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Antiretroviral adverse drug events reported among adult HIV patients in a Nigerian tertiary hospital: A retrospective study

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Abstract

Background: The use of Highly Active Antiretroviral Therapy (HAART) has changed HIV/AIDS from a near-certainly fatal illness to one that can be managed chronically. A significant constraint of HAART is the high prevalence of adverse drug events (ADE) among HIV patients taking them.

Objectives: The study determined the frequency and severity of reported antiretroviral adverse events among HIV-infected adults (≥ 16 years) at the Institute of Human Virology (IHV) Clinic of Nnamdi Azikiwe University Teaching Hospital Nnewi, Anambra State, Nigeria, within five years. Antiretroviral therapies implicated in the reported adverse drug events were also determined.

Method: Information on reported ADEs was extracted from the NAFDAC Pharmacovigilance forms in the Pharmacovigilance section of the IHV Clinic Pharmacy. The severity of ADEs was classified using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index for categorizing errors.

Results: A hundred and nineteen (119) patients reported 161 ADEs within the 5-year study period (2017-2021). Most ADE reports came from females (74.53%) and patients 36-55 years old. Dizziness (31.1%), Rashes (14.3%), and Fatigue (13.0%) were prominent among all the ADE reports documented. TDF/3TC/EFV (57.8%) and AZT/3TC/NVP (11.8 %) combinations were the frequently implicated antiretroviral regimen. All the ADEs reported were mild (Category 'E'). ADE reports appreciated in the second year and progressively declined afterwards.

Conclusion: There is a need to improve the system for antiretroviral ADE reporting through sensitization and developing a specific tool that enhances ADE reports from patients and healthcare providers.

Keywords: Antiretroviral; Adverse drug event; Pharmacovigilance report; Adults; HIV patients

1. Introduction

Sub-Saharan Africa has the highest number of people living with HIV/AIDS (PLWHA) [1]. The estimated number of people living with HIV/AIDS in central and West Africa by the end of 2023 is 4.8 million [4.2 million - 5.5 million], with 160,000 [110,000 - 250,000] new infections [2]. The introduction of antiretroviral drugs (ARVs), especially Highly

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Active Antiretroviral Therapy (HAART), has been revolutionary, changing HIV/AIDS from a near-certainly fatal illness to one that can be managed chronically [3,4]. The World Health Organization (WHO) recommends first-line regimens involving two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral (ARV) drug. Second-line regimens are started when the first-line regimens are ineffective [5]. The goal of HAART is to suppress HIV viral load, restore immune function, prevent resistance, improve quality of life, and prevent HIV transmission [3]. The advent of HAART has resulted in significant decreases in HIV-related mortality and morbidity in both the developed and developing world. HAART has been touted as one of the most important breakthroughs in the response to the HIV pandemic [6]. A major constraint of HAART is the high prevalence of adverse drug events (ADE) among HIV patients taking them. World Health Organization (WHO) defines an adverse drug event (ADE) as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function” [7]. ADEs are prevalent complications of antiretroviral therapy and a major reason for patients defaulting during HIV therapy [5]. More patients are taking antiretroviral drugs (ARVs) for extended periods, and this naturally results in more observed toxicity. Most toxic effects from ARV drugs result from adverse drug events of therapeutic doses of ARVs and drug-drug interactions. Overdose, either intentional or unintentional, with ARV is rare [3].

