DETERMINANTS AND OUTCOMES OF ADVERSE DRUG REACTIONS AMONG PATIENTS ON ANTIRETROVIRAL THERAPY IN NIGERIA FROM 2014 TO 2018

BY

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CERTIFICATION

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DEDICATION

This work is dedicated to God Almighty.

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ABBREVIATIONS

ADR	Adverse Drug Reactions
ARV	Antiretroviral
ART	Antiretroviral Therapy
HAART	Highly Active Antiretroviral Therapy
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
WHO	World Health Organization

ABSTRACT:

The occurrence of adverse drug reactions to antiretroviral therapy in the management and care of HIV/AIDS can significantly affect treatment adherence, prevent viral suppression and contribute to HIV associated morbidity and mortality. Clinical trials are not able to identify rare and long-term adverse drug reactions in diverse patient populations. Assessing the effects of long term ART has not received sufficient attention, particularly in resource-constrained settings like Nigeria. This study seeks to investigate the determinants, severity and outcomes of adverse drug reactions to antiretroviral therapy in Nigeria from 2014 to 2018.

This study employed a retrospective record review of individual case safety reports submitted to the National Pharmacovigilance Centre, Nigeria, and key informant interviews of healthcare providers involved in antiretroviral care and counselling. A total of 3398 individual case safety reports (ICSRs) were received by the National Pharmacovigilance Centre between 2014 to 2018. Adverse Drug Reactions were extracted from the individual case safety reports using the WHO System Organ Classification. Age of patient, sex, weight, duration of ADR, concomitant medicines used and ART regimen were extracted. Data from the quantitative analysis were analysed using descriptive statistics, chi-square, and multivariate logistic regression. Data from the Key Informant Interviews were transcribed and the themes were identified.

Over half (55.9%) of those who reported ADRs were aged 16-35, with a mean age 34.7 ± 11 years. Majority of the reported ADRs were from female patients (71.5%). Neuropsychiatric disorders (29.8%), Skin and appendages disorders (17.1%), Peripheral nervous system disorders (6.7%), Musculoskeletal disorders (4.3%) and Anaemia (2.1%) were the most commonly reported system organ categories reported. Female sex (OR= 1.4, p=0.03), Efavirenz based therapy (OR=5.5, p=0.00) and Tenofovir based therapy (OR=1.6, p=0.02) were associated with

Neuropsychiatric disorders. Being younger than 15 years old (OR=2.56, p=0.000) and use of Nevirapine based therapy (OR=3.7, p=0.000) were associated with cutaneous adverse drug reactions. Use of cotrimoxazole (OR=0.582, p=0.001) and Zidovudine based therapy (OR=32, p=0.000) were associated with anaemia. Healthcare providers reported a wide range of ADRs among patients on antiretroviral therapy. Treatment switching and referral for specialist care were used to manage patients with ADRs. Twenty-two percent (22%) of patients recovered from ADRs, 1.2% were fatal while 71.5% had unknown outcomes.

Adverse Drug Reactions to Antiretroviral therapy are common among patients in Nigeria. Active surveillance is required for the detection of ADRs among patients on ART. This will help prevent ART-associated morbidity and mortality

Keywords:

HIV/AIDS, Anti-retroviral therapy, Adverse drug reactions, pharmacovigilance

Word count: 395

CHAPTER ONE

1.1 BACKGROUND

The introduction of antiretroviral therapy about three decades ago changed the epidemiology of HIV worldwide. Antiretroviral therapy (ART) is the mainstay of treatment for HIV/AIDS and about 23.3 million people are currently accessing antiretroviral therapy worldwide(UNAIDS, 2019). World Health Organization (WHO) guidelines stipulate the use of three antiretroviral drugs concurrently in regimens known as Highly Active Antiretroviral Therapy. Current evidence shows that people living with HIV will take highly active antiretroviral therapy as a life-long therapy. HIV survivorship has increased worldwide due to expanding access to antiretroviral therapy; however, the use of antiretroviral therapy has been associated with a wide range of adverse drug reactions and toxicities. (Maartens, Celum, and Lewin, 2014; Bezabhe, Bereznicki, and Chalmers, 2015; Wolff, Giganti, Cortes, Cahn, Grinsztejn, Pape, Padgett, Sierra-Madero, Gotuzzo, Duda, McGowan, and Shepherd, 2017; World Health Organization, 2018).

