Introduction

Considerable progress has been made in providing global access to antiretroviral therapy (ART), with over three million people currently on ART around the world. ART has proved efficacious in reducing mortality and morbidity related to Human Immunodeficiency Virus (HIV) infection; however, is also associated with both short- and long-term drug-induced toxicities. These toxicities can vary significantly among individuals and may include nausea, vomiting, diarrhea, fatigue, and neuropsychiatric symptoms. Additionally, ART can interact with other medications, leading to increased toxicity or decreased efficacy.

In order to address these challenges, it is essential to monitor and manage patient responses to ART. This can be achieved through systematic drug use monitoring, which involves collecting data on the usage of medication, adverse reactions, and outcomes. By analyzing this data, healthcare providers can identify patterns and trends in medication use and adverse reactions, allowing for more effective and personalized care.

The importance of drug use monitoring cannot be overstated. It is critical for improving patient outcomes, reducing healthcare costs, and ensuring the safe and effective use of ART. By implementing drug use monitoring systems, healthcare providers can better understand the impact of ART on patients, identify potential drug interactions, and adjust treatment plans as needed. This ultimately leads to better patient outcomes and improved quality of life.
toxicities may reduce patient’s quality of life and adversely affect treatment adherence;[^4][^8] and consequently may lead to treatment failure. Nonetheless, they are severely under-reported.[^7] In Nigeria, there are 359, 181 patients receiving ART as of December 2010 in over 200 secondary and tertiary hospitals, with plans to decentralize to primary health care level.[^9][^10] However, information regarding the occurrence and types of adverse drug reactions (ADRs) in these patients is very limited.

The prevalence of stavudine-associated lipodystrophy was 50%–63% in developed countries[^8][^11] compared to 24.8% in a Rwandan cohort.[^12] Peripheral neuropathy occurred in 10% to 21% of persons exposed to stavudine in developed countries.[^13][^15] A study in Malawi reported that 56% of patients receiving stavudine therapy developed peripheral neuropathy.[^16] Previous studies reported nevirapine-associated rash rates of 3%–26%[^16][^21] whereas rates of nevirapine-associated hepatotoxicity ranged from <1% to 7%.[^16][^20]

In Nigeria, Cote d’Ivoire, Haiti, and India, the reported rates of Zidovudine-induced anaemia was 3%–12%.[^17][^18][^22][^23][^24] In a recent study in Nigeria, 54% of ADRs were reported by patients on Zidovudine (AZT)-based regimens, and the commonest ADRs reported were pain (30%) and skin rash (18%); 1% of the ADR were life threatening. The study also reported that ADR was less likely to occur in patients on Stavudine (d4T) and AZT compared to Tenofovir disoproxil fumarate (TDF).[^22]

Epidemiologic data support the existence of specific factors that increase the risk of general ADR, such as female gender.[^26][^27] The incidence of severe ADRs was 32.55% in patients <35 years of age compared to 19.44% in those >35 years of age, though the difference was not statistically significant.[^28] On the contrary, Eluwa et al. reported that age and gender were not significantly associated with ADRs.[^29] Another study reported the occurrence of the following ADRs: (19.5%) nausea/vomiting, (15.7%) skin rash, (23.9%) diarrhoea, (13.8%) dizziness, (11.9%) paraesthesia and (14.5%) bad dreams.[^29]

Spontaneous reporting of ADR is the foundation of national and international drug safety evaluation after licensing and approval for use in general population.[^30] It is a more popular method of pharmacovigilance, administratively simpler, covers potentially large and diverse population, and good for the identification of rare, serious drug-related or delayed adverse effects of medicines compared to cohort event monitoring.[^30][^31] However, under-reporting and strong biases in reporting are major problems with spontaneous reporting system (SRS).[^7][^30] Eluwa et al. reported that 45% of reported ADRs occurred within 12-24 months of commencing ART,[^32] supporting the need for long-term monitoring of patients on ART for delayed adverse effects. Individual Case Safety Report (ICSR) is a notification relating to a patient with an adverse medical event or laboratory test abnormality suspected to be induced by a medicine. It is an essential source of information for the achievement of the main objectives of pharmacovigilance and can involve several ADRs.[^32] This study evaluated the ICSRs from a spontaneous reporting program in HIV-positive patients receiving ART in Nigeria.

