors having a significant association with the occurrence of CNS adverse events. In support of

this finding, the study conducted at Mbagathi District Hospital's comprehensive care centre in Kenya reported that the presence of concomitant medical conditions was significantly associated with the occurrence of CNS adverse events.<sup>15</sup> However, concurrent use of other medication is negatively associated with CNS adverse events. This may be because concurrently used medications may sometimes mask symptoms of some of the adverse events

**Table 4** Clinical Factors Associated with Reported CNS Adverse Effects of Efavirenz

Variables	Category	CNS Adverse Event		COR (95% CI)	AOR (95% CI)	p-value
		No (%)	Yes (%)			
CD4 count	<200	47 (26.9)	128 (73.1)	1.00	1.00	<0.0001*
	≥200	116 (68.2)	54 (31.8)	0.171 (0.107–0.272)	0.120 (0.038–0.383)	
Viral load	Undetectable	70 (50.7)	68 (49.3)	1.00	1.00	0.935 0.513
	≤1000	41 (42.3)	56 (57.7)	1.406 (0.833–2.372)	0.953 (0.302–3.012)	
	>1000	21 (44.7)	26 (55.3)	1.275 (0.656–2.478)	1.618 (0.384–6.822)	
Disease stage	Stage 1	77 (96.3)	3 (3.8)	1.00	1.00	0.403 <0.0001* <0.0001*
	Stage 2	69 (92.0)	6 (8.0)	2.232 (0.538–9.266)	2.051 (3.81–11.041)	
	Stage 3	8 (5.5)	137 (94.5)	439.54 (113.27–1705.61)	907.41 (136.41–6010.50)	
	Stage 4	9 (20.0)	36 (80.0)	102.67 (26.212–402.12)	157.283 (28.01–883.228)	
Drug regimen	TDF+3TC+EFV	109 (40.1)	163 (59.9)	1.00	1.00	0.088
	AZT+3TC+EFV	54 (74.0)	19 (26.0)	0.235 (0.132–0.419)	0.188 (0.027–1.285)	
Duration of treatment	<1 year	32 (53.3)	28 (46.7)	1.00	1.00	0.365 0.976 0.975 0.450
	1–3 years	51 (42.9)	68 (57.1)	1.524 (0.817–2.843)	0.472 (0.093–2.397)	
	4–6 years	43 (50.6)	42 (49.4)	1.116 (0.576–2.613)	1.025 (0.207–5.088)	
	7–9 years	18 (50.0)	18 (50.0)	1.143 (0.500–2.613)	1.032 (0.150–7.119)	
	≥10 years	19 (42.2)	26 (57.8)	1.564 (0.717–3.409)	0.404 (0.038–4.240)	
Time of day the medication is taken	Morning	5 (50.0)	5 (50.0)	1.00	1.00	0.196 0.534
	Night	116 (46.0)	136 (54.0)	1.172 (0.331–4.150)	0.145 (0.008–2.704)	
	Both	42 (50.6)	41 (49.4)	0.976 (0.263–3.626)	0.344 (0.012–9.940)	
Medication taking in relation to meal	Before meal	17 (50.0)	17 (50.0)	1.00	1.00	0.238 0.349
	After meal	111 (47.6)	122 (52.4)	1.099 (0.535–2.257)	2.688 (0.521–13.871)	
	Both	35 (44.9)	43 (55.1)	1.229 (0.548–2.753)	2.452 (0.376–15.996)	
Concomitant medical condition	Yes	15 (34.9)	28 (65.1)	1.00	1.00	0.021*
No	148 (49.0)	154 (51.0)	0.557 (0.286–1.086)	0.107 (0.016–0.714)		
Concurrent use of other medication	Yes	42 (46.7)	48 (53.3)	1.00	1.00	0.008*
No	121 (47.5)	134 (52.5)	0.969 (0.599–1.568)	5.466 (1.545–19.336)		

**Note:** \*Significant association.

**Abbreviations:** CNS, central nervous system; COR, crude odds ratio; AOR, adjusted odds ratio; TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; AZT, zidovudine.

or may induce the metabolism of EFV which in turn reduces its plasma level and lead to lesser risk of an adverse event.

The result of multivariate logistic regression analysis indicated the absence of a significant association between CNS adverse events and the type of ART regimen. In line with this, Wambura reported that none of the EFV-based ART regimens had a significant association with the occurrence of CNS adverse events.<sup>15</sup> Even though a large proportion of alcohol users in our study reported CNS adverse events the association between alcohol use and occurrence of CNS adverse events was not significant ( $p=0.055$ ). In line with this, a retrospective study by Salome et al. reported that alcohol users were at no more risk of showing CNS adverse events than those who denied a history of

alcohol use.<sup>23</sup> Smoking status was not found to be significantly associated with the occurrence of CNS adverse events. This finding may not represent the true picture of association because of the smaller number of respondents (8.1% only) reporting as having a smoking history, which would probably be due to not being willing to disclose this information for personal reasons.

The results of the current study should be interpreted cautiously due to some limitations. Firstly, recall bias may affect the findings as patients may not be able to recall what happened since the start of their ART regimen. Secondly, being a cross-sectional study, all the limitations associated with this type of design may be manifested in our study. Thirdly, generalization of the findings may be difficult as it is a single center study.

## Conclusion

More than half of HIV patients taking efavirenz-based regimens at the University of Gondar Comprehensive and Specialized Hospital (UoGCSH) experienced CNS adverse events. Vivid dreams, confusion, insomnia and somnolence were the most frequently reported adverse events. Most of the CNS adverse events experienced by the respondents occurred in the first year of treatment and resolved within a month. Health-care providers should give attention to patients on efavirenz therapy to monitor for CNS adverse events, especially those patients who have low CD4 count, advanced stage disease, comorbidities, low income and are older in age.

## Data Sharing Statement

The datasets during and/or analyzed during the current study is available from the corresponding author on reasonable request.

## Consent to Publish

Participants consent was taken to publish this work.

## Ethics Approval and Consent to Participate

Ethical clearance was obtained from the ethical review committee of the School of Pharmacy, University of Gondar. The respondents were informed about the purpose of the study and their consent to participate was obtained.

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## Disclosure

The authors declare that they have no conflicts of interest for this work.

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