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PREVALENCE AND PREDICTORS OF ADVERSE DRUG REACTIONS AMONG HIV POSITIVE PATIENTS RECEIVING ANTIRETROVIRAL THERAPY AT A TERTIARY TEACHING HOSPITAL IN FREETOWN, SIERRA LEONE

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ABSTRACT

Background: Despite the benefits of Antiretroviral therapy (ART) in reducing morbidity and mortality related to Human Immunodeficiency Virus (HIV) infection, it is associated with adverse drug reactions (ADRs). This study was therefore conducted to assess the nature, prevalence, and severity of ADRs in HIV positive patients receiving ART since no such data is available in Sierra Leone. **Methods**: A cross-sectional descriptive study was conducted by interviewing and reviewing medical charts of 384 HIV-positive patients receiving ART at Connaught hospital in Freetown Sierra Leone. Information on socio-demographic characteristics of patients, details of medicines used, and adverse effects were collected and assessed. Binary logistic regression was used to determine the associations of the dependent variable with a 95% confidence interval and P-value <0.05 was considered as statistically significant. **Results**: Of the 384 patients sampled in this study, 157(40.8%) reported at least one ADR. Zidovudine/Lamivudine/Efavirenz accounted for 87(38.0%) of the ADRs, while symptoms associated with the nervous system like dizziness and sedation were the most frequently occurring ADRs 97(42.4%). Causality assessment conducted revealed that most of the ADRs were of 'possible' causal association with the ART 129(82.2%) while severity assessment showed that 108(68.8%) were mild. In the simple logistics regression analysis, only employment status (OR=0.558, 95%CI=0.367-0.846, *P*=0.006) and CD4 counts (OR=1.812, 95%CI=1.093-3.005, *P*=0.021) were significantly associated with severity of ADR. **Conclusion:** Adverse drug reactions were prevalent and some caused moderate and severe ADRs that necessitated a change in therapy and medical intervention.

KEYWORDS: Antiretroviral therapy, adverse drug reactions, HIV patients, prevalence, severity, nature.

INTRODUCTION

The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that 37.9 million (32.7- 44.0 million) people were living with HIV at the end of 2018 globally, while in Central and Western Africa, the number of people living with HIV/AIDS (PLWHA) was 5.0 million (4-6.3 million) and 51% (34%-66%) of these were on antiretroviral therapy [ART].[1] Acquired immune deficiency syndrome (AIDS)-related morbidity

and mortality worldwide declined by about one-third, from 2004 to 2018 as a result of the use of ART.[1]

The Sierra Leone demographic health survey report indicates that the Human Immunodeficiency Virus (HIV) prevalence for adults age 15-49 years is 1.7% and 41% were on ART at the end of 2018 which accounted for the reduction in AIDS-related death from 2,900 in 2010 to 2,100 in 2018.[1,2] Lakoh and colleagues reported an institutional prevalence of 24.3% from a study done at the Connaught hospital in Freetown, Sierra Leone.[3]

Like in many other low and middle-income countries, despite the aforementioned gains and successes in treating HIV patients with ART in Sierra Leone, adverse drug reactions (ADRs) are still an important public health concern that can undermine the confidence in the National AIDS Control Programme (NACP). When patients lose confidence in the safety of medicines, this can lead to poor adherence which will consequently result in treatment failures, poor prognosis, and the likelihood of developing drug resistance.[4] Several factors such as patient sex, age, antiretroviral (ARV) regimen, pre-existing diseases, duration of treatment, and disease biomarkers are known to be linked with the severity and type of ADRs among patients on ART.[5]

Studies done to assess ADRs in HIV/AIDS patients receiving ART in Ghana, Benin, Mali, and Cameroon have been documented.[6-9] A study conducted in South Africa revealed that neuropathy, neutropenia, and lipodystrophy were the predominant ADRs among HIV-positive patients.[10] Tatiparthi and Mamo in a study done in Ethiopia showed that of the 233 patients sampled, 70.8% developed ADRs and the most common ones were nausea, vomiting, and diarrhea at 18.9%, 15%, and 7.7% respectively, whereas the least common one was hepatotoxicity at 0.43%.[11]

Monitoring safety related to ART remains a challenge facing public health programmes.[12] In Sierra Leone, pharmacovigilance monitoring is coordinated by the National Pharmacovigilance Centre of the Pharmacy Board of Sierra Leone (PBSL) in collaboration with the NACP. Because the detection, assessment, understanding, and prevention of adverse effects of medicines may rely on people who have limited knowledge and expertise in pharmacovigilance, most adverse drug reactions remain overlooked or are not reported by patients and health care professionals thus affecting signal evaluation and generation to inform prudent therapeutic decisions by clinicians. This study was therefore conducted to assess the nature, prevalence, severity, and predictors of ADRs in HIV positive patients receiving ART at the Connaught Teaching Hospital in Freetown, Sierra Leone.