At the beginning of the ARV treatment, HIV-infected patients can frequently exhibit a wide variety of ADEs such as rashes, hypersensitivity syndrome reactions, urticarial or erythema multiform, Stevens-Johnson syndrome, hair loss, which present as a short-term course of adverse reactions within the first few weeks of antiretroviral therapy initiation [8]. The adverse events of ARV drugs are indeed a common reason for discontinuation of treatment in HIV patients. More than 25% of patients discontinue therapy in the first year because of these adverse events [9]. In a study done in India, 90.6% of all the patients on HAART developed an adverse drug reaction, with the central nervous and abdominal systems as the most affected [6]. Another study in Cameroun found an ADE prevalence of 19.5%, of which 21.2% were due to peripheral neuropathy [6]. Similar studies reported a high occurrence of antiretroviral adverse events in Ethiopia among HIV-infected patients with hyperlipidemia and lipodystrophy the highest prevalent [1]. Adverse Drug Events are becoming increasingly important in the efforts to fine-tune HAART to reduce toxicities [10]. The spectrum of adverse events associated with ARVs may vary between developed and developing countries [11]. Although HAART has been extensively used and studied in developed countries, with positive outcomes such as reduction in HIV-associated morbidity and mortality, this observation cannot be generalized to developing countries where the patterns, incidence, and severity of antiretroviral adverse events differ markedly owing to local environmental and genetic influences. These influences may compromise the effectiveness of HAART programs and lead to toxicity, drug interaction, intolerance, drug resistance, and loss of follow-up amongst diverse HIV-infected populations [12]. The current study was in two parts; the first part determined the frequency and severity of all adverse drug events reported from 2017 to 2021 among HIV-positive patients in Nnamdi Azikiwe University Teaching Hospital Nnewi, Anambra State, Nigeria. The second part determined the association between antiretroviral combinations and the reported adverse drug events.

Objectives of the study

- To determine the types of ADEs mostly reported among adult HIV patients in the study health institution.
- To determine the severity of the reported ADEs.
- To determine antiretroviral combinations mostly implicated in the ADEs reported.
- To determine the frequency of antiretroviral ADE reports within a 5-year study period among adult HIV/AIDS patients of Nnamdi Azikiwe University Teaching Hospital, Nnewi.

1.1. Inclusion and Exclusion Criteria

Only HIV/AIDS patients 16 years and above were included. ADEs reported on NAFDAC Pharmacovigilance forms were included only.

ADEs reported without evidence of documentation were excluded. ADE reports of patients under 16 years were also excluded from the study.

2. Material and method

2.1. Study Setting

The study was conducted at the Institute of Human Virology (IHV) clinic of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State, South-East Nigeria. The clinic cares for patients in and outside Anambra State with six comprehensive Health Centers in different parts of Anambra State. HIV care, treatment, and support services

are free for all patients enrolled in the program. The IHV clinic provides ambulatory HIV/AIDS care, treatment, and support to over 4000 patients. An average of 70 patients are attended to daily, and the clinic runs from Monday – Friday

2.2. Study Design

It was a retrospective cross-sectional study of reported antiretroviral adverse drug events (ADEs)

2.3. Study Population and Sample Size

HIV/AIDS patients 16 years and above on HAART who had documented evidence of ADE report on the National Agency for Food and Drug Administration and Control (NAFDAC) Pharmacovigilance reports form in the Pharmacovigilance section of the clinic's Pharmacy between January 2017 and December 2021. The total number of such patients was 119.

2.4. Data Collection

Socio-demographic, therapeutic, and antiretroviral adverse events information of eligible patients, including age, sex, type of HAART regimen, reported ADEs, severity, and number of ADE reported per year, were extracted from the copies of NAFDAC Pharmacovigilance forms documented in the Pharmacovigilance arm of the clinic's pharmacy. The source of ADE data included reports from patients and morphological changes as noticed by the Physicians, Pharmacists, and Nurses during routine drug pick-ups. The severity of ADEs was classified using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index for categorizing ADEs.

2.5. Data Analysis

The generated data was sorted, coded, entered into an MS Excel spreadsheet, and analyzed using SPSS version 25. Descriptive analysis was done using frequencies and percentages for qualitative (categorical) variables. Mean and Standard deviation were used to present quantitative variables. A test of association was done using Chi-Square (X^2) for categorical variables. All p-values were significant at <0.05 .

3. Results

3.1. A hundred and nineteen (119) patients reported antiretroviral ADEs within the 5-year study period, and all the 119 reports were included in the study.

