Drug Saf (2015) 38:629–639
DOI 10.1007/s40264-015-0295-7

ORIGINAL RESEARCH ARTICLE

Adverse Drug Reactions and Clinical Outcomes in Patients Initiated on Antiretroviral Therapy: A Prospective Cohort Study From Ethiopia

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Published online: 26 May 2015

Abstract

Introduction In Ethiopia, the use of antiretroviral therapy (ART) has been scaled up for HIV/AIDS over the past decade. Adverse drug reactions (ADRs) associated with ART pose a unique challenge in the treatment of the infection in this resource-limited setting.

Objectives The aims of this study were to examine the incidence and nature of ADRs, identify the risk factors associated with the development of ADRs, and assess their impact on treatment outcomes.

Methods A prospective cohort study was conducted in adult patients (≥18 years of age) with HIV/AIDS who commenced ART. All ADRs in the first 12 months of therapy were recorded, and the severity, causality, and preventability assessed. The impact of severe ADRs on self-reported adherence, immunological, and body mass index (BMI) outcomes were assessed.

Results Of the 211 patients included in the analysis, 181 (85.7 %) experienced at least one ADR and 66 (31.3 %) experienced at least one severe ADR within 12 months of commencing ART (incidence rates for any ADR and severe ADR of 14.8 and 3.2 per 100 person-months, respectively). Logistic regression analysis indicated that taking zidovudine-containing regimens (odds ratio [OR] 4.2, 95 % confidence interval [CI] 2.1–8.4) or being unemployed (OR 2.2, 95 % CI 1.1–4.3) were independent predictors of experiencing severe ADRs. Patients who experienced a severe ADR were less likely (OR 0.4, 95 % CI 0.2–0.9) to be ≥90 % adherent to ART. The mean gain in BMI was significantly lower in patients with severe ADRs after 3 and 12 months of therapy.

Conclusions ADRs were common within the first 3 months in patients initiated on ART. Severe ADRs were negatively associated with self-reported adherence and gain in BMI. Measures need to be implemented to routinely monitor for severe ADRs to improve ART adherence and treatment outcomes.

Key Points

One-third of patients initiated on ART experienced severe ADRs over a 1-year period.

Most severe ADRs were reported within the first 3 months and found to have negative impact on treatment outcomes in patients initiated on ART.

Almost half of the severe ADRs related to ART were found to be preventable, highlighting the importance of improving antiretroviral prescribing and monitoring practices.

1 Introduction

At the end of 2012, 35.3 million people were living with human immunodeficiency virus (HIV) and 9.7 million people (61 % of eligible patients) were receiving antiretroviral

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therapy (ART) worldwide [1]. ART has decreased mortality and morbidity, and improved the quality of life of patients with HIV [2]. However, ART can also cause undesirable adverse drug reactions (ADRs) that are among the most important reasons for medication nonadherence, treatment switch or discontinuation, and virologic failure [3–6].

A free ART programme was introduced in Ethiopia in 2005 [7, 8]. Over the past 10 years, decentralisation and scale-up of the programme has occurred [1] and 743 free ART centres have been established across the country. A total of 249,174 adult patients (86 % of eligible patients) were receiving ART as of 2011 [1, 9].

Detection of ADRs in Ethiopian ART clinics provides an important assessment of the burden of antiretroviral-associated morbidity in the HIV care programme. To our knowledge, only a few retrospective studies have attempted to identify the type and frequency of ADRs in Ethiopian adult patients receiving ART [10, 11], and given the poor documentation of ADRs in patients' medical charts, ADRs are underreported. In addition, the impact of ADRs on treatment outcomes (body mass index [BMI] and CD4 count) has not been evaluated. In resource-limited settings, BMI and CD4 count are useful surrogate markers of treatment outcomes [12].

The aim of this study was to prospectively examine the incidence and nature of ADRs, identify the risk factors associated with the development of ADRs, and assess their impact on treatment outcomes in Ethiopian patients with HIV/acquired immune deficiency syndrome (AIDS) who commenced ART.

2 Methods

This was a prospective cohort study in which adult patients (≥18 years of age) with HIV/AIDS who commenced ART were followed from the time of ART commencement (month 00) to 12 months (month 12) of therapy. The study was conducted from 18 December 2012 to 18 May 2014 at Felege-Hiwot and Gondar University Hospitals. Nurses and research pharmacists recruited patients from the ART clinics, and all participants provided written informed consent for their involvement in the study. Details of the study setting have previously been described [13].