METHODS

Study setting

The study was conducted at the Connaught Teaching Hospital which is one of the referral hospitals of the University of Sierra Leone Teaching Hospital Complex (USLTHC) situated in Freetown, the capital city of Sierra Leone with about 250 beds capacity. The hospital has an ART clinic that offers voluntary and provider-initiated HIV counselling and testing, ART services, and patients' medication adherence counselling. The hospital also has other departments such as: surgery, internal medicine, pharmacy, nursing, radiology, laboratory, ophthalmology, oral health, ear, nose, and throat to name but a few.

Study design

A cross-sectional descriptive study was done by interviewing and reviewing the medical charts of the study participants from March 2019 to July 2019.

Study population

The study involved all HIV-positive patients receiving antiretroviral treatment for at least six months at the Connaught hospital and were 15 years and above from January 2015 to December 2018. Patients over 55 years who may have co-morbidities and probably on many medicines that would make causality assessment more complex were excluded from this study. Patients charts with incomplete information were also excluded.

Sample size determination and sampling

Sample size was determined considering 70.8% prevalence of ADRs in a study done in Jimma City, Ethiopia,[11] 5% margin of error, 95% confidence interval, and a design effect of 1.5. The final sample size was 384 after adding 5% for non-response and other methodological exigencies. We then recruited a consecutive sample of 384 HIV positive patients.

Data collection

Both primary (patient interview) and secondary (patient medical records) data sources were used. A pre-tested, structured data collection questionnaire adapted from the ADR reporting form of the national pharmacovigilance centre of the Pharmacy Board of Sierra Leone which complies with the Council for International Organisation of Medical Sciences suspected adverse reaction report form (CIOMS form 1) was used to collect the data.[13,14] Several other studies have used similar data collection tools.[7,15] The questionnaire used for this study had 4 sections. Section 1 contained patient demographic information such as age, gender, and occupation while section 2 comprised medicine details like name, strength, dosage, route, start and end date of ARV regimen, CD4 count, viral load, and clinician's decision to change treatment following ADRs, change in treatment policy, immunologic failure or drug availability, pregnancy and opportunistic infections. Section 3 covered adverse reaction details including a description of the reaction, onset date, outcome of reaction, seriousness, and reason

for seriousness while section 4 was for details of the health facility reporting.

A list of common ART-related adverse effects was used based on the summary of product characteristics of the ARV medicines. Patients were asked if they had encountered any of the reactions from the list. Also, respondents were asked to report any other ADR experienced in the course of therapy. In such a way, the outcome of interest was the number and types of adverse drug reactions that had occurred at least once since they had initiated ART.

Ethical consideration

Ethical clearance was obtained from the Sierra Leone Ethics and Scientific Review Committee and permission was given by the hospital administration to conduct the study. All information obtained in the study was kept confidential during the collection and processing of data and used only for this study.

Outcome measures

The outcome measures in this study were the nature of ADRs encountered, their prevalence, severity, and predictors.

