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The Prevalence and Pattern of Adverse Drug Reaction in HIV/AIDS Patients on Antiretroviral Therapy in Kaduna State, Nigeria: Case Review Study

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Abstract

In Nigeria, Human immunodeficiency virus (HIV) infected patients on highly active antiretroviral therapy (HAART) are at higher risk of developing adverse drug reactions (ADRs). Objective: To assess the prevalence and pattern of ADR in HIV/AIDS patients on antiretroviral therapy. A Case review of 170 patients initiated on ARVs between July 2010 and July 2014 was carried out in eight health facilities in Kaduna state, Nigeria. Regimens prescribed include zidovudine /lamivudine, tenofovir/lamivudine, abacavir/lamivudine in combination with either nevirapine, efavirenz or lopinavir/ritonavir. Patient adverse drug reactions and offending drugs were noted and categorized using descriptive statistics. The prevalence of adverse drug reactions is 0.9%. Out of 170 documented cases of reported adverse drug reactions, 11.8% were male and 88.2% were female. The most reported ADR is anaemia (37.2%) associated with zidovudine (42.9%). ADR is most prevalent between the ages of 30 – 39, with reported cases of (46.4%). 91.8% of all patients with reported ADR recovered fully, 1.2% recovered with disability, 3.5% experienced life-threatening conditions, and 3.5% died. 22.4% of the patients are admitted. Adverse drug reaction occurred most (61.4%) among patients weighing between 41 and 61 kg. The 0.9% prevalence of adverse drug reactions among the study population is markedly lower than what has been reported in the USA, India, South Africa, Ethiopia, and Cameroon, but higher than the expected national target of 100/100000 (0.01 prevalence).

Keywords: *Adverse Drug Reaction (ADR), Antiretroviral Therapy (ART), Acquired Immune Deficiency Syndrome (AIDS), Human Immunodeficiency Virus (HIV).*

Introduction

Nigeria carries the second heaviest burden of HIV in Africa and has an expanding population of People Living with HIV (PLHIV). Despite challenges in scaling up access, institutional reforms, and political commitment to tackle the diseases, the country has seen more citizens placed on life-saving medication [1, 19].

Even though appreciable progress has been made in control of the pandemic and the treatment, care, and support for PLHIV, the preponderance of unwanted effects, side effects, adverse drug events, adverse drug reactions, and/or toxicities has tended to be a significant drawback to the use of ARVs. This is not different from the experience with many other chronic diseases, for which drugs are administered for prolonged periods [2, 15].

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The increasing development and availability of new medicines during the dawn of the 20th century resulted in the emergence of adverse drug reactions and other drug-related problems. This is typified by the thalidomide tragedy of the early 60s, where pregnant women exposed to the drug for morning sickness gave birth to phocomelic babies. The resultant uproar necessitated active monitoring of medicines by some developed countries, such as the United Kingdom, Australia, Canada, Sweden, and others. This reporting activity included the USA, which, fortunately, was spared the tragedy due to the diligence of the regulatory authority in requiring additional data before granting marketing authorization for the medicine [4, 7, 9, 20, 21].

The introduction of highly active antiretroviral therapy (HAART) in developed countries in the late 90s has been associated with a remarkable decrease in AIDS-related mortality. This decrease in mortality has changed the perspective of HIV infection from that of a rapidly fatal to a chronic, manageable infection. Clinical benefits of HAART are due to its effectiveness in decreasing disease progression in HIV infected patients by sustained suppression of viral replication. These clinical benefits, however, are not without adverse drug reactions (ADRs). An ADR is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product (which in this case is HAART), which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. ADRs have been one of the most critical limiting factors to the success of HAART because they are responsible for new co-morbidities noticeable by the patients or their families and may result in decreased adherence to treatment, which consequently might lead to virologic failure and poor prognosis. ADRs due to continuous exposure to antiretroviral drugs leave the caregiver with few options: decreasing the dosage of antiretroviral drugs, thus compromising efficacy, withdrawing the offending drug and substituting it with another drug, or symptomatically treating the ADR. However, substituting the offending drug by the caregiver is difficult, especially in resource-limited settings, because most HAART regimens exist as fixed-dose combinations (FDC) of different drugs, most of which are first-line drugs with high toxicity profiles. The advent of new generation drugs with relatively low toxicity into the antiretroviral armamentarium is some hope that the deleterious effects of HAART-related ADRs in HIV patients would decrease. This hope remains far-fetched in resource-limited settings, where, although the highest global HIV burden, HAART still relies on first-line treatment because new-generation drugs are still costly to be afforded by most national HIV control programs. More so, the inexistence of adequate drug toxicity monitoring and reporting schemes underestimates the burden of HAART-associated ADRs.