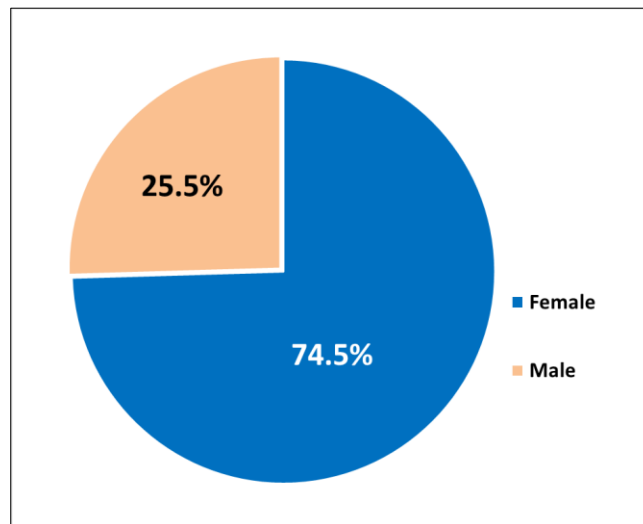


Figure 1 Gender distribution of antiretroviral ADE reported from 2017-2021

Fig 1 shows the Gender distribution of 119 HIV/AIDS patients who reported antiretroviral ADE in the study hospital within the 5-year period. Approximately 75 % of the ADE reports came from female patients.

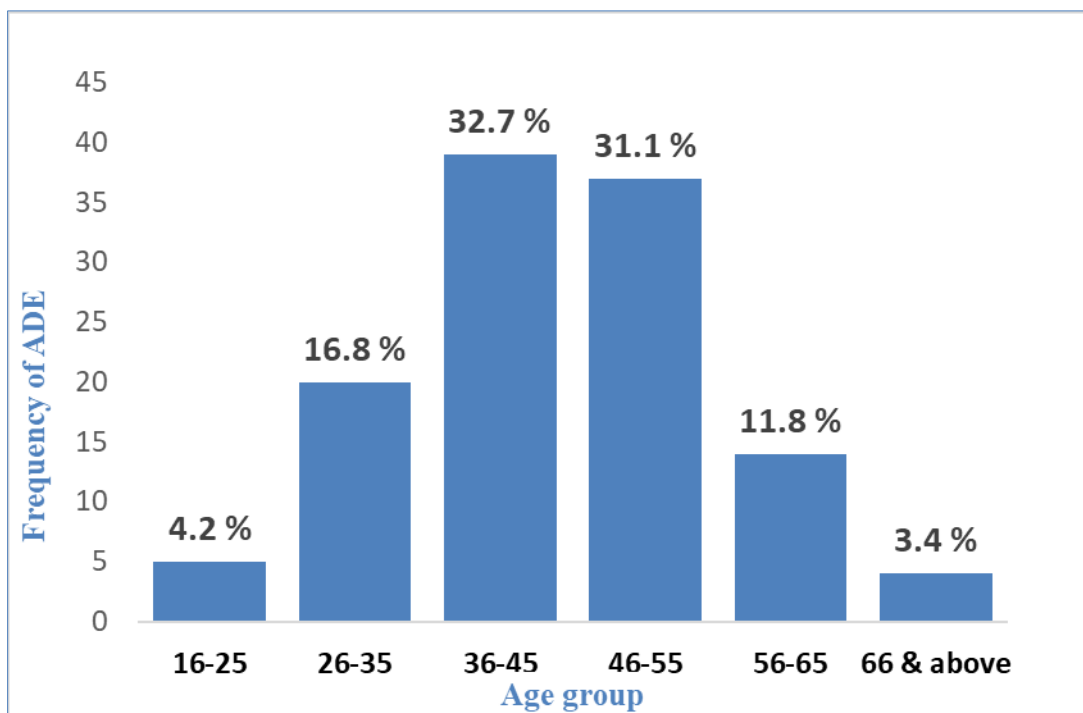


Figure 2 Age distribution of antiretroviral ADE reported from 2017-2021

Figure 2 shows the age distribution of the patients who reported antiretroviral ADEs. Patients between 36-45 years and those between 56-65 years had more reports (34.2 % and 31.1 %, respectively) than others.