Data analysis

The data collected was cleaned, coded, and entered into Statistical Package for Social Scientists (SPSS) version 20 (IBM Statistics, Armonk, NY, USA). The International Conference on Harmonisation (ICH) Safety Data Management: Definitions and Standards for Expedited Reporting guideline (ICH E2A) definition of an ADR was used in this study which defines an ADR as a noxious, unintended drug reaction that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy.[16] Prevalence of ADR was determined using descriptive statistics by considering the proportion of the study population who reported at least one ADR since they initiated ART expressed in percentage. The medical dictionary for drug regulatory activities (MedDRA 20.1) was used to code all ADRs.[17] The Naranjo scale was used to carry out a causality assessment of adverse reactions, which classifies the association between the drug and the ADR as definite, probable, possible, or doubtful.[18] This scale is a tool developed to assess the probable causal association between the suspected drug and the ADR encountered. It consists of 10 questions which include whether the event is documented, plausible temporal association, dechallenge and rechallenge information, the likelihood of alternative causes, dose-response relationship, presence of objective evidence, history of similar problems before with the same or similar medicines, and so on. The questions are answered as either "Yes", "No", or "Do not know". Different values were allocated for each question according to its importance such as −1, 0, +1, or +2. Based on the total score, the likelihood of drug-reaction relationship was categorised as "Certain", "Probable", "Possible" or "doubtful". The severity of the reactions was done by employing the modified Hartwig and Siegel scale that categories the reactions as mild, moderate, and severe based on six levels related to whether there was a need to change therapy, treat reaction pharmacologically, length of hospitalisation, disability and death.[19] Using severity of ADRs as a dependent variable; and sex, age, employment status, clinical staging, viral load, regimen, and CD4 counts as independent variables, we carried out both simple and multiple logistic regression analyses to ascertain factors that influence the severity of ADRs at 5% level of significance and 95% confidence interval.

RESULTS

Socio-demographic and clinical characteristics

A total of 384 participants were included in this study and the majority were, females 261 (68.0%), patients within 26-35 years 230 (59.9%), unemployed 254 (66.1%), had stage 1 disease 199 (51.8%), on TDF/3TC/EFV 157 (40.9%), had CD4 count between 250-350 cells/μL 182 (47.4%) and viral load less than 1000 copies/ml 194 (50.5). Among the 157 patients who developed ADRs, the majority were females 96 (67.6%), age range of 26-35 years 95 (66.9%), unemployed 82 (57.7%), had CD4 count between 250-350 cells/μL 182 (47.4%) and viral load less than 1000 copies/ml 194 (50.5%) [Table 1].

Table 1: Socio-demographic and clinical characteristics of respondents.

Biodata	Characteristics	n (%) N=384	Prevalence of ADR n = 142 n (%)
Sex	Male	123 (32.0)	46 (32.4)
	Female	261 68.0)	96 (67.6)
Age	15-25	51 (13.3)	18 (12.7)
	26-35	230 (59.9)	95 (66.9)
	36-45	97 (25.3)	25 (17.6)
	46-55	6 (1.6)	4 (2.8)
Employment status	Employed	73 (19.0)	68 (47.9)
	Self-Employed	57 (14.8)	28(19.7)
	Unemployed	254 (66.1)	46 (32.4)
Clinical staging	Stage 1	199 (51.8)	82 (57.7)
	Stage 2	185 (48.2)	60 (42.3)
CD4 count	≤ 200	90 (24.3)	33 (23.2)

Biodata	Characteristics	n (%) N=384	Prevalence of ADR n = 142 n (%)
Sex	Male	123 (32.0)	46 (32.4)
	Female	261 68.0)	96 (67.6)
	200-350	182 (47.4)	71 (50.0)
	>350	112 (29.2)	38 (26.8)
Viral Load	>1000	190 (49.5)	66 (46.5)
	<1000	194 (50.5)	76 (53.5)

Multivariate analysis of predictors associated with severity of ADRs

Using age, employment status, clinical staging, viral load, regimen, and CD4 counts as independent variables, we carried out both simple and multiple logistic regression analyses to ascertain factors that influence the occurrence of ADRs based on severity, and the results are presented in Table 5. In the Simple Logistics Regression analysis, only employment status (OR=0.558, 95%CI=0.367-0.846, *P*=0.006) and CD4 counts (OR=1.812, 95%CI=1.093-3.005, *P*=0.021) were significantly associated with the severity ADRs. In the multiple logistic regression analysis, our results showed that all variables investigated (sex, age, employment status, clinical staging, viral load, regimen, and CD4 counts) were not significantly associated with the severity of ADRs **(**all *P*-values > 0.05).

Table 2: Factors associated with the severity of ADRs: result of simple and multiple logistic regression analyses.