### MATERIALS AND METHODS

#### Research design

This descriptive study analyzed individual case safety reports (ICSRs) from a spontaneous reporting program in HIV-positive patients receiving ART between January 2011 and December 2011 in selected Nigerian hospitals.

#### Setting and study population

This study was conducted in 38 secondary hospitals providing comprehensive package of HIV prevention, treatment, care and support. These hospitals were selected from 20 out of 36 states plus Federal Capital Territory of Nigeria, and spread across the six geopolitical zones of Nigeria. HIV services are provided at no cost to the patients with funding from United States President Emergency Fund for AIDS Relief (PEPFAR) through United States Agency for International Development (USAID). SRS of the national pharmacovigilance program coordinated by National Agency for Food and Drug Administration and Control (NAFDAC) are operational in these hospitals. Suspected ADRs in patients on ART are reported using the national ICSR form (the yellow form). The original copies of ICSRs are forwarded to national pharmacovigilance center at NAFDAC for onward transmission to WHO Uppsala Monitoring Center while the duplicate copies are retained at the hospitals. All ICSRs in HIV-positive patients on ART between January 2011 and December 2011 in the study sites were included in this study.

#### Ethical consideration

The ethical approval for this study was obtained from National Health Research Ethics Committee (NHREC), Federal Ministry of Health Abuja Nigeria. Confidentiality was assured by excluding patients’ identifier during analysis.

#### Data collection

All ICSRs in HIV-positive patients on ART between January 2011 and December 2011 in the study sites were collated for analysis by researchers and trained research assistants. The national ICSR form (the yellow form) is a standard tool for spontaneous reporting of suspected ADR cases in Nigeria.
This tool included sections on the patients’ demographics, ADR description, treatment and outcome of reaction, suspected drug details and the concomitant medicines. The research assistants used patient identifiers to sort and filter out duplicate case reports and assigned a code to each of the patient’s case safety reports before data entry.

**Data analysis**

Data analysis was performed using Predictive Analytics SoftWare (PASW) statistics® version 18. Descriptive statistics including frequency distribution of key items and bivariate analysis was carried out to describe the relationship between reported ADRs and variables as age, gender and ART regimens. Chi-square statistic with Yates’ correction was used to test the association between reported ADRs and patients’ age, gender, and ART regimens. The association between reported ADRs and specific variables was assessed by an odds ratio (OR) at 95% confidence interval. The reported p values were 2-sided and p < 0.05 was used to determine statistical significance except where otherwise indicated.

**RESULTS**

**Adverse drug reaction description**

From 1237 individual case safety reports (ICSRs) in HIV-positive patients receiving ART collated from the study sites during the study period; only 1119 (90.5%) ICSRs were valid for analysis. Either or both key variables of interest (ADR description or/and suspected drug details) were missing in 118 (9.5%) ICSRs, and hence they were excluded in the analysis. The mean age of the patients who reported the ADR cases was 35.3 (95%CI, 35.1–35.5) years. Of the patients, 67.1% were females; 46.9% were aged 30–44 years old; and 54.3% received Zidovudine (AZT)/Lamivudine (3TC)/Nevirapine (NEV) regimen [Table 1]. There were a total of 1679 reported ADRs cases in these patients; an average (± Standard Deviation SD) of 1.5 (± 0.8) ADR cases per patient. Of the ICSRs, 62.0% of the patients received AZT based regimens that constituted 63.2% of the suspected ADRs cases whereas 9.6% received Stavudine (d4T) based regimens that constituted 8.2% of the suspected ADRs cases [Figure 1]. The suspected ADRs