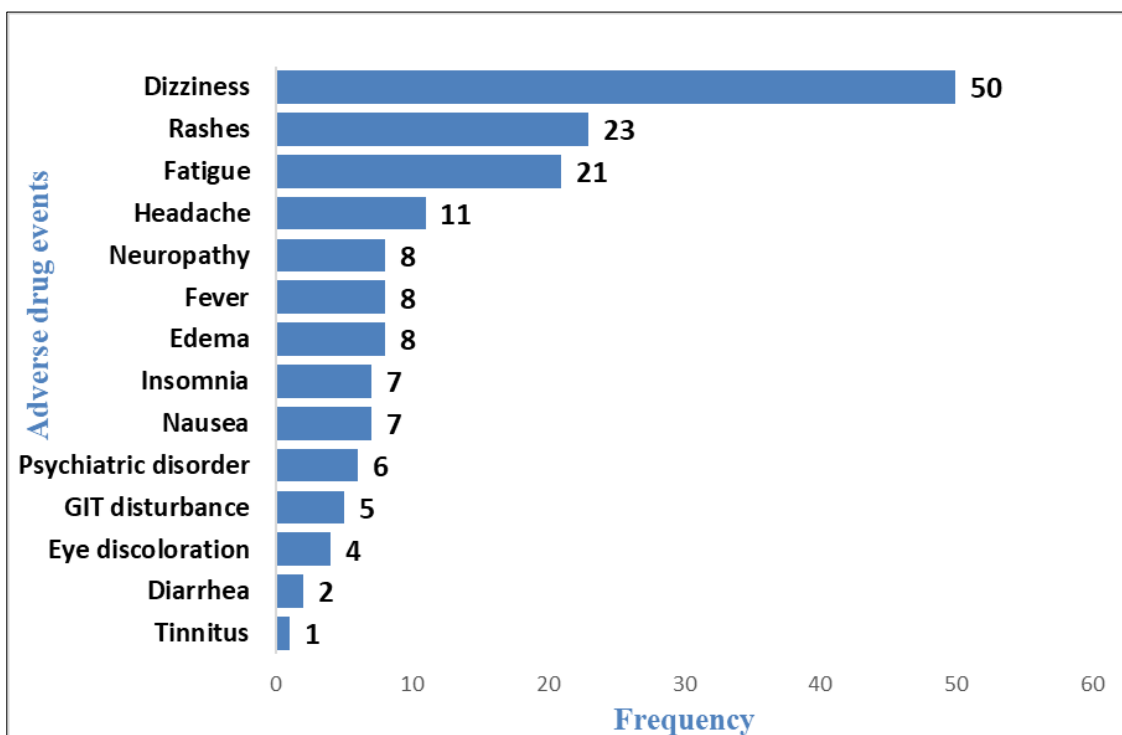


Figure 3 Specific antiretroviral ADEs reported from the year 2017-2021

A total of 161 ADEs were reported by the 119 patients reports reviewed. Prominent among the specific ADEs reported were Dizziness (31.1 %), Rashes (14.4 %) and Fatigue (13.0 %). Figure 3 has the details.