Several studies documented how ADRs contribute to patient morbidity and hospitalization in Africa. 4.5–8.4 percent of all hospital admissions were related to ADRs, 1.5–6.3% of patients were admitted as a direct result of ADRs, and 6.3–49.5% of all hospitalized patients developed ADRs. Moreover, ADRs accounted for the most frequent reason (45.5%) for treatment modification and interruptions in patients on ART [3, 5, 6, 8, 10, 11, 14, 15, 17, 18].

Counterfeit medicine is a growing threat worldwide, accounting for up to USD 75 billion in sales in 2010. WHO estimates that more than 30% of the medicines sold in some areas of Africa are counterfeit. In Kenya alone, about USD 65 to 130 million worth of counterfeit medicines are being sold each year. The use of substandard and counterfeit

medicines can lead to therapeutic failure, drug resistance, or even death [2, 4, 7].

In Nigeria in 2008, more than 80 children died, and many others were hospitalized after being given My Pikin Baby Teething Mixture®, a syrup containing a high level of the poisonous solvent diethylene glycol (DEG) [7].

In 2005, more than 60,000 people in Nigeria were inoculated with a counterfeit meningitis vaccine, resulting in about 3,000 deaths. The extent of morbidity and mortality caused by counterfeit medicines is unknown, as most events go undetected and unreported due to weak regulatory systems, inadequate enforcement, and the presence of unregulated markets [7, 9].

Medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while medication is in the control of the health care professional, patient, or consumer." The US Institute of Medicine in 2006 estimated that more than 1.5 million Americans are injured every year by medication errors. Analysis of a Moroccan database shows that 14% of all suspected ADRs were associated with preventable medication errors [4, 9].

Insufficient and inadequate resources to monitor the safety of medicines; the unreliable supply of quality, safety, and effective drugs; the lack of trained health workers; and the weak state of the health systems in Africa are likely to contribute to significant medicines-related harm.

Statement of Problem

Considerable progress has been made in providing global access to antiretroviral therapy, with 7.6 million people receiving antiretroviral therapy in Africa as of December 2012 [1, 19]. However, the

effectiveness of treatment programs is being compromised by problems related to toxicity,

Intolerance and drug-drug interactions. These adverse events, whether acute or chronic, mild or severe, are relatively common phenomena affecting both individual patients and public health, but are being only intermittently identified and scarcely systematically reported, especially in low- and middle-income settings.

It has been estimated that adverse drug reactions (ADRs) are the 4th to 6th largest cause of mortality in the USA. They result in the death of several thousand patients each year, and many more suffer from ADRs. The percentage of hospital admissions due to adverse drug reactions in some countries is about or more than 10%. Norway 11.5%, France 13.0% and the UK 16.0% [16, 17, 20].

In addition, suitable services to treat ADRs impose a high financial burden on health care due to the hospital care of patients with drug-related problems. Some countries spend up to 15-20% of their hospital budget on dealing with drug complications [17].

There is minimal information available on ADRs in developing countries and countries in transition. However, one might expect the situation to be worse rather than better. This problem is also caused by a lack, in some countries, of legislation and proper drug regulations, including ADR reporting, many substandard and counterfeit products circulating in their markets, a lack of independent information, and the irrational use of drugs [16].

Hospital admissions due to ADRs between 1970 and 1975 ranged from 4.2% to 6.0%, with a median of 5.8%. In 2000, drug-related morbidity and mortality cost the US an estimated 177.4 billion USD. In England, ADRs accounted for 6.5% of hospital admissions with a fatality rate of 0.15% and cost the National Health Service (NHS) £466 million/year. In contrast, the total estimated annual cost to society due to ADRs in the European Union (EU) is 79 billion euros. 70% of ADRs were considered avoidable. It is worthy to note, however, that these startling figures do not represent the whole picture as

they exclude ADRs caused by other drug-related problems such as overdose, drug abuse, misuse, poisoning, medication errors, and therapeutic failures [17, 20, 21].