Adverse drug reactions (ADRs) to antiretroviral therapy are an important public health problem and an important aspect of patient care. The World Health Organisation (WHO) defines an adverse drug reaction as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" (World Health Organization, 1972). Adverse drug reactions to antiretroviral therapy occur in over half of patients (Tumusiime, Venter, Musenge, and Stewart, 2014) and are a major cause of treatment substitution /switching, treatment discontinuations, reduced quality of life,and canlead to disability and death(Li, Marley, Ma, Wei, Lackey, Ma, Renaud, Vitoria, Beanland, Doherty, and Tucker, 2017). The occurrence of adverse drug reactions in the management and care of HIV/AIDS can significantly affect treatment adherence, which

could in turn prevent viral suppression and contribute to HIV associated morbidity and mortality(Prosperi, Fabbiani, Fanti, Zaccarelli, Colafigli, Mondi, Avino, Borghetti, Cauda, and Giambenedetto, 2012). This could also negatively affect treatment adherence and represent a risk for continued transmission of the disease (Prosperi et al., 2012; Kenneth A Agu and Oparah, 2013; Tadesse, Mekonnen, Tesfaye, and Tadesse, 2014; Bassi, Wadzani, Klungel, Alexander, Prosper, and Phyllis, 2017; Li et al., 2017).

Many studies have reported various adverse drug reactions experienced by people living with HIV on highly active antiretroviral therapy. These adverse drug reactions include but are not limited to peripheral neuropathy, neuropsychiatric disorders, lipodystrophy, metabolic disorders, lipid disorders, lactic acidosis, hepatotoxicity, anaemia, hypersensitivity rash, Steven Johnsons Syndrome (SJS), immune reconstitution inflammatory syndrome (IRIS), malaise, visual disturbances, hyperpigmentation amongst others. They affect various organs and could also be systemic (Shubber, Calmy, Andrieux-meyer, Shaffer, Vitoria, Hargreaves, Mills, and Ford, 2013; Isaac Okoh Abah, Akanbi, Abah, Finangwai, and Dady, 2015; Masenyetse, Manda, and Mwambi, 2015; Boer, Berk, Holten, Oryszcyn, and Dorama, 2016).

Reported risk factors for adverse drug reactions among HIV positive patients on highly active antiretroviral therapy include age, female gender, pregnancy, CD4count, type of ART regimen, use of concomitant medicines and presence of opportunistic infections and other comorbidities. Studies have reported increasing age as an independent determinant of the occurrence of adverse drug reactions to antiretroviral therapy. (Obiako O, Muktar M, Garko B, Tobi-Ajayi, Olayinka, Iyanda, Irohibe, Umar, and Abdu-Aguye, 2012; Isaac Okoh Abah et al., 2015; Quesada, Esteban, García, Sánchez, García, Alonso-Vega, and Ferrández, 2015; AngamoTarekegn, Chalmers, Curtain M, and Bereznicki, 2016).Other studies have also reported a female preponderance in the

occurrence and risk of development of ADRs. (Clark, 2005; Mehta *et al.*, 2011; Prosperi *et al.*, 2012; Abah *et al.*, 2015). In addition, different ARV drugs and ART regimens are associated with the different types of ADRs. Since current ART regimens include the use of three drugs from two classes, it is possible for a patient to experience overlapping toxicities.(Reust, 2011; Ford, Shubber, Pozniak, Vitoria, Doherty, Kirby, and Calmy, 2015a). The presence of co-morbidities such as anaemia and tuberculosis may necessitate the use of additional medicines among people on ART. Patients who have other co-morbidities such as hypertension and diabetes may lead to polypharmacy, thus increasing the risk for adverse drug reactions.(Subbaraman, Chaguturu, Mayer, Flanigan, and Kumarasamy, 2007; Gebo and Justice, 2009; Edelman, Gordon, Glover, McNicholl, Fiellin, and Justice, 2013; Gleason, Luque, and Shah, 2013; Rajesh, Vidyasagar, Varma, Naik, Hegde, Guddattu, and Kamath, 2013).

Adverse drug reactions are classified as serious or unserious. A serious ADR has any of the following characteristics: fatal, life-threatening, causes permanent disability, congenital abnormality or prolonged hospitalization. The seriousness of an ADR is different from its severity and is usually not graded. (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1994; World Health Organization, 2002; DAIDS, 2017).

