ORIGINAL PAPER

Antiretroviral treatment toxicity is the next challenge in HIV/AIDS management: institutional-based cross-sectional study

Getnet Teshome[1], Tsegaw Agezew[2]

[1]Department of Clinical Chemistry, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia
[2]University of Gondar Comprehensive Specialized Hospital ART Clinic, Gondar, Ethiopia

Abstract

Introduction: Even though the contribution of antiretroviral drugs is undeniable in the treatment of HIV/AIDS, they can cause mild to serious adverse effects. These drug-related side effects are considered reasons for change of treatment regimen, discontinuation, and poor adherence. The objective of this study was to assess the magnitude of associated factors of antiretroviral treatment (ART) toxicity in adult HIV-positive patients on ART.

Material and methods: A cross-sectional study was conducted among a total of 404 study participants. Both primary and secondary data were utilized. Primary data was collected by using questionnaires and physical examination. Secondary data were extracted from patients' charts by using a checklist. Binary logistic regression was applied to determine the associated with ART toxicity factors. Factors with a p-value of < 0.05 were recognized as statistically significant.

Results: Of 404 study participants, 68 (16.8%) experienced ART toxicity. Patients with opportunistic infections ($p < 0.001$) and those taking cotrimoxazole preventive therapy (CPT) ($p = 0.045$) were at higher risk of developing ART toxicity. Viral load ($p = 0.02$), WHO staging ($p < 0.05$), and media unavailability ($p = 0.045$) were also significantly associated factors.

Conclusions: Antiretroviral toxicity was higher in patients with an opportunistic infection, advanced WHO stage, increased viral load, and on CPT. Media availability was also an important factor. Therefore, healthcare providers should closely follow HIV/AIDS patients on CPT, advanced WHO stage, and those with increased viral load. HIV/AIDS patients with opportunistic infections need to be monitored carefully. Alternative information channels, which can be easily accessible, need to be considered by all stakeholders.

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Key words: HIV/AIDS, side effect, adverse reaction, ART toxicity, drug reaction.

Introduction

Acquired immune deficiency syndrome (AIDS) is a disease caused by human immunodeficiency virus (HIV), which progresses through the weakening of human immune system, leaving the body susceptible to secondary comorbidities and opportunistic infections [1]. Since the emergence of HIV, it is estimated that more than 74.9 million people are infected, and 32 million died worldwide. Globally, in 2018,

Address for correspondence: Getnet Teshome, Department of Clinical Chemistry, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia, e-mail: getnetfetene44@gmail.com

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37.9 million people were living with HIV (PLHIV), of which 62% of people were on antiretroviral therapy (ART) [2]. In 2016, about 25.73 million people were estimated to be living with HIV/AIDS in Africa, among which 741,000 died due to HIV/AIDS-related illnesses [3]. Sub-Saharan Africa is the most affected region by HIV/AIDS, and constitutes 76% of the total PLHIV in the world. Sub-Saharan Africa also accounts for 75% of HIV/AIDS-related deaths [4].

AIDS resulted in a significant socio-economic crisis for the last few decades. According to the Ethiopian Demographic and Health Survey in 2016 (EDHS 2016), the national HIV prevalence was 0.9%. In the same year, urban prevalence was estimated as 2.9%, which was seven times higher than that of rural (0.4%). There were around 414,854 adults and 21,146 children under the age of 15, who were taking ART [5]. Discovery of ART was a breakthrough in the management of PLHIV, resulting in a reduction in mortality and improvement in quality of life. ART is important to reduce viral load levels, improve survival, and reduce HIV transmission [6], which transformed HIV/AIDS from an untreatable and fearful condition into a chronic manageable disease [7]. However, the use of ART to manage HIV/AIDS has resulted in an increase in adverse drug reactions (ADR), some of which are life-threatening conditions [8, 9]. ADR is a harmful reaction to medicines given at standard doses through a proper route of administration for prophylaxis, diagnosis, or treatment. ADR are a potential desirable and undesirable effects produced by a drug [10]. Adherence to ART depends on several factors, but the most important factor is the type and severity of ADR experienced by patients. ADR are the most common reasons for poor adherence to treatment [11, 12].