Unfortunately, due to the dearth of research in this area in Nigeria, we do not have information on the extent of the burden of ADRs, including morbidity, mortality, and the financial drain on the health system. We can only presume that it is worse than what is reported in developed countries due to widespread irrational use of medicines in our environment.

New adverse events and toxicities are identified as people live longer on ART. The availability of numerous new drugs and drug combinations makes it critical to monitor more systematically adverse events linked to ARVs [12, 13].

Justification for the Study

Adverse drug reactions are a significant cause of morbidity and mortality and can affect adherence to treatment schedules and increase the risk of resistance and relapse of the disease.

Every medicinal product poses a safety challenge which may be due to its pharmacological properties, genetic disposition, diet and culture of patient, disease pattern, drug manufacture, distribution and use practices as well as inherent limitations of clinical trials. These justify the setting up of systems for safety monitoring of medicines.

Limitation of Study

This was a case review study which could not associate the causal-effect relationship.

The CNS effects attributable to efavirenz may have been due to drug interaction or patient lifestyle which our study did not control for.

The death experienced in this study could be due to other possible causes such as HIV/AIDS, TB/HIV co-infection, and other co-morbid conditions, which the study also did not control for.

Objective

To assess the prevalence and pattern of adverse drug reaction in HIV/AIDS patient on antiretroviral therapy.

Materials and Methods

Study Design

This is a case review study of documented adverse drug reaction of antiretroviral.

Study Site

The study was conducted at eight facilities (General Hospitals (GH) Kafanchan, GH Gwantu, GH Makarfi, GH Giwa, GH Kwoi, Yusuf Dantsoho Memorial Hospital, Barau Dikko Specialist Hospital and Hajiya Gambo Sawaba Hospital in Kaduna, Nigeria. They are public health facilities owned and managed by the Kaduna State Government, while HIV/AIDS services are supported by the Center for Integrated Health Programs (CIHP) through the Presidential Emergency Plan for AIDS Relief (PEPFAR).

The eight facilities provide ambulatory HIV/AIDS treatment to 17,440 patients with an average of 180 patients attended to daily, and the clinics run from Monday to Friday at GH Kafanchan while, the remaining facilities runs clinics from Monday through Thursday with exception of GH Giwa which has an average of 25 patient attended to daily and the clinic runs on Mondays and Wednesday.

Study Population and Sample Size

The cohort included 170 patients initiated on antiretroviral therapy (ART) with documented ADR between July 2010 and July 2014 and had at least one follow-up clinical visit after commencing antiretrovirals (ARVs).

Once eligible for ARVs, all patients are initiated on combination antiretroviral therapy consisting of two nucleoside reverse transcriptase inhibitor and a non-nucleoside

reverse transcriptase inhibitor or protease inhibitor for second line patients. All newly imitated patients are reviewed monthly for one year. Thereafter patients are dispensed two monthly prescriptions, if found tolerant and adherent to their medication. At each appointment, adherence was assessed and counselling provided. All ADR cases identified irrespective of the severity grades were documented in the National Agency for Foods, Drug Administration and Control (NAFDAC) pharmacovigilance forms. Socio-demographic and clinical information of patients including name, age, sex, weight, hospital number, suspected drug, reported ADR, concomitant drugs and outcome are transferred to an excel spread sheet. Reports of ADRs based on patients' complaints and/or morphological changes as noticed by physicians and pharmacists during routine drug pick-ups are documented using the NAFDAC pharmacovigilance forms and sent to the National pharmacovigilance centre under the jurisdiction of the NAFDAC.

Data Analysis

EPI INFO statistical software was used for data analysis. Descriptive statistics were conducted, including the frequency distributions of key variables. Patients noted in the ART register as having transferred out, died, stopped treatment, or lost to follow-up contributed to the analysis if they had reported ADRs, before been lost to follow up at the facility because, there were yellow form filled for them

Results

Table 1 below shows that the most prevalent adverse drug reaction by organ system is skin reaction accounting for 42.7% of all the reported cases followed by haematology 37.2% then, others 12.9% and the least is central nervous system 7.2%.