| Characteristics                                      | Frequency | Percent |
|------------------------------------------------------|-----------|---------|
| Sex                                                  |           |         |
| Male                                                 | 339       | 30.3    |
| Female                                               | 751       | 67.1    |
| Not indicated                                        | 29        | 2.6     |
| Age (years)                                          |           |         |
| <15                                                  | 26        | 2.3     |
| 15–29                                                | 264       | 23.6    |
| 30–44                                                | 525       | 46.9    |
| 45–59                                                | 204       | 18.2    |
| >59                                                  | 31        | 2.8     |
| Not indicated                                        | 69        | 6.2     |
| Regimens                                             |           |         |
| Stavudine/Lamivudine/Nevirapine (d4T/3TC/NEV)         | 104       | 9.3     |
| Stavudine/Lamivudine/Efavirenz (d4T/3TC/EFV)         | 3         | 0.3     |
| Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NEV)       | 608       | 54.3    |
| Zidovudine/Lamivudine/Efavirenz (AZT/3TC/EFV)        | 86        | 7.7     |
| Tenofovir/Lamivudine/Nevirapine (TDF/3TC/NEV)        | 72        | 6.4     |
| Tenofovir/Lamivudine/Efavirenz (TDF/3TC/EFV)         | 18        | 1.6     |
| Tenofovir/Emtricitabine/Nevirapine (TDF/FTC/NEV)     | 88        | 7.9     |
| Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV)      | 37        | 3.3     |
| Tenofovir/Lamivudine/Lopinavir-boosted with Ritonavir (TDF/3TC/LPVr) | 3 | 0.3 |
| Not indicated                                        | 100       | 8.9     |

![Table 1: Distribution of the characteristics of patients on antiretroviral therapy who had the individual case safety reports (ICSRs); N = 1119](image)

![Figure 1: Distribution of Individual Case Safety Reports (ICSRs) by regimen and adverse drug reaction](image)
included (12.0%) peripheral neuropathy reported as tingling, numbness and pain in the extremities; (11.4%) skin rash, (10.1%) pruritus and (6.5%) dizziness among others [Table 2]. Although all patients included were onART, the specific ART regimens received by patients were not indicated in 156 (9.3%) of ADR case reports.

The occurrence of the suspected ADRs was associated with ART regimens \( (P = 0.000) \), patients’ age \( (P = 0.021) \) and concomitant medicines \( (P = 0.001) \). The suspected ADRs that were associated with ART regimens included anaemia [AZT/3TC/NEV, OR = 6.4 (3.0 – 13.8); \( P < 0.0001 \)], peripheral neuropathy reported as tingling, numbness and pain in the extremities [d4T/3TC/
NEV, OR = 8.7 (5.8 – 30.0), P < 0.0001; d4T/3TC/EFV, OR = 7.4 (0.74 – 73.9), P = 0.0190 and TDF/Emtricitabine (FTC)/Efavirenz (EFV), OR = 2.1 (1.0 – 4.1), P = 0.0446 – Table 3. Of the ADR cases, 47.8%, 24.4%, 17.0% and 2.6% were reported by patients aged 30 – 44, 15 – 29, 45 – 59 and >59 years old respectively. In 5.9% of cases, the age of the patients were not indicated. The suspected ADRs that were associated with patients’ age included skin rash [<15 years, OR = 3.0 (1.3 – 6.6), P = 0.0056], peripheral neuropathy reported as tingling, numbness and pain in the extremities [45 – 59 years, OR = 1.9 (1.3 – 2.7), P = 0.0006], cough [<15 years, OR = 8.2 (2.9 – 22.1), P <0.0001], fever [15 – 29 years, OR = 2.4 (1.2 – 4.9), P = 0.0124] and visual disturbances (>59 years, OR = 7.0 (1.7 – 21.8), P = 0.0007]. Of the ADR cases, 61.1% and 13.3% were reported by patients taking Cotrimoxazole and Hematinics concomitantly with antiretroviral drugs (ARVs) respectively. The suspected ADRs that were associated with concomitant medicines included palpitation [Salbutamol, OR = 55.7 (4.9 – 349.6), P = 0.0000] and polyuria [Nonsteroidal anti-inflammatory drugs (NSAIDS)/Paracetamol, OR = 50.2 (0.9 – 562.1), P = 0.0040] – Table 4. Overall, the occurrence of the suspected ADRs was not associated with gender (P = 0.548). However, when a test of association was done for individual ADR cases, some of the ADR cases had significant association with gender. These ADR cases were peripheral neuropathy reported as tingling, numbness and pain in the extremities [male, OR = 1.4 (1.0 – 2.0), P = 0.0334], headache [female, OR = 1.7 (1.1 – 2.7), P = 0.0125] and malaise [male, 2.7 (1.2 – 6.5), P = 0.0177].