Table 1 Relationship between ADE reported and socio-demographic variables (Age, Sex)

Variables	ADE reported (%)	X ²	p-value
Age (years)			
16-25	5 (4.2)		
26-35	20 (16.8)		
36-45	39 (32.7)	0.0000	0.000
46-55	37 (31.1)		
56-65	14 (11.8)		
66 and above	4 (3.4)		
Sex			
Female	89 (74.5)	0.0000	0.000
Male	30 (25.5)		
Severity of ADE			
Category E	119 (100.0)	-	-

Results revealed that female patients (74.5 %) and patients within the age groups 36-45 (32.7%), 46-55 (31.1%) and ages 26-35 (16.8%) reported the highest number of antiretroviral ADEs. The reporting attitude was significantly influenced by both gender and age ($X^2 = 0.0000$; p-value < 0.001, respectively). All the ADEs reported were mild in severity (category E).

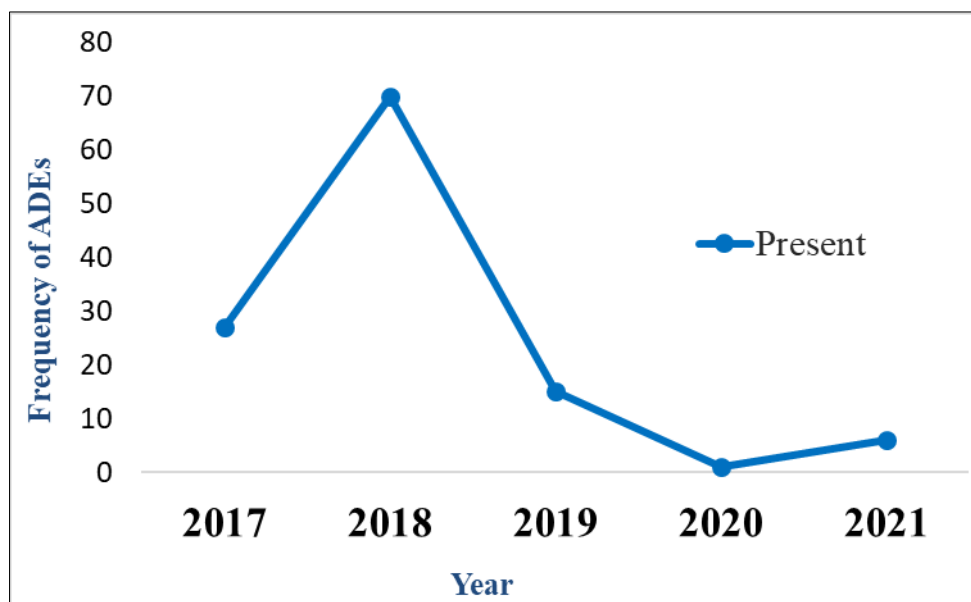


Figure 4 The flow of ADE reports within the five years studied (2017-2021)

Figure 4 shows the frequency of antiretroviral ADE reports for five years (2017-2021). The reports had a progressive trend between 2017 (27 reports) and 2018 (70 reports). After that, the trend declined, and the reported trend within the years was statistically significant ($X^2 = 0.0000$; p-value = <0.001)