Adult HIV-infected patients were eligible to start ART when their CD4 count was ≤350 cells/μL regardless of the clinical symptoms, or with any symptoms indicating a WHO clinical stage of 3 or 4, irrespective of CD4 count. ART initiation was informed by the *Ethiopian guidelines for management of opportunistic infections and antiretroviral treatment in adolescents and adults in Ethiopia 2008* and the WHO *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach 2010 revision* [14, 15]. ART-initiated patients had an appointment every month for the first 6 months and every 3 months thereafter at the ART clinics. A research pharmacist was assigned to each hospital's ART clinic to assess ADRs throughout the study period. Patients were also asked to report any potential ADRs. ADRs that continued for subsequent appointments without recovery were reported once. The research pharmacists, who were experienced in clinical care in public health facilities, interviewed patients, caregivers and physicians, reviewed patients' medical records and documented detailed information for each of the potential ADRs that patients experienced. According to the WHO definition, an ADR was defined as "a response to a drug that is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [16]. ADRs were evaluated based on the clinical signs and symptoms, and laboratory tests. The severity, causality, and preventability of ADRs were assessed using the Division of AIDS Adverse Events (DAIDS AE) grading table [17], Naranjo's probability scale [18], and the Schumock and Thornton criteria [19], respectively. The management and outcomes of ADRs were also recorded. These data were independently reviewed by a second research pharmacist, blinded to the first pharmacist's assessment, to ensure their accuracy and validity. When there was a disagreement in the assessment of an ADR, the pharmacists resolved their disagreement through discussion until consensus was reached.

Sociodemographic and clinical information, such as age, sex, level of education, employment status, comorbidities, WHO stage of HIV/AIDS, weight and height, and laboratory test results performed in the hospitals, including CD4 count, haematocrit, white blood cell (WBC) count, absolute neutrophil count, platelet count, liver function and renal function, were recorded from each patient's medical record. Similarly, details of the ART regimen and other concomitant medications were also recorded. An increase in CD4 counts of more than 50 cells/μL from baseline was defined as immunological response [20].

Dose adherence to ART was measured using a modified AIDS Clinical Trial Group (ACTG) self-reported adherence questionnaire that asks patients how many doses they missed in the last 7 days. Similarly, time adherence was measured using the four-item Likert-type modified ACTG questionnaire [21]. Details of multiple medication adherence measures have previously been reported [13]. Responses to the two questions were translated into dose and time adherence scores ranging from 0 to 100 % over the 7-day period, and the average of the two measures was taken as a combined indicator of dose and time adherence.

The frequency of ADRs was described using descriptive statistics. Characteristics of patients who experienced ADRs and those who did not were compared using Pearson's Chi-square tests for sex, age, level of education, employment status, immunological response (CD4 count), WHO HIV stage, history of drug allergy, type of ART regimen, comorbidities, concomitant medications, and self-reported adherence. Logistic regression analysis was undertaken to determine the independent predictors of severe ADRs (grades 3 and 4 using the DAIDS AE grading table), cutaneous reactions, gastrointestinal complaints, and neuropsychiatric reactions where univariate analyses suggested association with multiple risk factors. Factors with a p value ≤ 0.2 on univariate analysis were entered into the logistic regression model after checking multicollinearity. Results are presented in terms of odds ratio (OR) for each risk factor followed by a 95 % confidence interval (CI). Mean changes in BMI after 3 and 12 months of ART were compared between patient groups with independent sample t-tests. Data were analysed using SPSS version 21 (IBM Corporation, Armonk, NY, USA). A p value <0.05 was considered statistically significant.

Ethical approvals were received from the Tasmanian Health and Medical Human Research Ethics Committee (H0012722) and Bahir-Dar University's Ethics Committee (RCS/567/2004).

Table 1 Baseline patient characteristics ($n = 211$)

Characteristic	*N* (%)	Median	IQR
Women	127 (60.2)		
Age, years		32	27–38
Education level			
Illiterate	115 (54.5)		
Literate	96 (45.5)		
Employment			
Unemployed	116 (55)		
Employed	95 (45)		
BMI, kg/m^2		19.4	18.0–21.9
History of drug allergy	16 (7.6)		
Baseline WHO staging[a]			
Stage I and II	97 (46.0)		
Stage III and IV	105 (49.8)		
ART regimen			
Zidovudine-based	112 (53.1)		
Tenofovir-based	97 (46.0)		
Stavudine-based	2 (0.9)		
Efavirenz-based	109 (51.7)		
Nevirapine-based	102 (48.3)		
Baseline CD4, cells/μL[b]		183	94–252