Types of Adverse Drug Reactions and Distribution by Organ System

Table 1. Types of ADR

Adverse Drug Reaction by Organ System		**Frequency/Percentage**
Haematology	Anaemia	37.2%
Skin Reaction	Rash	31.4%
	SJS	5.9%
	Pigmentation of palm & nail	5.4%
Sub Total		**42.7%**
Central Nervous System	Insomnia	3.0%
	Nightmares	1.8%
	Dizziness	1.2%
	hallucination	1.2%
Sub Total		**7.2%**
Others	Nausea, Vomiting, Diarrhea, elevated lft, jaundice, peripheral neuropathy, oedamatous face, arm & feet, weakness, unusual fatigue.	12.9%
Sum Total		**100%**

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Table 2 below shows that the most suspected drug causing adverse drug reaction is azt/3tc/nvp accounting for 76.5% of all the implicated drugs while all the other drugs combine accounted for 23.5%.

Percentage Distribution of Suspected Drugs causing Adverse Drug Reaction

Table 2. Suspected Drug Causing ADR

Suspected drug	Percent
abc/3tc/nvp	0.6%
azt/3tc/efv	5.9%
azt/3tc/lpv/r	0.6%
azt/3tc/nvp	76.5%
cotrim	4.1%
d4t/3rc/nvp	0.6%
d4t/3tc/nvp	1.2%
heamatinic	0.6%
Suiphadoxine/pyrimethamine	0.6%
tdf/3tc/efv	5.3%
tdf/3tc/nvp	2.9%
tdf/3tc/lpv/r	0.6%
tramadol	0.6%
Total	**100.0%**

From table 3 and the statistical analysis below, the median duration of admission due to adverse drug reaction is seven (7) days.

The Median Duration of Admission as a Result of Adverse Drug Reaction

Table 3. Median Duration of Admission due to ADR (days)

Duration of admission (days)	Percent
2	12.0%
3	4.0%
5	8.0%
7	40.0%
10	4.0%
12	4.0%
14	20.0%
15	4.0%
21	4.0%
Total	**100.0%**

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Socio-demographic Characteristics of the Patient

Figure 1 below, adverse drug reaction is more prevalent among adults age 30 – 39 years accounting for 46.7% of total population followed by young adult age 18 – 29 year accounting for 27%, them adult ages 40- 49 year (15.4%), children age 1 – 9 year (1.5%), then adult age 50 years and above (4.8%) and least among adolescent age 10 – 17 year (1.2%)

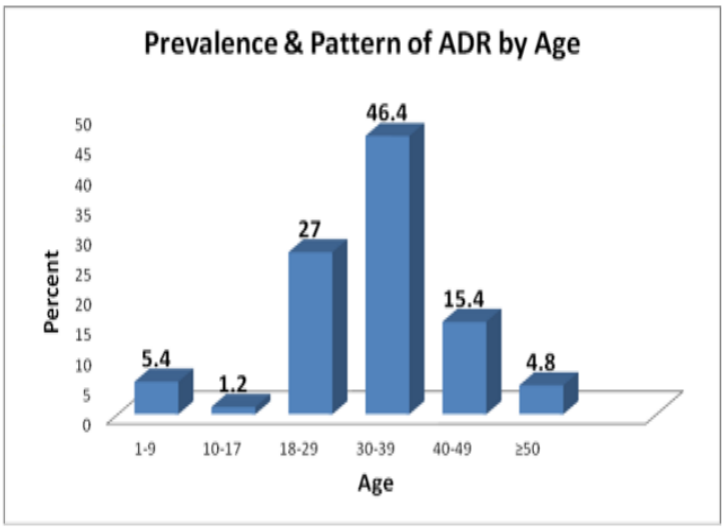

Figure 1. Prevalence & Patterns of ADR by Age

Socio-demographic Characteristics of the Patient

Figure 2 below, adverse drug reaction is more prevalent among females, contributing 88.2 % of reported cases than males contributing only 11.8% of the reported cases of adverse drug reaction.