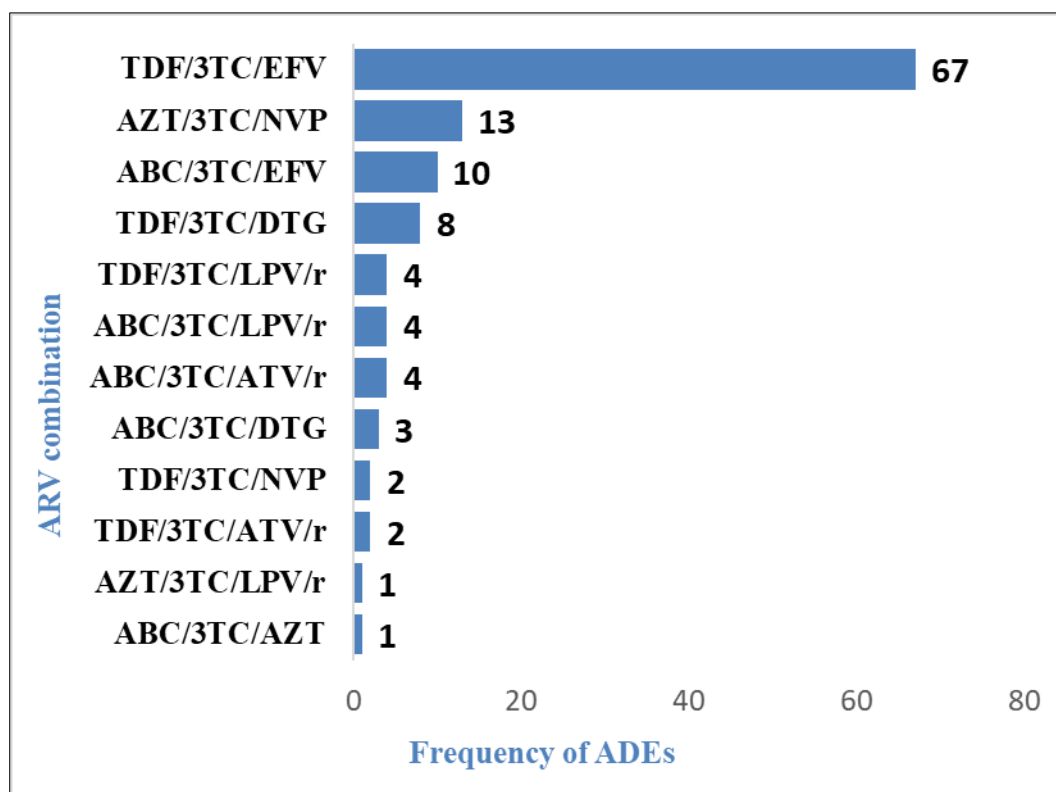


Figure 5 Distribution of Antiretroviral drug combinations implicated in the reported ADEs

The antiretroviral combinations that contributed to the 119 ADE reports are presented in Figure 5. Top among them included 67 reports from TDF/3TC/EFV (57.8 %), 13 reports from ZT/3TC/NVP (11.8 %), and ten reports from ABC/3TC/EFV (8.1 %) combinations. The frequency of the ADE reports was dependent on the antiretroviral combination (χ^2 ; p-value <0.001).

4. Discussion

The use of Highly Active Antiretroviral Therapy (HAART) resulted in an appreciable improvement in the prognosis of HIV/AIDS disease [13]. HAART includes the combination of three different types of highly effective anti-HIV-1 drugs, including Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease inhibitors [13]. However, HAART requires adequate monitoring of the potential and actual adverse events to the antiretroviral (ARV) drugs [14]. This study identified commonly reported adverse events and antiretroviral combinations implicated in the reported events among HIV-infected adults (>16 years) at the Institute of Human Virology (IHV) Clinic, Nnamdi Azikiwe University Teaching Hospital Nnewi Anambra State, Nigeria.

Findings from this study showed that from 2017 to 2021, adverse drug events were reported and documented in 119 adult HIV-positive patients, and most of the reports came from females and patients between 36 – 45 years. This is similar to studies conducted in Mali [9] and Ethiopia [1], where a larger percentage of respondents were women. The female predominance in HIV cases and subsequent reports of antiretroviral ADEs can probably be explained by more frequency of heterosexual transmission and the biological vulnerability of women to HIV/AIDS. Also, women's socioeconomic vulnerability places them at a higher risk of HIV transmission [9]. Studies have also shown that women frequently visit the hospital for myriad reasons and are subjected to tests, including HIV test [15]. Hence, females would most likely visit the hospital for complaints and possible reports of ADEs more than males. Studies of ADE in Mali [9] and South Africa [16] recorded age ranges of 26-27 and 30-44, respectively with higher female higher dominance.