Adverse drug reactions experienced by HIV positive patients have varying outcomes. Adverse drug reactions may be transient, resolve with therapeutic management, and result in hospitalizations, disability or death. The occurrence of adverse drug reactions among these patients may result in new co-morbidities, further affecting the management of the disease. (Isaakidis, Varghese, Mansoor, Cox, Ladomirska, Saranchuk, da Silva, Khan, Paryani, Udwadia, Migliori, Sotgiu, and Reid, 2012; Manickum and Suleman, 2012; Pulagam, Rajesh, Vidyasagar, and Varma,

2012; Kenneth A Agu and Oparah, 2013; Kenneth A Agu, Isah, Oqua, Habeeb, Agada, Samuel, Ali, Iyaji, King, Aiyenigba, Torpey, Chabikuli, and Wutoh, 2013; AngamoTarekegn et al., 2016).

1.2 PROBLEM STATEMENT

One million people are currently accessing antiretroviral therapy across various centres in Nigeria(UNAIDS, 2019), and this number is expected to increase to meet the global 95-95-95 targets. The incidence of adverse drug reactions among patients on antiretroviral therapy ranges from 4.6% to 90% in developing countries. (Pulagam et al., 2012; Kenneth A Agu et al., 2013; Shet, Antony, Arumugam, Dodderi, Rodrigues, and Decosta, 2014). In Nigeria, the prevalence of ADRs to antiretroviral therapy ranges from 6.3% to 11.81%.(Eluwa, Badru, and Akpoigbe, 2012; Obiako O et al., 2012; Kenneth A Agu et al., 2013; I A Oreagba et al., 2014).

Assessing the effects of long term ART has not received sufficient attention, particularly in resource-constrained settings like Nigeria. Current, nationally representative data on the types of adverse drug reactions reported by HIV patients on current ART regimens in Nigeria is scarce. Factors associated with adverse drug reactions due to current ART regimens are also unknown. In addition, there is a paucity of data on adverse drug reactions associated with second-line ART regimens and their determinants in Nigeria. There is also a lack of adequate systems, structures and funding for pharmacovigilance for HIV/AIDS programmes in resource limited settings. The absence of adequate strategies for the monitoring of drug toxicities and other drug safety issues may compromise efforts in the provision of and adherence to antiretroviral therapy. (Bakare, Edwards, Stergachis, Pal, Holmes, Lindquist, Duncombe, Dodoo, Novendstern, Nwokike, Kuchenbecker, Aberg, Miller, and Strobos, 2011; Miller, Nwokike, and Stergachis, 2012).

Many of the previous studies identified and investigated adverse drug reactions associated with older, phased-out regimens (e.g. Stavudine based regimens) and thus do not give a true representation of the extent of the problem in recent times. In addition, many of these studies did not include pregnant women on Efavirenz, as EFV was not used in pregnant women as at the times the studies were conducted. However, in the 2014 and 2016 HIV treatment guidelines in Nigeria, Efavirenz based therapy was indicated as first line therapy for PMTCT in Nigeria. Furthermore, previous studies had a small sample size of patients on Tenofovir based regimens and recommended that future studies should include more patients on Tenofovir based regimens. Hence, the study sought to identify the pattern and determinants of adverse drug reactions to current antiretroviral therapy in Nigeria.

1.3 JUSTIFICATION

In recent times, adverse drug reactions associated with antiretroviral therapy have been the focus of studies in patient safety, especially with increasing reports of toxicities in both developing and developed countries.(Obel, Farkas, Kronborg, Larsen, Pedersen, Riis, Pedersen, Gerstoft, and Sørensen, 2010; Obiako O et al., 2012; Shet et al., 2014; Hoffmann et al., 2017b). The study of adverse drug reactions associated with ART is necessary because clinical trials may not identify rare, late onset and bizarre adverse drug reactions due to the short duration of the trials. There is also a marked difference between drug use in clinical trial participants and actual patients in real world use. This is due to strict inclusion, exclusion and follow-up of clinical trial patients that do not apply in real world use of the drugs. Thus, there is a need togenerate real world evidence as to the adverse reactions that occur in clinical settings.