IQR interquartile range, *BMI* body mass index, *ART* antiretroviral therapy

[a] Total does not add up to 211 due to missing data

[b] One missing value

3 Results

During the 4-month recruitment period (18 December 2012–17 March 2013), 337 adults (≥18 years of age; 191 females and 146 males) commenced ART at the two sites. Of these, 246 patients (143 females and 103 males) enrolled in this study. The remaining 91 patients did not take part in this study because of our exclusion criteria (patients who were initiated on ART in the study clinics but whose follow-up was in outlying areas were excluded) and not consenting to participate in the study. There were no significant differences in the WHO stage of HIV/AIDS, sex, age, CD4 count and weight between subjects who did and did not participate in the study. Thirty-five patients who did not complete at least 3 months of follow-up (9 lost to follow-up, 11 withdrawn, 10 died, and 5 transferred to other clinics) were excluded from this analysis. As shown in Table 1, of the 211 patients included in the study, 60 % were female. Their median baseline CD4 count and BMI were 183 cells/μL and 19.4 kg/m^2, respectively.

All patients were receiving an ART regimen containing three drugs—two nucleoside reverse transcriptase inhibitors (NRTIs) [zidovudine plus lamivudine, or tenofovir plus lamivudine] plus one non-NRTI (NNRTI) [efavirenz or nevirapine] at baseline. Overall, 112 (53 %) patients were taking a zidovudine plus lamivudine-containing regimen, and 109 (52 %) patients were taking an efavirenz-containing regimen. Self-reported dose adherence in the study sample was 97.7 % at 3 months. The rate of adherence considering the combined (dose and time) indicator was 93.8 % at 3 months.

Throughout the study period, 370 ADRs were identified (Table 2). Twenty-one ADRs were excluded from analysis as their causal relationship with ART regimens was rated as doubtful according to Naranjo's scale; 66.5 and 31.8 % of ADRs had a possible and probable causal relationship with the ART regimen, respectively, as shown in Table 3. Most ADRs were rated as grade 1 (52.7 %) and grade 2 (25.2 %) using the DAIDS AE grading table; 22.1 % were graded as severe (grades 3 and 4).

ADRs were common; 181 (85.7 %) patients experienced at least one ADR and 66 (31.3 %) experienced severe (grade 3 or 4) ADRs. The prevalence of ADRs was similar in females (86.6 %) and males (84.5 %). Ninety-seven (45 %) patients reported more than one ADR; 78 (37 %) patients had two or three ADRs, and 19 (9 %) patients had four or five ADRs.

The onset and distribution of ADRs within the study period are shown in Fig. 1. Ninety percent of ADRs (314)