Variable	B	OR (95% CI)	*P*-value
Simple logistic regression			
Sex	-0.144	0.866(0.424 -1.769)	0.692
Age	-0.189	0.828(0.479 - 1.431)	0.499
Employment status	-0.584	0.558(0.367 - 0.846)	**0.006**
Clinical Staging	0.443	1.557(0.793 - 3.058)	0.199
Viral Load	-0.033	0.967(0.493 - 1.896)	0.923
Regimen	-0.102	0.903(0.647 - 1.260)	0.549
CD4 Count	0.594	1.812(1.093 - 3.005)	**0.021**
Multiple logistic regression			
Sex	0.357	1.429(0.275 - 7.444)	0.671
Age	-0.359	0.698(0.211 - 2.309)	0.556
Employment status	0.175	1.191(0.477 - 2.976)	0.708
Clinical Staging	0.343	1.409(0.353 - 5.626)	0.627
Viral Load	0.181	1.198(0.303 - 4.740)	0.797
Regimen	-0.338	0.713(0.341 - 1.493)	0.370
CD4 Count	0.646	1.909(0.654 - 5.570)	0.237

Bold figures represent statistically significant values (p<0.05).

Details of Antiretroviral Drugs

Table 3 shows that the most frequently prescribed antiretroviral regimen among study participants was Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV) 157 (40.9%) followed by Zidovudine/Lamivudine/Efavirenz (AZT/3TC/EFV) 125 (32.6%). Thirty-eight (38.0%) of the ADRs were due to AZT/3TC/EFV, while the least (0.4%) was due to ABC/3TC/EFV (Table 4).

Table 3: HIV-positive patients prescribed antiretroviral regimens.

No.	Antiretroviral regimen	Frequency	%
1	TDF/3TC/EFV	157	40.9
2	AZT/3TC/FFV	125	32.6
3	AZT/3TC/NVP	83	21.6
4	ABC/3TC/EFV	1	.3
5	AZT/3TC/Lopinavir	18	4.7
	Total	**384**	**100.0**

TDF=Tenofovir, 3TC=Lamivudine, EFV=Efavirenz, AZT= Zidovudine, NVP=Nevirapine, ABC= Abacavir

Among the 76 patients who had a change in treatment regimen, 52(68.4%) were due to ADR whereas 24(31.6%) were as a result of immunological failure (Figure 1).

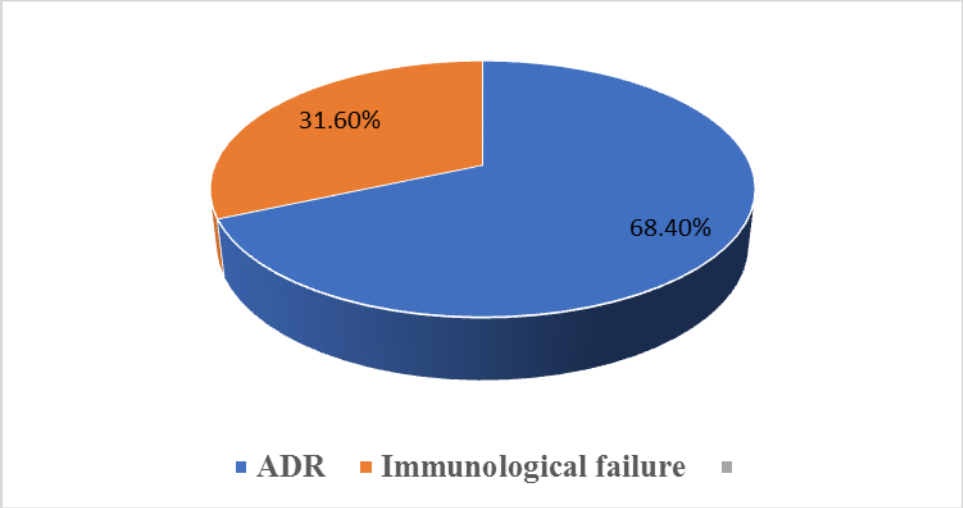

Figure 1: Reasons for change of patients' treatment.

Details of Adverse Drug Reactions

Adverse drug reactions experienced by patients on antiretroviral medicines were also evaluated in this study and the results presented in Table 4 revealed that the most common ADRs experienced by patients were nervous system disorders [dizziness 32 (14.0%), headache 26 (11.4%), and sedation 27 (11.8%)], followed by skin and subcutaneous tissue disorders [rash 25 (10.9%),

pruritus 19 (8.3%), nails discoloration 9 (3.9%) and skin hyperpigmentation 6(2.6%)] and gastrointestinal disorders [abdominal pain 21 (9.2%), diarrhoea 7 (3.1%), vomiting 8 (3.5%) and nausea 15 (6.6%)].