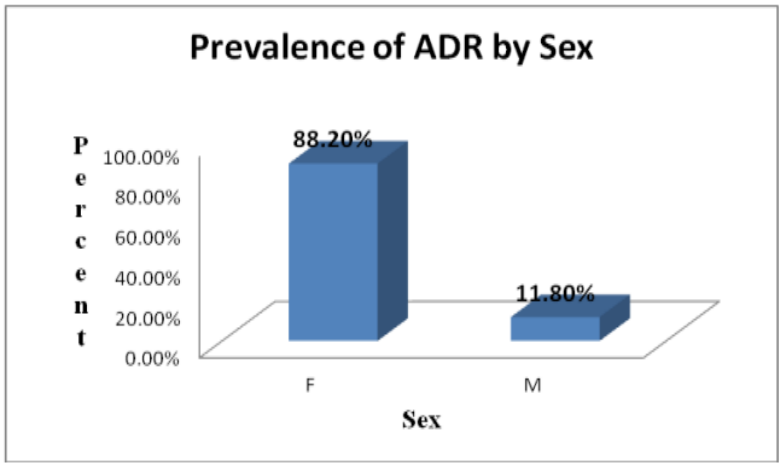

Figure 2. Prevalence of ADR by Sex

Prevalence of Adverse Drug Reaction by Weight Distribution

Figure 3 below shows that adverse drug reaction is most prevalent among patients weighing 41 – 60kg accounting for 61.4% of the reported cases followed by those weighing 61 – 80kg (21.6%) then, those weighing 21 – 40kg (11.4%), next those weighing 1 – 20kg (4.2%) and least among patient weighing above 80kg (2.4%).

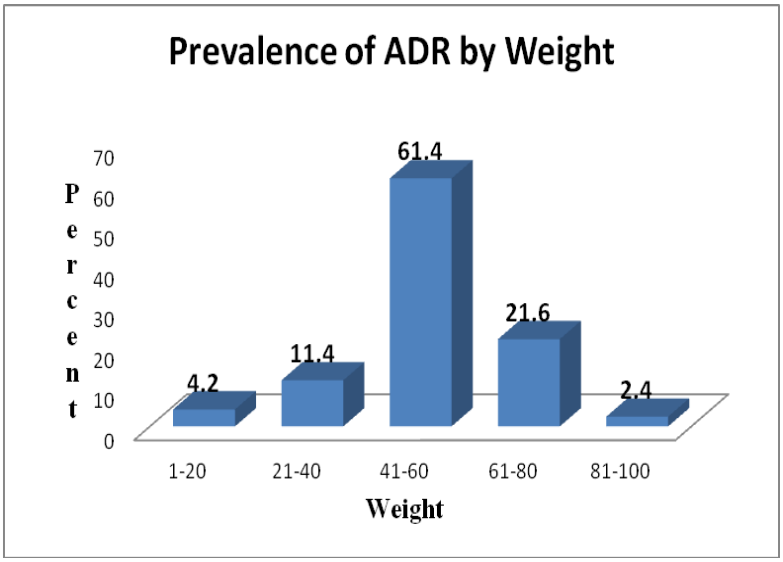

Figure 3. Prevalence of ADR by Weight

Figure 4 below shows that only 22.4% of the patients experiencing adverse drug reactions were admitted, while most of the patients, 77.6% were not admitted.