The most commonly encountered toxicity-related causes for alteration of regimens are nausea, rash, anemia, and peripheral neuropathy [13]. Comorbidities in patients with advanced diseases and concomitant treatments for opportunistic infections could affect antiretroviral drug tolerance and thus, increase the risk of toxicities [13]. This could be as a result of pill burden, which need to be taken simultaneously to treat both AIDS and opportunistic infection. Some toxicity profiles may be potentiated by concomitant therapy demands, rigorous clinical monitoring, and early recognition and management of ADR. A spectrum of clinical signs and symptoms, which thought to be associated with immune recovery completed by a response to ART, is commonly known as 'immune reconstitution inflammatory syndrome'. Before initiating ART, patients should be carefully evaluated at baseline and periodically for the rest of their lives to monitor toxicity, intolerance, poor response, or failure to treatment [5].

Information about the development of ADR among ART active patients is vital for reducing and monitoring the risks. However, there was limited information in Ethiopia. Therefore, the objective of this study was to assess the ART toxicity and associated factors among HIV/AIDS patients on ART.

Material and methods

Study design and period

A cross-sectional study design was used to assess ART toxicity of HIV/AIDS patients on ART attending University of Gondar Comprehensive Specialized Hospital, Gondar, Northwest Ethiopia, from January 1, 2019, to February 29, 2020.

Source population and study population

All adult HIV/AIDS patients, who attended treatment and follow-up at the University of Gondar Comprehensive Specialized Hospital ART clinic were considered as a source population.

All adult HIV/AIDS patients, who visited the ART clinic for their ART follow-up during the study period was considered as a study population.

Inclusion and exclusion criteria

Inclusion criteria: All adult HIV/AIDS patients, who visited the hospital ART clinic and who were on ART treatment during the study period was included in the study.

Exclusion criteria: HIV/AIDS patients' charts with incomplete data, pregnant women, patients with known liver and kidney disease, hepatitis B- and C-positive patients, and severely ill patients were not included. Also, naïve HIV-positive patients were not included in this study. Those participants, who were taking drugs other than ART known to cause liver and kidney dysfunction were excluded from this study.

Sample size and sampling techniques

The sample size was calculated based on a single population proportion formula by taking 50% prevalence to achieve a maximum sample size. The total number of HIV/AIDS patients at the hospital was 5,500.

$$n = \frac{N * X}{X + N - 1}$$

Where, $X = Z_{\alpha/2}^{\ 2} \times p \times (1 - p)/MOE^2$, and $Z_{\alpha/2}$ is the critical value of normal distribution at $\alpha/2$ (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), MOE is the margin of error (0.05), p is the sample proportion (50%), and N is the population size (in our case it was 5,500). Note that a finite population correction was applied to the sample size, and a 12.2% non-response rate was considered.

Therefore, we included a total of 404 study participants. To recruit, a systematic random sampling technique was used. During their hospital visit, every fourteenth HIV/AIDS patient was included in the study.

Variables of the study

Dependent variable was ART toxicity, which was defined by physicians working at the ART clinic based on the National Guideline for Comprehensive HIV Prevention, Care, and Treatment published in August, 2018. Both clinical characteristics and laboratory findings were used to define presence of ART toxicity.

Independent variables: socio-demographic characteristics, such as sex, age, residence, educational status, occupation and marital status, and monthly income. Behavioral factors, such as smoking, alcohol drinking, and chat chewing. Psycho-social factors, including family support, social factors (stigma and discrimination). Environmental factors, such as distance to ART clinic, availability of transportation, and access to media, like TV and radio. Clinical characteristics, including HIV co-infection/OIs, presence of comorbidity, type of ART regimen, functional status, WHO clinical stage, CD4+ count, duration of ART, BMI, and viral load.

Operational definition

Comorbidity was defined as the presence of any chronic disease associated with HIV/AIDS (diabetes mellitus, heart failure, or hypertension). Substance abuse was characterized as patients who smoke cigarettes, chew chat, and drink alcohol after ART initiation. Social factors were described as perception of patients' presence of stigma and discrimination from the society, and presence of support from family [14].

Data collection procedures and quality control

Both primary data and secondary data were used. Secondary data was extracted from patients' hospital charts by using a checklist. Primary data was collected through interviews and clinical examination of patients while visiting the hospital ART clinic for a drug re-filling. Data extraction checklist was prepared in English, and the interview questionnaire was translated into Amharic, a local language for participants' convenience. Data was collected by appropriately trained data collectors. Three healthcare professionals (nurses) collected the data under the supervision of principal investigator, and the presence of ART toxicity was determined by a physician working at the ART clinic following the National guidelines.