Table 2 Frequency of potential adverse drug reactions of antiretroviral therapy

Specific ADR by organ	No. of cases (%) [$n = 211$]	TDF + 3TC + EFV (%) [$n = 87$]	TDF + 3TC + NVP (%) [$n = 10$]	ZDV + 3TC + EFV (%) [$n = 22$]	ZDV + 3TC + NVP (%) [$n = 90$]
Gastrointestinal	115 (54.5)	28 (32.1)	6 (60.0)	12 (54.5)	66 (73.3)
Nausea	60 (28.4)	11 (12.6)	3 (30)	8 (36.4)	38 (42.2)
Vomiting	30 (14.2)	8 (9.2)	3 (30)	2 (9.1)	16 (17.7)
Anorexia	4 (1.9)	1 (1.1)	–	1 (4.5)	3 (3.3)
Diarrhoea	3 (1.4)	1 (1.1)	–	–	2 (2.2)
Gastric discomfort	12 (5.7)	4 (4.6)	–	1 (4.5)	5 (5.5)
Gastritis	6 (2.8)	3 (3.4)	–	–	2 (2.2)
Neuropsychiatric	113 (53.5)	76 (87.3)	2 (20)	20 (90.9)	14 (15.5)
Headache	37 (17.5)	19 (21.8)	2 (20)	4 (18.2)	10 (11.1)
Nightmare	17 (8.0)	14 (16.1)	–	3 (13.6)	–
Confusion	9 (4.2)	7 (8.0)	–	2 (9.1)	–
Somnolence	1 (0.5)	–	–	–	1 (1.1)
Insomnia	10 (4.7)	7 (8.0)	–	1 (4.5)	2 (2.2)
Vertigo	23 (10.9)	16 (18.4)	–	7 (31.8)	–
Anxiety	1 (0.5)	–	–	1 (4.5)	–
Tingling	1 (0.5)	1 (1.1)	–	–	–
Dizziness	5 (2.4)	4 (4.6)	–	–	1 (1.1)
Numbness	1 (0.5)	1 (1.1)	–	–	–
Hearing loss	1 (0.5)	–	–	1 (4.5)	–
Psychosis	1 (0.5)	1 (1.1)	–	–	–
Hallucination	2 (0.9)	1 (1.1)	–	1 (4.5)	–
Depression	2 (0.9)	2 (2.3)	–	–	–
Lethargy	1 (0.5)	1 (1.1)	–	–	–
Trouble remembering	1 (0.5)	1 (1.1)	–	–	–
Agitation	1 (0.5)	1 (1.1)	–	–	–
Cutaneous reaction	66 (31.3)	24 (27.6)	4 (40)	9 (40.9)	28 (31.1)
Skin rash	39 (18.5)	17 (19.5)	2 (20)	6 (27.3)	14 (15.5)
Allergic dermatitis	5 (2.4)	–	–	1 (4.5)	4 (4.4)
Nail pigmentation	3 (1.4)	–	–	–	3 (3.3)
Pruritus	15 (7.1)	7 (8.0)	2 (20)	3 (13.6)	3 (3.3)
Erythema multiforme	1 (0.5)	–	–	–	1 (1.1)
Erythema	1 (0.5)	–	–	–	1 (1.1)
Hepatotoxicity	2 (0.9)	1 (1.1)	1 (10)	–	–
Nephrotoxicity	2 (0.9)	2 (2.3)	–	–	–
Systemic signs/symptoms	23 (10.9)	4 (4.6)	–	3 (13.6)	15 (16.6)
Fever	10 (4.7)	3 (3.4)	–	1 (4.5)	6 (6.6)
Fatigue	13 (6.2)	1 (1.1)	–	2 (9)	9 (10)
Musculoskeletal	12 (5.7)	3 (3.4)	1 (10)	2 (4.5)	6 (6.6)
Arthralgia	7 (3.3)	2 (2.3)	–	2 (4.5)	3 (3.3)
Muscle pain	5 (2.4)	1 (1.1)	1 (10)	–	3 (3.3)
Haematological	16 (7.6)	4 (4.7)	–	5 (22.7)	7 (7.7)
Anaemia	13 (6.2)	1 (1.1)	–	5 (22.7)	7 (7.7)
Thrombocytopenia	3 (1.4)	3 (3.4)	–	–	–

ADR adverse drug reaction, *TDF* tenofovir, *3TC* lamivudine, *ZDV* zidovudine, *EFV* efavirenz, *NVP* nevirapine

Table 3 Assessment and management of adverse drug reactions

	Adverse drug reactions								
	Gastrointestinal [*n* (%)]	Neuropsychiatric [*n* (%)]	Cutaneous reaction [*n* (%)]	Hepatotoxicity [*n* (%)]	Nephrotoxicity [*n* (%)]	Systemic signs/ symptoms [*n* (%)]	Musculoskeletal [*n* (%)]	Haematological [*n* (%)]	Total [*n* (%)]
No. of cases	115	113	66	2	2	23	12	16	349
Causality									
Definite	–	–	–	–	2 (100)	–	–	4 (25)	6 (1.7)
Probable	32 (27.8)	4 (3.5)	52 (78.7)	2 (100)	–	3 (13)	6 (50)	12 (75)	111 (31.8)
Possible	83 (72.2)	109 (96.5)	14 (21.2)	–	–	20 (86.9)	6 (50)	–	232 (66.5)
Severity									
Grade 1	46 (40)	83 (73.4)	32 (48.5)	–	–	12 (52.2)	5 (4.2)	6 (37.5)	184 (52.7)
Grade 2	21 (18.3)	25 (22.1)	25 (37.8)	1 (50)	–	7 (30.4)	6 (50)	3 (18.7)	88 (25.2)
Grade 3	45 (39.1)	5 (4.4)	6 (9.1)	–	–	4 (17.4)	–	2 (12.5)	62 (17.7)
Grade 4	3 (2.6)	–	3 (4.5)	1 (50)	2 (100)	–	1 (8.3)	5 (31.3)	15 (4.3)
Preventability									
Yes	24 (20.9)	2 (1.7)	8 (12.1)	2 (100)	2 (100)	3 (13.0)	2 (16.7)	16 (100)	57 (16.3)
No	91 (79.1)	111 (98.3)	58 (87.9)	–	–	20 (87)	10 (83.3)	–	292 (83.7)
Intervention									
Yes									
Drug withdrawal	3 (2.6)	1 (0.9)	6 (9.1)	1 (50)	2 (100)	1 (4.3)	–	8 (50)	22 (6.3)
Symptomatic treatment	12 (10.4)	6 (5.3)	12 (18.2)	–	–	5 (21.7)	4 (33.3)	2 (12.5)	41 (11.7)
No	100 (86.9)	106 (93.8)	48 (72.7)	1 (50)	–	17 (73.9)	8 (66.6)	1 (6.25)	281 (80.5)