Investigating these adverse drug reactions and their predisposing factors will help guide national ART guidelines. It will also help program managers, physicians, pharmacists and other health care

workers involved in HIV care to identify high-risk groups and adequately monitor for the occurrence of adverse drug reactions. It will also help guide safety guidelines and warnings for both regulators and ARV manufacturers.

Drug safety studies are not given priority in developing countries due to resource constraints and different donor objectives (Bakare et al., 2011). This study will complement efforts by both government agencies and donors to improve care of PLWHIV. This study will generate evidence on the safety and tolerability of different ART regimens in Nigeria. In addition, this study will identify adverse drug reactions unreported or underreported during clinical trials. Furthermore, this study will add to the pool of signals stored by NAFDAC and WHO-Uppsala Monitoring Centre. It will also provide evidence to demonstrate a need to modify current ART regimens to include safer alternatives.

Surveillance of adverse drug reactions due to highly active antiretroviral therapy in public health programs in developing countries is quite necessary for the following reasons. Many of the clinical trials of these agents are carried out in developed countries but are used much more in developing countries like Nigeria, which have a higher burden of HIV/AIDS. In addition, as highly active antiretroviral therapy is life-long, many late-onset adverse events occur during the course of therapy, which were not detected during clinical trials. Furthermore, due to resource constraints in developing countries, there is a lack of laboratory monitoring of adverse drug reactions. Importantly, many of the HIV positive patients in developing countries have pre-existing comorbidities such as tuberculosis and anaemia which make them predisposed to adverse drug reactions. Effective pharmacovigilance systems can help in the provision of safe and effective healthcare for people living with HIV/AIDS (Subbaraman et al., 2007; Eluwa et al., 2012; Miller et al., 2012).

1.4 OBJECTIVES:

1.41 Broad Objective: To identify pattern and determinants of adverse drug reactions due to highly active antiretroviral therapy among patients in Nigeria.

1.42 Specific Objectives:

1. To assess the pattern of adverse drug reactions among people living with HIV on highly active antiretroviral therapy.
2. To investigate determinants of adverse drug reactions among people living with HIV on highly active antiretroviral therapy.
3. To determine outcomes of adverse drug reactions among people living with HIV on highly active antiretroviral therapy.

CHAPTER TWO

LITERATURE REVIEW

An adverse drug reaction is "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product". Adverse drug reactions can be classified into six categories: dose-related (augmented), non-dose-related (bizarre), dose-related and time-related (chronic), time-related (delayed), withdrawal (end of use) and unexpected failure of therapy (failure). (Edwards and Aronson, 2000).

2.1 Pattern of Adverse Drug Reactions:

There are various adverse effects of antiretroviral therapy reported in literature. They are varied and affect different organs and systems. These adverse drug reactions include, but are not limited to neuropsychiatric adverse reactions, systemic adverse reactions, lipodystrophy syndromes, anaemia and hepatotoxicity.

2.11. Neuropsychiatric Adverse Reactions

Neuropsychiatric adverse reactions are important adverse events that have been associated with ART. As HIV infection already impacts negatively on the mental health of patients, neuropsychiatric adverse reactions further complicates patients' mental health status, thus

affecting their quality of life(Drury, Gleadow-Ware, Gilfillan, and Ahrens, 2018; Sumari-de Boer, Schellekens, Duinmaijer, Lalashowi, Swai, de Mast, van der Ven, and Kinabo, 2018). NPAEs have also been associated with decreased adherence and treatment discontinuation, thus increasing the risk of resistance (Cespedes and Aberg, 2006; Nelson, Stellbrink, Podzamczer, Banhegyi, Gazzard, Hill, Van Delft, Vingerhoets, Stark, and Marks, 2011; Ford et al., 2015a). They are often associated with EFV-based regimens and are more pronounced among people of African ancestry with a variant of a metabolic enzyme, CYP2B6 (Isaac Okoh Abah et al., 2015). Neuropsychiatric adverse events have also been reported among people on INSTI-based therapy.(Hoffmann et al., 2017b). Neuropsychiatric ADRs due to ART include hallucinations, insomnia, anxiety, depression, dizziness, somnolence and nightmares.

Although neuropsychiatric adverse reactions like dizziness and headaches may resolve without treatment; hallucinations, depression and insomnia may negatively impact the mental health of patients on ARV. As HIV infection is already linked with depression and a poor quality of life (Drury et al., 2018), the development of neuropsychiatric adverse reactions during ART will further complicate mental health issues among patients on ART.