Socio-demographics, such age, sex, marital status, educational level, residence, occupation, and monthly income were collected by face-to-face interviews. Media availability, distance from the clinic, and availability of social support were also collected. ART duration, presence of comorbidity (diabetes, hypertension, cardiovascular disease), information about isoniazid (INH) preventive therapy (IPT), and cotrimoxazole preventive therapy (CPT) were collected from hospital charts. Presence of OIs was determined by laboratory investigation if physical examination indicated the presence of signs and symptoms of OIs. Recent viral load and CD4+ count of the last six months were extracted from hospital charts since the national guideline recommends these tests to be performed every three to six months. Liver function tests (alanine aminotransferase and aspartate aminotransferase) and renal function tests (creatinine and urea) were collected by both chart review and sample analysis. Patients, who were not tested for liver and renal function within the last three months during their follow-up were consented to give five milliliter blood sample. The serum was used to analyze these tests with Beckman Coulter DxC 700 AU clinical chemistry analyzer. Study participants were screened for hepatitis B and hepatitis C using one-step cassette style hepatitis B surface antigen (HBsAg) rapid test and EUGENE® anti-hepatitis C virus antibody (anti-HCV) rapid test, respectively. Quality of each test was maintained by strictly following standard operating procedures. In addition, both negative and positive quality control for hepatitis B and C, and normal and pathological quality control were performed prior to sample test.

Training of data collectors was conducted on the objective of the study, and how to collect information according to data extraction checklist and interview questionnaire. The principal investigator was supervising the overall process. A pre-test was done on 5% of questionnaires. Quality control was performed before sample analysis. Data was daily verified for completeness, accuracy, and clarity by the principal investigator.

Data processing and analysis

After cleaning and coding, data was entered into EPI info version 7.2.1.0, and it was exported to SPSS version 20 statistical software for analysis. Descriptive and summary statistics were presented by using tables and charts to show frequency distribution. Both univariable and multivariable logistic regression model was applied to identify predictors of ART toxicity in HIV/AIDS patients on ART. Each socio-demographic and clinical variables were examined one-by-one if they showed association with ART toxicity in univariable logistic regression model. Those variables (factors) with a p-value ≤ 0.2 in univariate logistic regression were transferred to multiple binary logistic regression analysis. A p-value < 0.05 was considered statistically significant.

Ethical considerations

Ethical clearance was obtained from the Institutional Review Board of University of Gondar. A permission letter was received from the hospitals. No financial compensation was given to the study participants. Written informed consent was obtained from each study participant before data collection. To ensure confidentiality of data, study participants were identified using codes and unauthorized persons had no access to the collected data. Bioethics Committee approval for the research was obtained, with an approval No. of 374/12/2019.

Table 1. Socio-demographic, anthropometric, and clinical characteristics of HIV/AIDS patients, Gondar, Northwest Ethiopia, 2021

Variables	Number (%)
Sex	
Female	247 (61.1)
Male	157 (38.9)
Age	
18-30	93 (23.0)
31-45	193 (47.8)
46-60	110 (27.2)
> 60	8 (2.0)
Marital status	
Married	209 (51.7)
Single	61 (15.1)
Divorced	70 (17.3)
Widowed	60 (14.0)
Other	4 (1.0)
Residence	
Urban	291 (72.0)
Rural	113 (28.0)
Level of education	
Not educated	96 (23.8)
Informally educated	31 (7.7)
Elementary (1-8)	51 (12.6)
Secondary (9-12)	104 (25.7)
Higher education	122 (30.2)
Occupation	
Unemployed	151 (37.4)
Housewife	10 (2.5)
Private	20 (5.0)
Government	66 (16.3)
Daily laborer	66 (16.3)
Monthly income	
< 1,000 ETB	254 (62.9)
≥ 1,000 ETB	157 (37.1)
Presence of OIs	
No	324 (80.2)
Yes	80 (19.8)
CD4+ count	
< 100	96 (23.8)
≥ 100	308 (76.2)
Viral load	
Unsuppressed	205 (50.7)
Suppressed	199 (49.3)
Presence of clinical toxicity	
Yes	68 (16.8)
No	336 (83.2)
WHO clinical stage	
Stage I	39 (9.7)
Stage II	117 (29)
Stage III	212 (52.5)
Stage IV	36 (8.9)
Functional status	
Working	229 (56.7)
Ambulating	134 (33.2)
Bedridden	41 (10.1)
ART regimen type	
TDF+3TC+EFV	156 (38.6)
TDF+3TC+NVP	52 (12.9)
AZT+3TC+EFV	45 (11.1)
AZT+3TC+NVP	122 (30.2)
ABC+3TC+NVP or ABC+3TC+EFV	29 (7.2)
ART duration	
< 1 years	83 (20.5)
1-2 years	178 (44.1)
≥ 2 years	143 (35.4)
Comorbidity	
No	351 (86.9)
Yes	53 (13.1)
Substance abuse	
No	334 (82.7)
Yes	70 (17.3)
Media availability	
Yes	301 (74.5)
No	103 (25.5)
Transport availability	
Yes	371 (91.8)
No	33 (8.2)
Distance from clinic	
< 10 km	224 (55.4)
≥ 10 km	180 (44.6)
IPT taken	
Yes	255 (63.1)
No	149 (36.9)
CPT	
Yes	287 (71.0)
No	117 (29.0)
Social support	
Yes	274 (67.8)
No	130 (32.2)