were reported within the first 3 months of ART. Seventy-seven severe ADRs were reported throughout the study period, and 69 (89.6 %) of these occurred within the first 3 months. The total duration of follow-up time was 2362 person-months, yielding an incidence rate of patients experiencing ADRs as 14.7 per 100 person-months. The corresponding incidence rate for severe ADRs was 3.2 per 100 person-months.

Using univariate analyses, unemployment ($p = 0.05$), zidovudine-based regimens ($p < 0.001$) and nevirapine-based regimens ($p < 0.001$) were associated with the occurrence of severe ADRs. Logistic regression analysis indicated that taking zidovudine-containing regimens (OR 4.2, 95 % CI 2.1–8.4) or being unemployed (OR 2.2, 95 % CI 1.1–4.3) were independent predictors of experiencing severe ADRs (Table 4). The most common classes of ADRs were gastrointestinal complaints (54.5 %) followed by neuropsychiatric disorders (32.4 %) and skin reactions (31.3 %). Nausea (28.4 %), followed by skin rash (18.5 %) and headache (17.5 %), were the most frequently reported specific ADRs (Table 2). Regimens containing zidovudine were significantly associated with the development of gastrointestinal ADRs ($p = 0.001$) and anaemia ($p < 0.05$). There was a significant association between regimens containing efavirenz or zidovudine and neuropsychiatric reactions ($p < 0.001$). Female sex ($p < 0.05$) and a previous history of allergy to any medications ($p < 0.05$) were risk factors for cutaneous reactions. History of allergy (OR 5.3, 95 % CI 1.7–16.3) was more strongly associated with the occurrence of skin reactions in a logistic regression

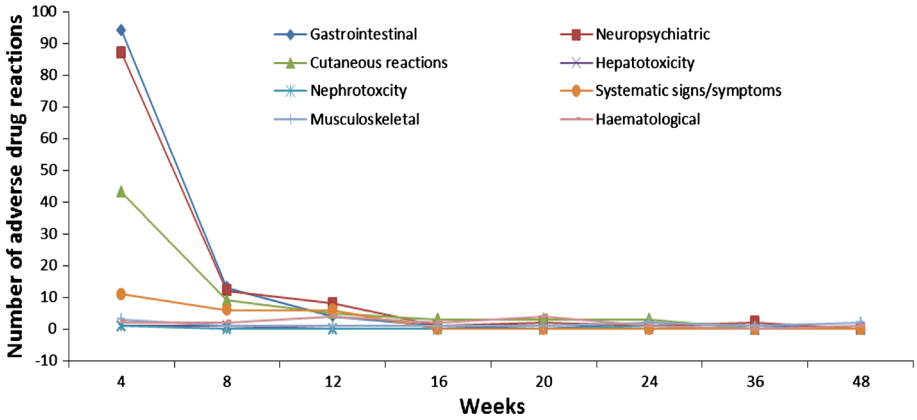

Fig. 1 Distribution and time of onset of adverse drug reactions

Table 4 Risk factors for adverse drug reactions

Adverse drug reactions	Variables associated with ADR	Chi-square test		Logistic regression	
		OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Severe ADR	Zidovudine-based regimens	3.5 (2.0–6.9)	<0.001	4.2 (2.1–8.4)	<0.001
	Nevirapine-based regimens	3.5 (1.9–6.4)	<0.001	–	–
	Unemployed	1.9 (1.0–3.5)	0.050	2.2 (1.1–4.3)	0.024
	WHO stage III and IV	0.6 (0.3–1.1)	0.123	0.6 (0.3–1.2)	0.163
	Eating once per day	1.6 (0.8–3.3)	0.194	1.6 (0.7–3.5)	0.266
Gastrointestinal	Zidovudine-based regimens	2.6 (1.5–4.6)	0.001	2.5 (1.4–4.5)	0.002
	Education: no	0.7 (0.4–1.1)	0.153	0.7 (0.4–1.3)	0.316
Neuropsychiatric	Efavirenz-based regimens	7.24 (3.8–13.7)	<0.001	8.0 (4.0–15.9)	<0.001
	Tenfovir-based regimens	3.7 (2–5)	<0.001	–	–
	Female sex	1.5 (0.9–2.7)	0.190	0.7 (0.4–1.5)	0.394
	BMI ≤19.5 kg/m^2	1.5 (0.8–2.5)	0.220	1.3 (0.6–2.5)	0.535
	Age ≤30 years	1.6 (0.9–2.7)	0.124	1.5 (0.8–3.0)	0.237
	Eating once a day	1.70 (0.8–3.5)	0.200	1.8 (0.8–4.1)	0.165
Skin reactions	Female sex	2.0 (1.1–3.8)	0.0413	2.0 (1.1–3.9)	0.034
	History of drug allergy	5.3 (1.7–16.2)	0.003	5.3 (1.7–16.3)	0.004
Haematological	Zidovudine-based regimens	4.0 (1.1–14.5)	0.050	–	–