Studies carried out worldwide have reported prevalence of neuropsychiatric ADRs among patients on ART ranging from 3.0% to as high as 57.6% (Nelson et al., 2011; Tadesse et al., 2014; Isaac Okoh Abah et al., 2015; Fred S. Sarfo, Sarfo, and Chadwick, 2016; Mugusi, Ngaimisi, Janabi, Mugusi, Minzi, Aris, Bakari, Bertilsson, Burhenne, Sandstrom, and Aklillu, 2018). Studies have also reported NPAEs among patients on different classes of ARVs such as NRTIs, NNRTIs and PIs (Treisman and Soudry, 2016; Dalwadi, Ozuna, Harvey, Viljoen, and Schetz, 2018). Despite reports of NPAEs with different ARVs, majority of the studies have focused on NNRTI-associated NPAEs, particularly EFV. In addition, female sex, underlying comorbidities, stage of HIV disease

and older age have also been reported as risk factors for neuropsychiatric ADRs among patients on ART (Gazzard, Balkin, and Hill, 2010; Hoffmann et al., 2017b)

In a Nigerian cohort, 3.0% of patients on EFV-based therapy developed neuropsychiatric ADRs, with an incidence rate of 29.9 per 1000 person-years. 62.5% of the neuropsychiatric ADRs occurred with longer duration of ART (Isaac Okoh Abah et al., 2015). The study reported that female sex, age<40, advanced HIV disease and stavudine/zidovudine containing regimens were risk factors for the occurrence of neuropsychiatric adverse events. In Germany, neuropsychiatric adverse reactions led to a discontinuation rate of 14%, associated with dolutegravir, as compared to other INSTIs. Female sex, older age >60 years, and abacavir therapy were risk factors for neuropsychiatric adverse events in this population (Hoffmann et al., 2017b). In a cross sectional study in Cameroun, neuropsychiatric symptoms reported include headache, insomnia, depression, nightmares and anxiety. They affected 54.9%, 26.6%, 18.8% and 6.3% of study participants respectively. Neuropsychiatric symptoms also accounted for 27.4% of treatment changes too (Tadesse et al., 2014).

Women have been reported to have a higher risk of developing neuropsychiatric adverse reactions than men, as shown in studies carried out in Nigeria and Germany, which reported a 2 -9 fold increased risk of developing neuropsychiatric adverse events among females(Prosperi et al., 2012; Isaac Okoh Abah et al., 2015; Hoffmann et al., 2017b). A possible explanation of this may be women having higher plasma concentrations of NPAE associated ARVs. Studies have shown increased plasma concentrations of Efavirenz in women as compared to men(Umeh and Currier, 2006; Greig and Anderson, 2014). There is also a higher prevalence of HIV in women in Nigeria, thus there are more women on ARVs, thus more women experiencing NPAEs (UNAIDS, 2019).

A systematic review and meta-analysis of neuropsychiatric adverse events associated with EFV-based therapy, neuropsychiatric adverse events affected 29.6% of 3954 patients across 13 studies. Severe CNS events affected 6.0% of patients. Other neuropsychiatric symptoms reported include insomnia, abnormal dreams, dizziness, impaired concentration, depression, anxiety, headache and suicide ideation with proportions of 6.00%, 8.4%, 12.8%, 2.90%, 3.30%, 3.40%, 6.80% and 0.60% respectively. The adverse events also led to a higher rate of discontinuation from efavirenz-based therapy, as compared to other first line options (Ford et al., 2015a).

In a retrospective analysis of ART-associated ADR reports in South Africa, neuropsychiatric events accounted for 9.0% of ADRs reported over a five-year period. The neuropsychiatric events reported were dizziness, psychosis/hallucinations and sleep disturbances (Birbal, Dheda, Ojewole, and Oosthuizen, 2016)