ART – antiretroviral therapy, CPT – cotrimoxazole preventive therapy, IPT – isoniazid (INH) preventive therapy

Results

Characteristics of study participants

The mean ± SD age of the study participants was 40.5 ± 10.4 years, ranging between 19 and 70 years. Overall, there were 157 (38.9%) males and 247 (61.1%) females. Of the total participants, 291 (72%) lived in urban areas. About 17.3% of the participants reported using of some form of substance. The majority (61.4%) of the participants were at advanced stages of HIV (stages 3 and 4), and 96 (23.8%) had a CD4+ count of < 100 (Table 1).

A greater proportion of ART toxicity was found among HIV/AIDS patients, who were on TDF+3TC+NVP, which accounted for 25% of patients prescribed with TDF+3TC+NVP, followed by AZT+3TC+NVP, which resulted in 21.3% among those, who received AZT+3TC+NVP during the study period. The lowest proportion of ART toxicity was observed in HIV/AIDS patients receiving ABC+3TC+NVP/EFV, which was only 6.9% among those assigned for ABC+3TC+NVP/EFV treatment (Figure 1).

The percentage value is calculated out of each regimen type, and it is not taken from the total sample.

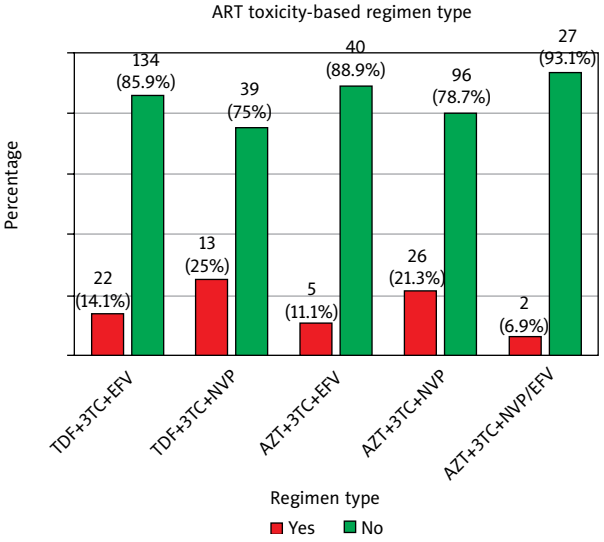

Figure 1. Distribution of antiretroviral therapy (ART) toxicity based on ART regimens

Predictors of drug toxicity based on WHO criteria

Both univariable and multivariable logistic regression was performed to assess the factors associated with ART toxicity among HIV/AIDS patients. The overall prevalence of ART toxicity was 16.8% (range, 13.6-20.8%). The absence of opportunistic infection was less likely associated with ART toxicity (0.06; range, 0.03-0.11). The unsuppressed viral load (2.3; range, 1.1-4.7) was significantly associated with the presence of ART toxicity. Considering WHO clinical staging, patients with WHO stages I, II, and III were at lower risk of developing ART toxicity, as compared to WHO stage IV. TDF+3TC+EFV (5.8; range, 1.1-34.7), TDF+3TC+NVP (8; range, 1.2-53.5), AZT+3TC+NVP (10.3; range, 1.7-62.6), and CPT prophylaxis (2.6, range, 1.1-6.5) were significant predictors of ART toxicity (Table 2).