Admission Resulting from Adverse Drug Reaction

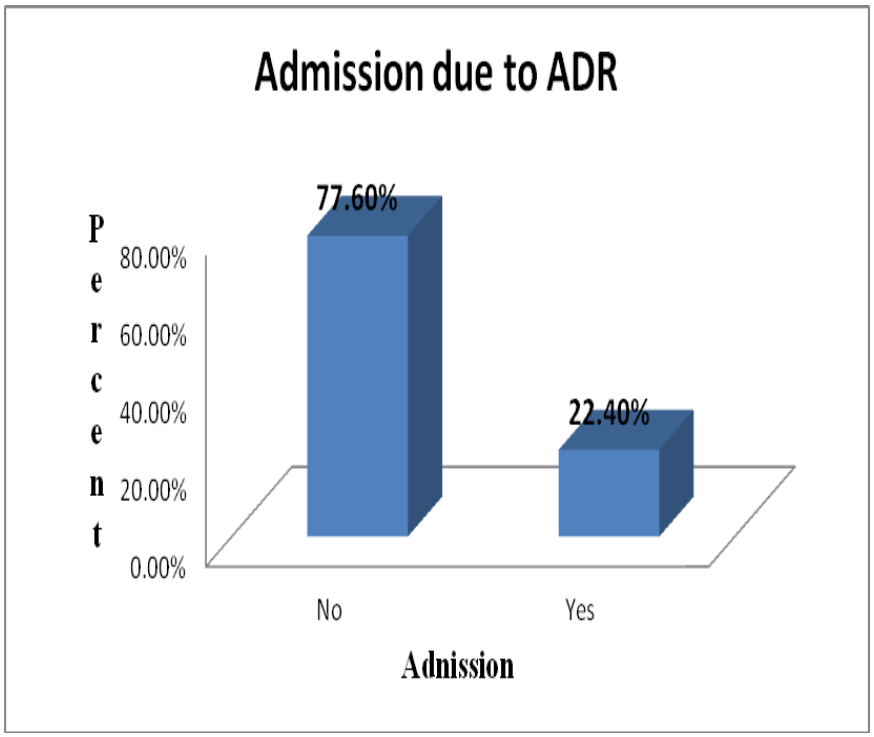

Figure 4. Admission due to ADR

Treatment of Adverse Drug Reaction with Resultant Continuation or Discontinuation of Suspected Drug

Figure 5 below shows that, 51.8% of the patients were counsel to continue suspected drug and treated of adverse drug reaction while. 48.2% of the patient discontinued their medication and also treated of the resultant adverse drug reaction.

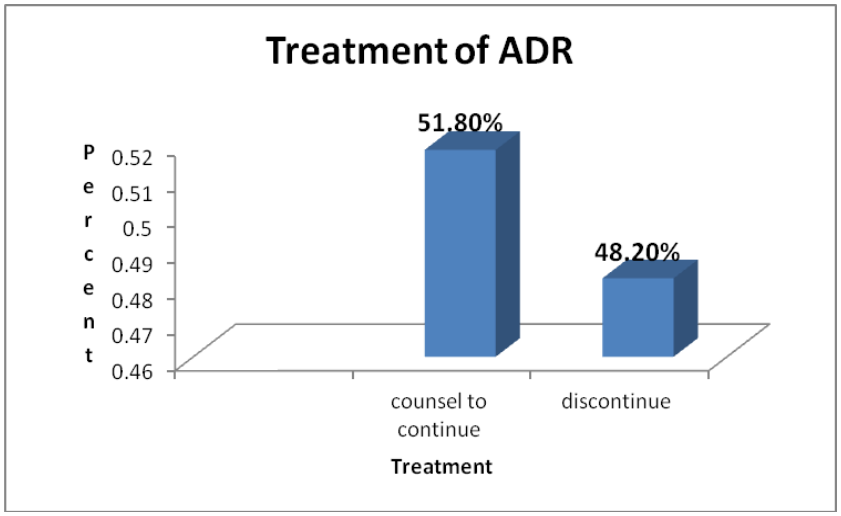

Figure 5. Treatment of ADR

Figure 6 below shows that most of the patients 91.8% recovered fully from their adverse drug reaction while, 3.5% died as a result of adverse drug reaction, another 3.5% experienced life-threatening adverse drug reaction with only 1.2% of the patient that, recovered with disability.