2.12 Hepatotoxicity:

Drug induced hepatotoxicity refers to liver injury and liver disturbances caused by drugs. HAART induced hepatotoxicity is often identified by elevation of liver enzymes (usually majorly of alanine aminotransferase and aspartate aminotransferase) and/or jaundice. The Hy's phenomenon states that the presence of jaundice together with the high liver enzymes is an indication of a poorer prognosis of hepatotoxicity (Núñez, 2010; Wondemagegn, Bokretsion, Ambahun, Genetu, and Abera, 2013). ART induced hepatotoxicity presents can be acute or chronic, and presents as jaundice, elevation of liver enzymes, lactic acidosis, liver fibrosis, portal hypertension, hyperplasia and hypersensitivity reactions (Núñez, 2010; Jones and Núñez, 2012). ART induced hepatotoxicity can lead to liver failure and death, especially if not detected early(Wondemagegn et al., 2013). The severity of ART induced liver toxicity is divided into four grades depending on the level of

elevation of liver enzymes. However, the mechanisms by which liver toxicity of ARVs occur are not fully understood. (Jones and Núñez, 2012).

Reported risk factors for ART induced liver toxicity include concurrent viral hepatitis (Hepatitis B or Hepatitis C coinfection), Nevirapine based therapy and elevated baseline liver enzyme levels. Multiple studies have identified Hepatitis C coinfection as an independent marker of ART hepatotoxicity (Gao, Gui, Deng, Zhang, Liang, Yang, Yan, and Rong, 2010; Griensven, Zachariah, Rasschaert, Mugabo, Atté, and Reid, 2010; Snijdewind, Smit, Godfried, Nellen, Wolf, Boer, and Ende, 2012). Alcohol use and concomitant use of anti-tuberculosis drugs have also been reported as risk factors for HAART induced hepatotoxicity.(Kalyesubula, Kagimu, Kc, Kiguba, Cf, Wf, and Et, 2011; Wondemagegn et al., 2013). Hepatic adverse events and liver toxicities have been associated with use of abacavir, all NNRTIs(Efavirenz, Nevirapine and Etravirine) ,all PIs and Entry inhibitors(Maraviroc) (Hawkins, 2010).

Incidence of ART induced hepatotoxicity ranged from cases per 5.4 cases per100 person-years to 24.1 cases per 100 person-years in studies carried out in South Africa, China andThailand. (Chu, Boulle, Ford, Goemaere, Asselman, and Van, 2010; Gao et al., 2010; Chalermchai, Hiransuthikul, Tangkijvanich, Pinyakorn, Suteeraporn Avihingsanon, and Ananworanich, 2013).However, ART induced hepatotoxicity may be grossly undected and underreported in HIV/AIDS programmes, particularly in developing countries. This is because liver toxicity is generally identified through laboratory investigations. As pharmacovigilance and spontaneous reporting is overlooked in public health programmes, it is unexpected that active pharmacovigilance, which involves the use of more resources will be given any attention(Núñez, 2010; Bakare et al., 2011; Kenneth Anene Agu, Oparah, and Ochei, 2012).

A nested case-control study in Thailand reported that in patients with normal liver enzyme levels at baseline, and no concurrent viral hepatitis, male sex and high BMI were associated with the occurrence of chronic hepatitis while on ART. The study utilized data from a clinical trial, with patients followed up for 10 years (Chalermchai et al., 2013). A strength of this study was that patients had normal liver enzyme levels at baseline and did not have concurrent viral hepatits, thus reducing the presence of potential confounders. The hepatitis recorded in this study can thus be attributed to the ART, and no other sources.

Concurrent viral hepatitis is a risk factor for ART hepatotoxicity. Chronic hepatitis B is prevalent in Nigeria, with a prevalence of 14% among adults (Moghaddasifar, Lankarani, Moosazadeh, Afshari, and Malary, 2016), and a prevalence of 4.2% among HIV positive pregnant women in Nigeria(Ezechi, Oliver Chukwujekwu Kalejaiye, Olufunto Olufela Gab-Okafor, Chidinma Vivian Oladele, Oke, Musa, Ekama, Ohwodo, Agahowa, Gbajabiamilla, Odunukwe, Onwujekwe, and Ujah, 2014). This portends a greater risk of ART induced hepatotoxicity among Nigerians, due to the high prevalence of HBV/HIV co-infection.