Discussion

People living with HIV, once introduced to treatment, remain on the treatment for a lifetime. As with other drugs used for treatment of illnesses, ART drugs are not free from drug adverse effects. ART drugs indeed have an effect on the improvement of quality of life and also in the progression and management of HIV/AIDS. Despite their importance, ART can result in adverse side effects that can be detected by clinical manifestation and laboratory investigation [5]. These adverse effects can negatively affect both the outcome of treatment and healthcare expenditure. Rationale for the emergence of this toxicity is defined by different potential factors. The purpose of this study was to assess the ART toxicity rate and associated factors determining its' occurrence among HIV/AIDS patients.

In our study, the overall prevalence of ART toxicity was found to be 16.8 (range, 13.6-20.8), comparable with studies from Arba Minch, South Ethiopia [15] and Eastern Ethiopia [16], but higher than the prevalence reported by Etsegenet *et al.* in Northwest Ethiopia [17]. The difference might be related to sample size (404 < 602) and study design: retrospective cohort versus cross-sectional (the present study).

The absence of opportunistic infections (AOR: 0.05; 95% CI: 0.02-0.1%) was a negative predictor of ART toxicity, whereas CPT (AOR: 2.6; 95% CI: 1.1-6.5%) was significantly associated with ART toxicity. The presence of concomitant opportunistic infections can influence pharmaco-dynamic and pharmaco-kinetic interactions between ART drugs and medicines used to treat opportunistic infections [18]. In addition, clinical conditions may be worsened in HIV/AIDS due to an active immune response to opportunistic infections despite virological suppression of ART [19]. Infection-associated inflammation was reported to lower the level of cytochrome enzymes, important enzymes in metabolism of ART drugs that lead to 20-70% of cytochrome enzymes' substrates, including ART drugs [20, 21]. Concomitant opportunistic infections and drug side effects may also be the reasons for poor adherence to prescribed drugs [22]. Clinically significant drug interaction was demonstrated by Oreagba *et al.*, who identified drug interaction in 84% of HIV/AIDS patients' pharmaco-kinetic interactions. They also indicated that most of potentially and clinically significant drug interaction involved cotrimoxazole, which accounted for 68% [23]. Consistently, our study indicated that increased viral load had a statistically significant association with the presence of ART toxicity. A similar finding was observed by Mihanović *et al.* in Croatia [24]. The possible explanation can be the presence of high concentrations

Table 2. Binary logistic regression analysis of associated factors with clinical toxicity in patients living with HIV, Gondar, Northwest Ethiopia, 2021

Variables		Univariable		Multivariable	
	n	COR with 95% CI	*p*-value	AOR with 95% CI	*p*-value
Presence of OIs					
No	324	0.06 (0.03-0.11%)	< 0.001	0.05 (0.02-0.1%)	< 0.001
Yes	80	1.00	–	1.00	–
CD4+ count					
< 100	96	2.2 (1.2-3.8%)	0.007	0.9 (0.4-1.8%)	0.70
≥ 100	308	1.00	1.00	1.00	–
Viral load					
Not suppressed	205	2.3 (1.3-4.0%)	0.003	2.3 (1.1-4.7%)	0.02
Suppressed	199	1.00	–	1.00	–
WHO clinical stage					
Stage I	39	0.2 (0.03-0.8%)	0.03	0.5 (0.1-0.9%)	0.042
Stage II	117	1.2 (0.5-2.9%)	0.6	0.6 (0.3-0.8%)	0.045
Stage III	212	0.4 (0.2-0.9%)	0.02	0.6 (0.2-1.6%)	0.30
Stage IV	36	1.00	–	1.00	–
ART regimen type					
TDF+3TC+EFV	156	2.2 (0.5-10.0%)	0.30	5.8 (1.1-34.7)	0.04
TDF+3TC+NVP	52	4.5 (0.9-21.6%)	0.06	8 (1.2-53.5)	0.032
AZT+3TC+EFV	45	1.7 (0.3-9.3%)	0.50	3.6 (0.5-26.8)	0.21
AZT+3TC+NVP	122	3.7 (0.8-16.4%)	0.09	10.3 (1.7-62.6)	0.012
ABC+3TC+NVP or ABC+3TC+EFV	29	1.00	–	1.00	–
Comorbidity					
No	351	0.5 (0.2-0.9%)	0.02	0.4 (0.1-0.7%)	0.03
Yes	53	1.00	–	1.00	–
Substance abuse					
No	334	0.6 (0.3-1.0%)	0.07	1.00	–
Yes	70	1.00		1.37 (0.60-3.10%)	0.30
Media availability					
No	103	1.2 (1.1-4.5%)	0.03	2.5 (1.02-6.1%)	0.045
Yes	301	1.00	–	1.00	–
CPT					
Yes	287	1.00	–	2.6 (1.1-6.5%)	0.045
No	117	1.7 (0.9-3.2%)	0.09	1.00	–