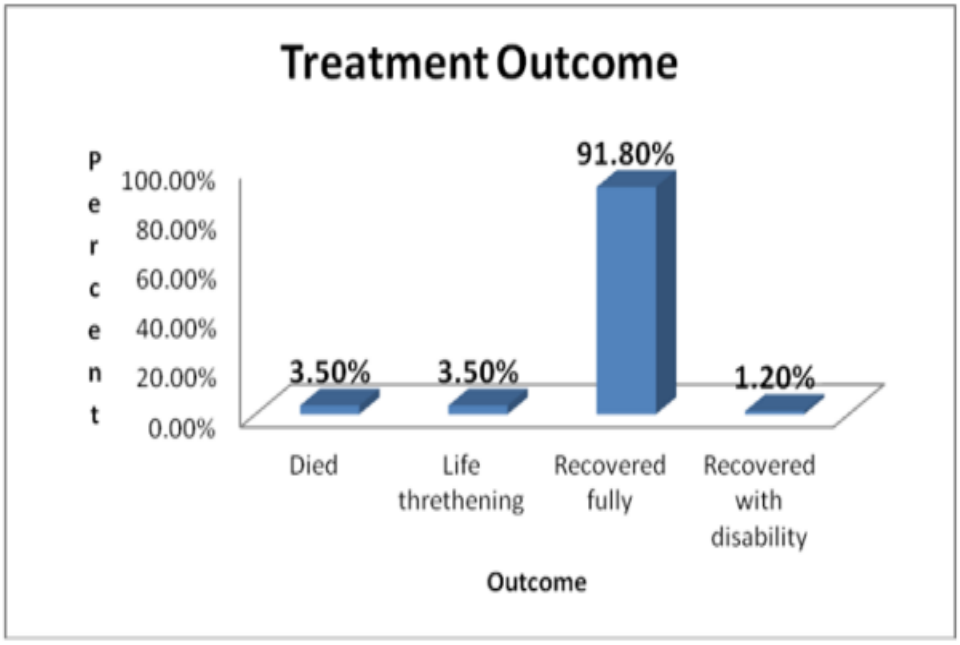

Figure 6. Treatment Outcome

Discussion

This study shows that 170 of the 17,440 patients on HAART reported ADRs, with a prevalence of 0.9%. This is markedly lower than what was reported in the USA, India, South Africa, Ethiopia, and Cameroon, but more than the expected national target of 100/100000 (0.01 prevalence). Reported ADR was highest among adults aged 30-39 years (Fig. 1), accounting for 46.4% of the reported ADR, and lowest, 1.2%, among adolescents aged 10-19 years. This aligns with the Ethiopian study. Figure 2 shows that more females (88.2%) reported ADRs than males (11.8%), just as in similar studies in India and Nigeria. This is statistically significant and could suggest hormonal factors in the development of ADR. Prevalence of ADR by

weight (Fig. 3) is highest among study population weighing between 41 – 60kg (61.4%). This is similar to the Ethiopian study, with 63% of the study population weighing between 40 and 59kg. This is statistically significant and could suggest hormonal factors in the development of ADR. This could be because adverse drug reactions are more prevalent among adults aged 30 – 39 years in this study. The most reported ADR by organ system (Table 1), skin reaction contributing 42.7% of the total ADRs, this is closely followed by heamatology (37.3%), others (12.9%) and central nervous system (7,2%). The most common ADR (Table 1) is anaemia (37.2%), which could be majorly attributable to zidovudine and this is closely followed by rash (31.4%). This could be attributed mainly to Nevirapine, as in Table 2, where zidovudine/lamivudine/nevirapine was the most implicated drug (76.5%). This is in line with a similar study in Nigeria with 23.4% and 15.9% of ADRs were anaemia and rash. Additional ADRs attributable to zidovudine include darkened or hyperpigmented nails (5.4%), while those attributable to nevirapine include Stevens-Johnson syndrome (5.9%). This outcome of Stevens-Johnson syndrome was higher than Nigeria and Indian studies (1%). The central nervous system represented 7.2% of reported ADR and was primarily associated with Efavirenz. This is lower than the results of a similar Nigerian study (13.6%) and an Ethiopian study (35.7%). However, fewer ADRs are associated with tenofovir and efavirenz; this may be because fewer patients are on this regimen than on zidovudine and nevirapine. Hospital admission (Fig. 4) due to ADR is 22.4% with the majority of the patients, 77.6% not admitted, and the median duration of admission (Table 3) is 7 days. This result is in line with similar studies in U.S.A(5.8%) and U.K (6.5). Figure 6 on treatment of ADR shows that, 51.8% of the patients are counseled to continue their ARVs, while, 48.2% of the patients discontinued their medication due to associated ADRs that become unbearable even after counseling and treatment. The result of this study was lower than that of Cameroonians, where discontinuation of medication was 68.2%. However, 91.8% of the patients recovered fully, 1.2% recovered with disability, 3.5% experienced a life-threatening reaction, and 3.5% of the patients died (Fig. 6), probably as a result of ADR or co-infection. This was a higher rate than a similar study in Nigeria, with 1% life-threatening adverse drug reaction. Research on zidovudine associated adverse drug reactions, such as palm and nail pigmentation, needs to be explored.

Conclusion

Adverse reactions due to the use of ARVs, if not closely monitored and promptly treated, may severely jeopardize confidence in the safety of ARVs and alter patient adherence to therapy, reduce the treatment efficacy, and ultimately increase morbidity and mortality, as well as increase the risk for the emergence of secondary drug resistance. It is important that in disease conditions such as HIV/AIDS, where drugs are to be taken for a prolonged period of time, patients and caregivers need to be conversant with adverse ADRs that are to be expected in the course of treatment. This will help implement treatment strategies that reduce or ameliorate these issues, improve medication adherence, prevent treatment failure, minimize the waste of other resources, and preserve future treatment options.

Conflict of Interest

There is no conflict of interest.

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