ADR adverse drug reaction, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index

model than was female sex (OR 2.0, 95 % CI 1.1–3.9) (Table 4).

Fifty-seven (16.3 %), and 38 (47.5 %) ADRs and severe ADRs, respectively, were preventable based on the Schumock and Thornton criteria (Table 3). Symptomatic treatments and substitution of the offending antiretroviral agents were reported for 41 (11.7 %) and 22 (6.3 %) ADRs, respectively. Alteration of the ART regimen occurred in 28 (13.3 %) patients throughout the study period and, of these, 22 (78 %) were due to the development of severe ADRs. Twenty (35 %) preventable severe ADRs were gastrointestinal complaints associated with zidovudine-containing regimens; of these, only three patients received symptomatic treatment. Nineteen (33 %) preventable ADRs were due to inadequate laboratory monitoring of drug toxicities; of these, 12 (63 %) ADRs were anaemia associated with zidovudine-containing regimens. Skin reactions were the third most important class of preventable ADRs in this study, behind gastrointestinal complaints and anaemia. Among 34 female patients who had a baseline CD4 count more than 250 cells/μL, 21 (60 %) were inappropriately taking a nevirapine-based regimen according to Ethiopian guidelines [14]. Of these, seven patients developed skin reactions, three of which were severe.

The potential influence of severe ADRs on treatment outcomes was evaluated with consideration of the combined self-reported 7-day recall dose and time adherence to ART and increased absolute CD4 count and BMI. Patients who experienced a severe ADR within the first 3 months were significantly less likely (OR 0.4, 95 % CI 0.2–0.9; $p < 0.05$) to be adherent when using combined dose and time (≥90 %) adherence to ART within the first 3 months of treatment. However, after 3 months of ART, there was no significant association between severe ADRs and adherence.

The mean BMI at baseline was 20.0 ± 3.1 kg/m^2 in those who experienced severe ADRs, and 20.0 ± 3.4 kg/m^2 in those who did not experience severe ADRs. There were significant differences between these patient groups in terms of mean change in BMI at 3 and 12 months of therapy ($p \leq 0.05$). Among those who experienced severe ADRs, the mean change in BMI increased by 0.6 ± 2.7 kg/m^2 over 12 months, and among those who did not experience severe ADRs, the mean BMI increased by 1.5 ± 2.2 kg/m^2 over the study period. However, there were no significant differences in immunological response (CD4 count) in these patient groups at different time points (Table 5).

4 Discussion

This is the first prospective cohort study assessing the incidence, type, severity, causality, preventability, predictors, and treatment outcomes of ADRs in patients who were initiated on ART in Ethiopia. The study revealed that the incidence rate of severe ADRs over 1 year was 3.2 per 100 person-months, with 89.6 % of severe ADRs reported within the first 3 months of ART. Most of the severe ADRs were gastrointestinal complaints, haematological, and skin reactions. Taking zidovudine-based regimens and being unemployed were shown to be independent risk factors for severe ADRs. The findings of this study regarding patient groups at risk of ADRs are especially important in that they suggest a number of practical interventions that could be readily implemented in clinical practice to minimise patients' risk of developing ADRs. This would represent a significant advance in HIV/AIDS management in Ethiopia as our study demonstrated that severe ADRs were associated with not only self-reported non-adherence with therapy (the importance of optimal adherence to ART in