Adverse drug events (ADE) play a significant role in the success of antiretroviral regimens because they compromise adherence once they occur. A varied and broad spectrum of adverse events was identified in the ADE reports studied (Figure 3) and the most common were Dizziness, Rashes, Fatigue, headache, neuropathy, fever, and Edema. Similar ADEs were also identified in studies conducted in Nigeria [17] and South Africa [16]. None of the reported ADEs caused permanent harm or resulted in hospitalization to the patients. They were temporary harm-requiring interventions

(Category E), according to the National Council for Medication Error Reporting and Prevention Index for categorizing errors. A study conducted in Mali had similar result [9].

The most common therapeutic combination in this study comprised of two Nucleoside Reverse Transcriptase Inhibitors NRTIs [Tenofovir (TDF) and Lamivudine (3TC)] plus one Non-Nucleoside Reverse Transcriptase Inhibitors [Efavirenz (EFV)]. Notably, WHO has widely recommended NNRTI-based regimens for African countries [9]. This study showed that about two-thirds of the adverse events documented resulted from Efavirenz-based combinations. Similar studies by Birbal et al [16] also linked dizziness and rashes to EFV-based combinations. A study in Denmark reported the neuropsychiatric disturbances caused by EFV-based combination, which includes dizziness, Insomnia, hallucinations, and nightmares, and this led to discontinuation of the drug in more than half of the patients [18]. The study also linked about 10 % of the reported ADEs to Nevirapine (NVP)-based combination. The result of a similar study as well linked NVP use in adults to gastrointestinal disturbances, nausea, rash, and neuropathy in line with the current study [19]. Ocular manifestation has been linked to intake of HAART [20], similar to what the current study has revealed.

This study showed a decline in the ADE reported by patients, especially from 2019 to 2021. Similar studies from Nigeria [21], Italy [22], and India [23] have reported that there is a decline in the reporting of adverse drug events. This can be attributed to some documented factors like ignorance (only severe ADEs need to be reported), lethargy (procrastination, lack of interest or time to find a report card or other excuses), diffidence (fear of appearing ridiculous for reporting merely suspected ADRs), complacency (only safe drugs are allowed on the market) and insecurity (it is nearly impossible to determine whether or not a drug is responsible for a particular adverse event) [24]. Furthermore, post-COVID-19 pandemic, health systems in developing countries were somewhat destabilized, possibly resulting in the relaxation of activities like documentation of ADEs in the management of chronic diseases like HIV/AIDS.

5. Conclusion

Adverse Drug Events of Highly Active Anti-Retroviral Therapy (HAART) are enormous and common among people living with HIV/AIDS (PLWHA). They can present life-threatening conditions or disability sometimes among PLWHA. Although all the ADEs reported in this study were non-life threatening, they may have resulted in poor adherence and abrupt stop of medications, thereby jeopardizing the desired therapeutic outcome of patients. It is essential that ADEs are reported to reveal the nature of the events and help strategize measures to prevent them. The study showed a progressive decline of ADE reports within the study years as seen in related studies, suggesting a need to strengthen Pharmacovigilance and ADE detection/reporting systems in the study healthcare facility and in all Nigerian healthcare institutions at large.

Compliance with ethical standards

Acknowledgments

The authors appreciate the NAUTH community and NAUTH management for study site approval and the cooperation to carry out the study in her institution.

Disclosure of conflict of interest

The authors declare that there is no conflicting interest

Statement of ethical approval

This study was done within a study that aimed at determining the “Feasibility and effectiveness of HIV medication adverse event detection model in adult HIV Positive Patients of a Nigerian hospital.” Ethical approval was obtained from the NAUTH Research Ethics Committee prior to the study (Ethics approval code = NAUTH/CS/66/VOL.12/036/2019/020). Approval was also gotten from the NAUTH management for the use of the NAUTH HIV/AIDS clinic as the study site (site authorization code = NAUTH/CS/66B/VOL.2/073)

Statement of informed consent

Informed consent was obtained from the focal Pharmacist in-charge of Pharmacovigilance in the IHV clinic of the study hospital. This allowed us access to the copies of the NAFDAC Pharmacovigilance forms used in tracking reported ADEs.

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