ART – antiretroviral therapy, CPT – cotrimoxazole preventive therapy, OIs – opportunistic infections

of inflammatory markers in response to viral loads [25]. This inflammation and immune activation may in turn affect ART drugs' metabolism and eliminate increasing toxicity [20, 21].

Our results also indicated that the presence of comorbidity significantly affected the presence of ART toxicity (AOR for the absence of comorbidity: 0.4; 95% CI: 0.1-0.7%). On the one hand, the reason that the presence of comorbidity affected ART predisposes to concomitant infection. However, comorbidity influences metabolism of the drugs prescribed for HIV/AIDS and non-AIDS [26], which lead to drug-to-drug interaction. Furthermore, comorbidity alters immune response of patient [27].

WHO clinical stage was a significant predictor of ART toxicity. WHO clinical stage I (OR: 0.5; 95% CI: 0.1-0.9%) and stage II (OR: 0.6; 95% CI: 0.3-0.8%) were less likely to develop ART toxicity as compared to WHO clinical stage IV. Even though there was a tendency to be less likely affected, we found no statistically significant difference between WHO clinical stage III (OR: 0.6; 95% CI: 0.2-1.6%) and

stage IV. Similar findings were reported previously by Shet *et al.* [28], Weldegebreal *et al.* [16], and Berheto *et al.* [29], who reported that advanced WHO clinical stages were more likely affected by ART toxicity. Possibly, HIV/AIDS patients with advanced clinical stage might not be able to withstand ART drug side effects, therefore result in toxicity. Besides, taking additional medications other than ART by patients with advanced stages of HIV/AIDS increases probability of toxicity, which may result in toxicity overlapping. Furthermore, taking additional drugs other than ART can result in a pill burden, which may lead to poor adherence to treatment. As well-known, poor adherence reduces treatment efficacy [30].

The study participants, who had no television and/or radio in their house were vulnerable to ART toxicity (AOR: 2.5; 95 CI%: 1.02-6.1%). Mass media play a central role in providing information about the causes, transmission routes, pathogenesis, and treatment options as well as the importance of treatment adherence. This may increase the knowledge and change of attitude in the adherence, preventing opportunistic infections and other comorbidities. A study from China identified that mass media sources, such as television programs, radio, newspapers, and magazines, were more frequently used information channels about HIV/AIDS than inter-personal sources, such as friends and service providers [31].

Limitation of the study

The primary limitation of this study is that it did not show temporal relationship between dependent (outcome) and independent variables since it was a cross-sectional study. Also, it didn't show progressive stage of each subject; it demonstrated a point of time condition of each participant. Data collected by interviews, such as alcohol drinking, chat chewing, and social support condition might be undetermined due to social fear.

Conclusions

Based on our results, 16.8% of the study participants experienced ART toxicity. Opportunistic infection, CPT use, increased viral load, and advanced WHO clinical stage were significant predictors of ART toxicity. The presence of comorbidity and availability of media were found to be associated with ART adverse effects. Health practitioners and healthcare providers should focus their attention on HIV/AIDS patients with opportunistic infections, on CPT, and advanced WHO stages. We also recommend that HIV/AIDS patients must be evaluated for additional comorbidities for early detection and management of the consequences related to ART toxicity. Mass media channels, such as television, need consistent electric power supply, which is limited in our rural setup Therefore, to increase awareness, we want to recommend the government and stakeholders to consider easy access to alternative media channels. Lastly, we recommend that further large-scale prospective cohort study should be conducted to determine the prevalence and cause-effect relationship with clinical and laboratory examinations.

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Conflict of interest

The authors declare no conflict of interest.

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