Table 4: Frequency and nature of adverse drug reactions and their system organ class (SOC).

ADR Description	No. of Patients taking Drug Regimen				
	AZT/3TC/NVP	AZT/3TC/EFV	TDF/3TC/EFV	ABC/3TC/EFV	
Gastrointestinal disorders					
Vomiting	0	5	3	0	
Diarrhoea	0	5	2	0	
Nausea	0	10	5	0	
Abdominal pain	1	14	6	0	
Skin and subcutaneous tissue disorders					
Skin hyperpigmentation	6	0	0	0	
Nail discoloration	7	0	2	0	
Rash	21	2	2	0	
Pruritus	16	0	3	0	
Nervous system disorders					
Dizziness	1	10	20	1	
Insomnia	0	6	6	0	
Headache	0	13	13	0	
Sedation	1	11	15	0	
Metabolism and nutrition disorders					
Anorexia Nervosa	0	1	2	0	
Decreased appetite	0	6	1	0	
General disorders and administration site conditions					
Body pain	2	1	2	0	
Asthenia	1	3	3	0	
TOTAL (%)	56/229	87/229	85/229	1/229	
Percentage	24.5	38.0	37.1	0.4	

Causality assessment done using Naranjo's algorithm revealed that 129 (82.2%) of ADRs had a possible causal association with the ARV medicines while 28 (17.8%) had a probable association with the ARVs (Figure 2).

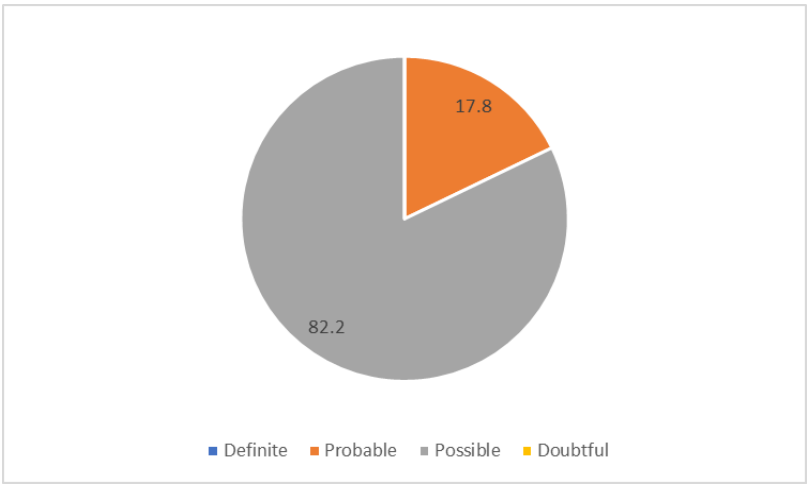

Figure 2: Causality assessment of adverse drug reactions using Naranjo's algorithm.

Using the modified Hartwig and Siegel's scale to assess the severity, 108 (68.8%) ADRs were mild in severity while 41 (26.1%) were moderate (Figure 3).

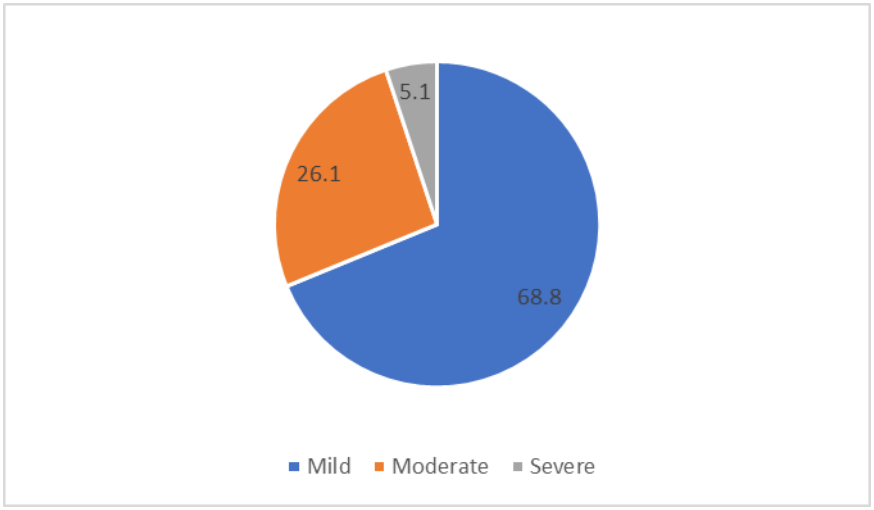

Figure 3: Severity assessment of ADRs using the modified Hartwig-Siegel Scale.