Table 5 Clinical outcomes and adverse drug reactions

Adherence or gain in BMI or CD4 cells	Severe ADR [*n* (%)]	No severe ADR [*n* (%)]	Chi-square test	
			OR (95 % CI)	*p* value
Adherent (≥90 %) patients at month 3	43 (27.2)	115 (72.8)	0.4 (0.2–0.9)	0.046
Adherent (≥90 %) patients at month 6	49 (31.6)	106 (80.9)	1.1 (0.5–2.6)	0.882
Adherent (≥90 %) patients at month 9	45 (28.8)	111 (84.8)	0.7 (0.3–1.5)	0.448
Adherent (≥90 %) patients at month 12	39 (27.9)	101 (72.1)	0.7 (0.3–1.4)	0.385
Gain CD4 ≥+50 cells/μL within 6 months	38 (31.4)	83 (68.6)	1.0 (0.4–2.4)	1.000
Gain CD4 ≥+50 cells/μL within 12 months	41 (31.8)	88 (68.2)	1.2 (0.5–3.0)	0.826
			t test	
BMI (kg/m^2) change within 3 months	+0.29 ± 1.52	+0.88 ± 1.59		0.017
BMI (kg/m^2) change within 12 months	+0.61 ± 2.73	+1.50 ± 2.22		0.027

BMI body mass index, *ADR* adverse drug reaction, *OR* odds ratio, *CI* confidence interval

optimising patient outcomes is well-recognised [22, 23]) but also a poorer patient outcome in terms of gain in BMI.

In the study period, 86 % of patients reported at least one ADR and more than one-third experienced a severe ADR. The high prevalence of ADRs in this study might be associated with intensive prospective data collection, which assisted to identify mild ADRs that might be unreported in other studies. Studies that followed a similar methodology in Iranian and Indian patients who commenced ART had also reported a high prevalence of ADRs—88 and 90 %, respectively, over 2-year study periods [24, 25].

Zidovudine-containing regimens were a risk factor for gastrointestinal, haematological, and severe ADRs. Other studies had also reported NRTIs as a risk factor for the occurrence of gastrointestinal problems [26]. The overall prevalence of gastrointestinal complaints (54.5 %) was lower than reported in a cohort of Iranian patients (67.3 %), where 81 % of patients were taking a zidovudine-based regimen [24]. However, the prevalence in this sample was higher than reported in Nigerian patients (34 %), of whom 57.7 % were taking zidovudine-containing regimens [27]. Although most of the gastrointestinal problems were mild and self-limiting; they were typically observed in the first 8 weeks of therapy and therefore had the potential to strongly influence patients' perceptions of their treatment. Perhaps because of this, gastrointestinal ADRs are one of the documented reasons for medication non-adherence [28].

The prevalence of anaemia in this study was low (6.2 %) and was similar to that in studies reported in Nigeria (4 %), India (3.1 %), and Haiti (4.7 %) [29–31]. Given that many patients with HIV/AIDS in Ethiopia have coexisting malnutrition and chronic diseases, and 60 % of study participants were female, the relatively low prevalence of anaemia was unexpected. Prospective cohort studies in Iranian and Indian patients reported higher incidences of anaemia (22 and 10.3 %, respectively), although more than 94 % of patients who developed anaemia in these studies were receiving zidovudine-based ART regimens [24, 25]. One possible explanation for the relatively lower prevalence of anaemia in the current study is the lower rate of use of zidovudine-based regimens compared with these previous studies.

Neuropsychiatric ADRs generally appeared within the first few days of treatment and resolved after 4–8 weeks of therapy. However, this short-term ADR may be intolerable and may be the cause of patient dropout, as reported in our previous study [32]; thus, patient education and regimen switch may improve adherence to ART and retention in care.

The prevalence of cutaneous reactions reported in this study (31.3 %) was similar to that reported in Nigeria (26.2 %) [27], and higher than reported in Côte d'Ivoire (14 %) [33] and India (9.2 %) [34]. There was no significant difference in rates of skin reactions between nevirapine- and efavirenz-containing regimens in this sample, unlike studies reported elsewhere [4, 35]. In our logistic regression analysis, female sex and a previous history of allergy were implicated as risk factors for experiencing cutaneous reactions. Hormonal and metabolic factors may play a role in the observed sex disparity in the development of NNRTI-associated rash [36–38]. Our data suggest the need for close monitoring when nevirapine or efavirenz is initiated in patients with these risk factors.