### Adverse drug reactions treatment

The actions taken to manage the reported ADRs were indicated in 712 (39.6%) of ADR cases. These actions included 47.9% drugs initiated to treat ADR and 21.5% counseling on ADR management. Of these actions, 78.9% cases of blood transfusion and 23.8% cases of treatment stop were secondary to anaemia; 100.0% cases of dose reduction were related to skin rash; 33.9% cases of drugs substitution and 15.8% cases of a new treatment initiation to treat ADR were related to peripheral neuropathy reported as tingling, numbness and pain in the extremities [Table 5].

### Adverse drug reactions outcomes

Of patients who reported ADRs, 19 (1.7%) were hospitalized due to ADR whereas 515 (46.0%) were not. However, 585 (52.3%) did not indicate whether they were hospitalized or not due to ADR. Of patients who were already hospitalized, 46 (4.1%) of them reported that the duration of their hospitalization was prolonged due to ADRs. Of patients who reported ADRs, outcomes of ADRs reported were 208 (18.6%) recovered fully, 5 (0.4%) recovered with disability, 5 (0.4%) life threatening, 1 (0.1%) death due to ADR, 153 (13.7%) were still recovering at the time of ADR reporting whereas 747 (66.8%) did not indicate the outcomes. For those who recovered with disability, the nature of this disability was not indicated.

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**Table 3: Significant suspected adverse drug reactions segregated by antiretroviral treatment regimens; Values are Odds ratio at 95% Confidence Interval (CI), n = 1679**

| ADR descriptions | ART Regimens | Odds Ratios (95% CI) | p-value |
|------------------|--------------|---------------------|---------|
| Anemia           | AZT/3TC/NEV  | 6.4 (3.0 – 13.8)    | <0.0001 |
| Pedal Oedema     | TDF/3TC/FTC  | 30.5 (0.0 – 449.3)  | 0.0423  |
| Tingling, numbness and pain in the extremities | d4T/3TC/EFV | 8.7 (5.8 – 30.0) | <0.0001 |
| Dizziness       | AZT/3TC/EFV  | 2.1 (1.0 – 4.1)     | 0.0446  |
| Hallucination    | AZT/3TC/EFV  | 1.8 (1.0 – 3.3)     | 0.0454  |
| Depression       | AZT/3TC/EFV  | 5.7 (1.9 – 18.8)    | 0.0004  |
| Nausea/Vomiting  | AZT/3TC/NEV  | 15.6 (2.1 – 134.1)  | 0.0013  |
| Polyphagia       | TDF/3TC/EFV  | 19.7 (2.1 – 183.6)  | 0.0002  |
| Epigastric pain  | Not indicated| 12.6 (2.9 – 56.3)   | <0.0001 |
| DYSMENORRHEA     | d4T/3TC/NEV  | 11.9 (2.5 – 57.0)   | 0.0002  |
| Insomnia         | TDF/3TC/EFV  | 6.8 (2.2 – 19.9)    | 0.0001  |
| Visual disturbances | TDF/3TC/FTC  | 31.7 (0.0 – 467.8)  | 0.0380  |
| Nightmaires      | AZT/3TC/EFV  | 13.0 (2.6 – 79.1)   | 0.0001  |
| Erectile dysfunction | TDF/3TC/EFV | 12.0 (1.6 – 71.7) | 0.0075 |
| Lipodystrophy    | TDF/3TC/EFV  | 78.9 (0.0 – 3007.0) | 0.0002  |

Where, AZT = Zidovudine; 3TC = Lamivudine; EFV = Efavirenz; TDF = Tenofovir; NEV = Nevirapine; FTC = Emtricitabine.

**Table 4: Significant suspected adverse drug reactions segregated by concomitant medicines; Values are Odds ratio at 95% Confidence Interval (CI), n = 2024**

| ADR descriptions | Concomitant Medicines | Odds Ratios (95% CI) | P-value |
|------------------|-----------------------|----------------------|---------|
| Pedal Oedema     | Not indicated         | 2.2 (1.0 – 4.7)      | 0.0364  |
| Cough            | Haematinics           | 3.59 (1.4 – 4.7)     | 0.0011  |
| Polyphagia       | Antituberculosis drugs | 14.7 (0.3 – 119.8)   | 0.0011  |
| Epigastric pain  | Metronidazole and Others* | 15.2 (0.3 – 128.4) | 0.0006  |
| Steven Johnson Syndrome | Antimalarials** | 10.4 (1.1 – 48.1) | 0.0071  |
| Insomnia         | Antimalarials**       | 6.1 (0.7 – 26.9)     | 0.0069  |
| Polyuria         | Metronidazole         | 8.9 (0.9 – 4.8)      | 0.0156  |
| Palpitation      | NSAIDS/Paracetamol    | 50.2 (0.9 – 562.1)   | 0.0004  |
| Palpitation      | Salbutamol            | 55.7 (4.9 – 349.6)   | 0.0000  |