DISCUSSION

Regardless of the effectiveness of ARTs in decreasing HIV/AIDS morbidity and mortality, antiretroviral medicines frequently cause adverse reactions, ranging from mild symptoms to moderate and severe effects.

This study found a higher prevalence of ADRs in females which is similar to findings by Masenyetse *et al.*[10] but in contrast to a study done by Jha *et al.*[20] where the ADR prevalence was higher among males compared to females. Patients between the ages of 26-35 years reported over half of the ADRs in this study. However, age and gender were not significantly associated with the occurrence of ADRs in this study as in other studies done conducted in Ethiopia and Nigeria.[5,21] Though it has not been proven irrefutably, the aforementioned variations may be associated with the study designs employed, sample size, socio-demographic disparities of patients, hormonal effects, immunological status, drug susceptibility, drug pharmacokinetics, or pharmacogenetics.[22] In our study, only employment status and CD4 count were independently associated with ADR severity. In addition to ADRs to the ART, the high unemployment level among study patients may lead to psychosocial and psychological problems such as depression, stress, and anxiety which can predispose patients to mental health problems and have an impact on treatment adherence and outcome.[23,24] Like in our study, other studies done by Lartey *et al.*[25] Rajesh *et al.*[26] Shet *et al.*[14] and Reginald *et al.*[27] in Ghana, India and Nigeria have reported that relatively higher CD4 cell counts (200 cells/mm3 or more) were linked with more likelihood of developing severe ADRs. This is in contrast to results from previous studies done by Hagos *et al.*[28] Onoya et al.[29] and Srikanth et al.[30] in Eritrea, South Africa, and India. Other studies have linked the occurrence of ADRs to CD4 count and the type of ARV medicine the patient is using; patients with high CD4 count have a predisposition for Nevirapine-associated

hepatotoxicity and hypersensitivity.[31,32] while the inverse is true for Zidovudine-associated anemia.[33,34]

This study revealed that the most prescribed regimen was TDF/3TC/EFV followed by AZT/3TC/ EFV. This is consistent with results from a study done by Tatiparthi and Mamo in India.[11] In our study, patients taking AZT/3TC/EFV experienced more ADRs compare to those on other regimens. This is comparable to a study done in India and Ghana which is an indication that the drugs used to manage PLWHA in Sierra Leone are similar across countries.[7,35]

The overall prevalence of ADRs in this study was 40 8 %. Luma *et al*.[8] and Divakar *et al.*[36] reported lower ADR occurrences in Cameroon (29.6%) and India (26.8%) respectively, whereas results of higher prevalence have been reported in Mali (61.2%) and Ethiopia (70.8%) by Qumar *et al.*[6] and Tatiparthi *et al.*[11] correspondingly. For specific prevalence concerning regimens used in this study, AZT/3TC/EFV accounted for 38.0% whereas TDF/3TC/EFV for 37.1%. This variance in prevalence may be explained by ADR reporting practices in different ART clinics across settings, ethnic predispositions to ADRs, variances in the patient socio-demographics, differences in the regimen prescribed, and polypharmacy due to co-morbidities and opportunistic infections. This study demonstrated a relatively higher frequency of ADRs and as stipulated by Mehta *et al.*[37] most ART-associated ADRs are usually unavoidable and this makes treatment of these ADRs challenging. This can give rise to an additional economic burden for the NACP and the Ministry of Health and Sanitation that is already inundated with other competing health priorities such as infant and maternal mortality and access to medicines. The pharmacovigilance ADR reporting system of the National AIDS Control Programme (NACP) should therefore be strengthened particularly for vulnerable populations, new products, and those with narrow therapeutic index.[38]