Most severe ADRs were reported within the first 3 months. Patients who experienced severe ADRs were non-adherent, as reported in other studies [25, 39], and experienced a lower increase in BMI. Early non-adherence to first-line regimens is associated with emergence of early and late regimen failure [22, 40] and increasing treatment costs [41]. To our knowledge, no previous studies have reported that severe ADRs were associated with a decreased gain in BMI. ADRs such as nausea reduce food intake and, subsequently, a gain in BMI. In addition, patients who took zidovudine-containing regimens, as reported elsewhere [26], as well as the unemployed, were more likely to develop severe ADRs in this sample. Studies in sub-Saharan patients [42], including our previous study [32], reported that eating insufficient food, which is more likely related with unemployment, exacerbated ADRs with ART. The relationship between severe ADRs and unemployment may be mediated by the diagnosis of advanced HIV/AIDS. A previous study reported that diagnosis of advanced HIV/AIDS, which decreases labour productivity and the chance of employment [43], increased the severity of ADRs with ART [44]. In other studies, the complexities of ART regimens (e.g. number of doses per day, number of pills per dose) are related with poor adherence [45]. In our unpublished data, we found no association between dosing frequency and adherence.

In this study, we found that severe ADRs were more likely to be preventable than less severe ADRs, as reported elsewhere [46]. Almost half of the severe ADRs in patients initiated on ART were preventable, which is considerably less than a preventability rate (82.7 %) reported in a similar study in India [31]. In this study, medication errors related to preventable ADRs occurred more frequently at the prescribing and monitoring stages of therapy than at the dispensing stage. Nevirapine was prescribed in more than 60 % of female patients who had baseline CD4 count >250 cells/μL, although treatment guidelines recommend the use of abacavir or efavirenz in these patients [14]; this increased these patients' risk for developing skin reactions. Interventions (e.g. dietary modification, patient reassurance) to manage gastrointestinal complaints associated

with zidovudine-containing regimens were rarely implemented, which potentially increased the severity of these ADRs. Similarly, inadequate laboratory monitoring for zidovudine-related toxicities may have increased the risk of developing severe anaemia in this study.

Immunologic outcomes throughout the study period were not different in patients with and without severe ADRs. Non-adherence associated with short-term ADRs may not prevent patients making gains in CD4 count. Messou et al. [47] reported that patients who had detectable viral load achieved comparable CD4 counts at 6 months with those with undetectable viral load. Outcomes of ART in patients who experience short-term severe ADRs may be better monitored using viral-load measurement.

The strengths of our study include its prospective nature, which permitted more precise recording of symptoms and assessment of severity, causality, and preventability of ADRs. To minimise the occurrence of a Hawthorne effect, data were collected through research pharmacists working for our study project only. Staff members working in the ART clinics were neither involved in data collection nor received feedback about the results of the study before its completion.

This study has several limitations. Laboratory ADRs were underreported in our findings due to the limited number of laboratory tests being performed for monitoring ADRs in these resource-limited hospitals. In addition, there was a lack of continuity with healthcare providers in ordering the recommended laboratory tests, according to treatment guidelines.

The majority of severe ADRs were associated with errors in prescribing and monitoring of regimens that contained zidovudine and/or nevirapine. This study highlights the significance of improving prescribing and monitoring practices in Ethiopian ART clinics to decrease the risk of severe ADRs. Changing the paper-based prescribing practice in the ART clinics to a computer-based prescribing practice has the potential to decrease errors by providing feedback and suggestions to providers to select the recommended antiretrovirals, and to order laboratory tests for monitoring ADRs in time. Future implementation of the WHO 2013 ART guideline [48], which downgrades zidovudine from a preferred first-line agent, may improve the success of the ART scale-up programme in Ethiopia by reducing the incidence of anaemia and severe ADRs.

5 Conclusions

We found that the majority of severe ADRs were reported within the first 3 months of ART. Taking zidovudine-based regimens and being unemployed were significant risk factors for the development of severe ADRs. We observed that severe ADRs were negatively associated with self-reported adherence and gain in BMI within the first 3 months. Future studies should focus on prescribing and monitoring of ART, particularly in treatment-naïve patients who are vulnerable to severe ADRs, to improve ART adherence and treatment outcomes.

Funding This study was financially supported by the Division of Pharmacy, School of Medicine, University of Tasmania, Hobart, TAS, Australia.

Conflict of interest Woldesellassie M. Bezabhe, Luke R. Bereznicki, Leanne Chalmers, Peter Gee, Desalew M. Kassie, Mekides A. Bimirew, and Gregory M. Peterson have no conflicts of interest to declare that are directly relevant to the content of this study. Gregory M. Peterson is the principal investigator in the Ethiopian HIV Evaluation (EHIVE) Project.

Acknowledgments The authors are grateful to Mr. Adane Minayehu, Mr. Zemene Demelash, and Mr. Dawit Demelash who worked as research pharmacists. We are also grateful to the study participants who volunteered for this study, and healthcare providers in the ART clinics who assisted in the recruitment process.

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