*Included Ciprofloxacin, Ofloxacino, erythromycin, amoxycillin, sternoids, Acyclovir, Amitryptiline and Antihypertensive, **Included Sulphadoxine Pyrimethamine, Artemether/Lumefantrine, and Artesunate/Amodiaquine, NSAIDS = Nonsteroidal anti-inflammatory drugs.
Peripheral neuropathy was also found to be associated with tenofovir/emtricitabine/efavirenz regimen. This has not been reported previously to our knowledge; therefore close monitoring of patients receiving this regimen is very imperative. One-third cases of drugs substitution and one-sixth of new drug initiation to treat ADR were related to peripheral neuropathy.

Nevirapine-associated rash rate reported in this study was consistent with rates of 3%–26% reported in previous studies.[16–21] Of cases of skin rash, over three-quarter were reported in patients who received nevirapine-based regimens. All cases of dose reduction to treat ADR were related to skin rash which are likely to be associated with nevirapine use. The major clinical toxicity of nevirapine is a rash, which has been reported in between 32% and 48% of patients.[33,34] Rashes were often accompanied by fever, usually began within 2 to 4 weeks after starting treatment, and typically resolved after stopping the drug.[34] The National treatment guidelines recommend that a patient starting nevirapine should receive a 2-week lead-in dose (200 mg once daily) to reduce the risk of rash of any severity.[8] Skin rash, peripheral neuropathy and visual disturbances were associated with patients aged <15, 45–59 and >59 years old respectively. In general, the occurrence of ADR was higher in patients <44 years of age (72.2%) compared to those >44 years of age (19.6%). This is similar (but two-fold higher for those aged <44 years) to previous research findings, though the difference was not statistically significant[29] contrary to this study finding. Similarly, Eluwa et al. reported that age was not significantly associated with ADRs[29] contrary to this study finding. This needs to be evaluated further. Over 50% of ADRs were reported by patients who were taking cotrimoxazole concomitantly.
with antiretroviral drugs (ARVs). The occurrence of palpitation and polyuria were associated with concomitant use of salbutamol and NSAIDS respectively. One of the most common adverse reactions associated with use of salbutamol inhalation aerosol is palpitations (occurring in <10% of patients).\(^5\)

In general, the occurrence of ADRs was not associated with gender contrary to previous reports that female gender increases the risk of general ADR.\(^26,27\) However; this is consistent with findings by Eluwa \textit{et al.} which reported that gender was not significantly associated with ADRs.\(^28\) When a test of association was conducted for each reported ADR with gender, peripheral neuropathy and malaise had significant association with male gender; while headache was associated with female gender. The differences in the study findings may indicate a significant association of specific ADRs with gender and this need to be further evaluated.

There were very few cases (<2%) of new hospitalization due to ADR. However, the duration of existing hospitalizations were prolonged by ADR in more (4.1%) HIV-positive patients receiving ART compared to those whose initial hospitalization was related to ADR. Less than one-fifth of patients who reported ADR recovered fully. This study suffered the same limitations of spontaneous reporting system (SRS) of pharmacovigilance. This included the limitations in the reliability of the data from SRS and severe under-reporting of ADRs which may under-estimate the occurrence of reported ADRs. No confirmatory clinical investigations were conducted at the time of the ADR reporting. This has the potential to over-estimate ADR occurrence if HIV or opportunistic infections related signs and/or symptoms was reported as ADRs. Data on seriousness or severity grades of the reported ADR cases were not available. This limited the analysis of the reported ADR cases by seriousness or severity grades.

**CONCLUSION**

ADRs were less likely to occur in patients on stavudine-based and tenofovir-based regimens compared to zidovudine-based regimens. The commonest ADRs reported were peripheral neuropathy, skin rash, pruritus and dizziness. Peripheral neuropathy was also found to be associated with tenofovir. This has not been reported previously to our knowledge, and may require further evaluation.

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