Studies conducted by Qumar *et a*l.[6] and Zannou *et al.*[9] showed that nervous system ADRs were the most commonly reported in Mali (40.4%) and Benin Republic (64.6%) respectively, which are akin to our study findings. In contrast, another study in India reported that the maximum proportion of ADRs were related to the gastrointestinal system (31.25%), followed by skin and subcutaneous tissue system (23.75%) and nervous system (16.25%).[39] In our present research, dizziness was the most common ADR followed by sedation and this was similar to studies done in India.[39,40] Efavirenz-based regimens such as AZT/3TC/EFV and TDF/3TC/EFV were associated with a high prevalence of neuropsychiatric manifestations such as dizziness, sedation, insomnia, and other central nervous system ADRs which are well documented.[41-43]

Dermatologic ADRs such as rash and itching have been reported with Nevirapine use in PLWHA. This has been demonstrated earlier in preclinical studies using rats in which the 12-hydroxy metabolite of nevirapine was causally associated with rash.[44,45] Van Oosterhou *et al*.[46] reported skin rash (26%) as the most common skin and subcutaneous tissue ADRs in a study done in Malawi which is comparable with this study in which Nevirapine-based regimens such as TDF/3TC/NVP and the AZT/3TC/NVP accounted for the maximum prevalence of skin and subcutaneous ADRs. Nevirapine-based regimens were also found to be associated with other skin and subcutaneous tissue ADRs such as pruritus and hyperpigmentation.[47] These usually resolve following withdrawal of the medicine.[7] Hence, prompt recognition and withdrawal of suspected medicines and appropriate treatment of related adverse reactions are crucial for the rapid resolution of ADRs.

Gastrointestinal tract (GIT) symptoms were mostly associated with AZT/3TC/EFV and to a lesser extent with TDF/3TC/EFV. Sehgal and colleagues reported that TDF/3TC/EFV was linked to all the GIT symptoms (11.6%) recorded in their study.[40] Gastrointestinal ADRs such as diarrhea and nausea have occurred in the clinical trials with tenofovir,[48] while 7.6% of gastrointestinal events were also recorded with efavirenz in a study from India by Shet and colleagues.[15]

In this study, of the patients that experienced ADRs, about two-thirds of them had their regimen changed as a result of ADR. This finding is supported by studies done in Cameroon and India where ADR was the most common reason for change in therapy.[8,49] This observation indicates that ADRs can affect the adherence of patients to ART and the consequences will be interruption of treatment, lack of retention of patients, and increasing the risk of resistance to the ARV regimen.

Kumari *et al.*[35] in a study done in India reported that most of the adverse reactions (83%) had a possible causal association to the ART. This study is consistent with our study which revealed that the majority of the ADRs were of possible causal association to the ARV medicines taken by the patients. This may be based on the fact that the clinical features of HIV/AIDS are similar to some of the ADRs associated with the ARV medications or due to the retrospective design employed for this study.

Hartwig and Siegel's ADR severity assessment showed that about two-thirds of the ADRs were mild and comparable to another study conducted in India by Kumar and colleagues.[50] Polypharmacy and the immunocompromised status of patients are two factors found to be associated with the risk of having a severe ADR.[51]

Limitations of this study include, patient files were inadequately filled and many data were missing. The ADRs were self-reported and could lead to over-reporting of ADRs or under-estimation of ADRs which

might have been detected clinically. Factors that may contribute to the development of ADRs such as concomitant medicines, alcoholism, drug abuse, co-infection with tuberculosis were not explored. Also, the results from this single study site cannot be generalized, hence a larger multi-centre study needs to be conducted.

CONCLUSION

Adverse drug reactions to ARTs were prevalent and some of them caused moderate to severe adverse effects that necessitated a change in therapy and medical intervention. The commonly prescribed regimen was TDF/3TC/EFV while nervous system-related-ADRs such as dizziness and sedation topped the list for the most common SOC ADRs. Employment status and CD4 count were predictors of ADR severity. Most of the ADRs had a possible causal association with the ART. These findings will help the NACP and healthcare professionals understand the nature, prevalence, severity, and predictors of ADRs among PLWHA on ART and inform prudent therapeutic decisions as well as the implementation and continuous monitoring and, supportive supervision for a robust pharmacovigilance system within the NACP.

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