Concomitant use of other hepatotoxic drugs like anti tuberculous drugs is also a risk factor for the occurrence of ART induced hepatotoxicity. With prevalence of HIV/TB coinfection as high as 44% in some centres in Nigeria (Ibadin and Enodiana, 2019), there is an elevated risk of ART induced hepatotoxicity in this population. In a hospital based cross sectional study in Brazil, 22% of patients on ART had severe drug induced liver injury. Use of anti-tuberculous drugsand increased liver enzyme levels at baseline were associated with ART hepatotoxicity.In Uganda, researchers enrolled 240 patients on first-line ART regimens in a prospective cohort and monitored alanine aminotransferase levels for 14 weeks (Kalyesubula et al., 2011). The incidence of transaminitis was 27.5% with 4.2% having grade 2-4 transaminitis. Patients on NVP regimens

developed transaminitis faster than those on EFV based regimens, with a log rank value of 12.1. However, only concurrent use of anti-tuberculosis drugs was associated with an occurrence of grade 2-4 toxicity.

A systematic review of NVP and EFV based adverse events by Shubber and colleagues reported that NVP use was more associated with severe hepatotoxicity than EFV with an odds ratio of 3.3.(Shubber et al., 2013). Hepatotoxicity in PLWHIV on HAART in a cross sectional study in Ethopia was responsible for 4.8% of treatment changes among these patients, based on chart reviews. (Tadesse et al., 2014).

The APROCO (Antiprotease Cohort) study by Duval et al. reported that elevated transaminase levels was the most commonly reported adverse event, accounting for 29% of all serious adverse drug reactions. Risk factors for elevated transaminase levels included plasma HIV RNA level, creatinine clearance rate, aspartate aminotransferase level, HBV and HCV infections(Duval, Journot, Leport, Chene, Dupon, Cuzin, May, Morlat, Waldner, Salamon, and Raffi, 2004).

In a retrospective cohort of ART-naïve adults initiating NVP based ART in South Africa, researchers reported an incidence rate of early hepatotoxicity of 7.6 per 100 person-years, with a median time to early hepatotoxicity of 32 days. Early hepatotoxicity was measured using serum levels of alanine aminotransferase. The researchers found no association between age, gender, baseline CD4 count, weight and early hepatotoxicity, thus suggesting an idiosyncratic relationship. However, the overall incidence of hepatotoxicity (both early and late) was not reported in the cohort.(Chu et al., 2010). In contrast, the median time to hepatotoxicity in a Spanish population was 200 days, indicating long term occurrence of hepatotoxicity.(Knobel, A, Montero, Carmona, Luque, Berenguer, and Gonzalez, 2008)

2.13 Lipodystrophy Syndromes

HAART-associated lipodystrophy syndrome (HALS) is an important complication of antiretroviral therapy. Lipodystrophy syndromes are a group of rare disorders that affect the adipose tissues, consisting of lipoatrophy and lipodystrophy. Lipodystrophy may present as fat loss in face, buttocks, extremities and abdomen. It may also present as enlarged breasts in men (gynaecomastia) and women, central fat accumulation, buffalo hump, loss of subcutaneous fat in the face, buttocks and extremities. Lipodystrophy is often associated with dyslipidemia and insulin resistance, thus increasing the risk of adverse CVD events among PLWHIV on ART.

However, as HIV itself also causes lipodystrophy syndromes, it is often difficult toascertain whether the cause of lipodystrophy syndromes is the disease or ART. There is equally no standard method of diagnosing and evaluating lipodystrophy syndromes, thus different studies report disfferent methods of diagnosis. Physical examination and use of dual energy absorptiometry are some methods of diagnosing lipodystrophy syndromes. (Hawkins, 2010; Domingo, Gutierrez, Gallego-escuredo, Torres, Gracia, Villarroya, Santos, and Domingo, 2014; Brown, Araujo-vilar, Cheung, Dunger, Garg, Jack, Mungai, Oral, Patni, Rother, Schnurbein, Sorkina, Stanley, Vigouroux, Wabitsch, and Williams, 2016). NRTI use, PI use and long term ART use are reported risk factors for the occurrence of HALS. In addition, genetics have also been investigated as risk factors associated with the occurrence of HALS in PLWHIV.(Peraire, Vidal, Domingo, Vilade, Leal, Villarroya, and Arnedo, 2011; Paruthi, Gill, and Mantzoros, 2013)

A study in Ethopia investigating the prevalence and risk factors of metabolic outcomes among patients on ART reported that the prevalence of lipodystrophy among patients on ART from 2007 to 2008 was 68.3%. The study reported that stavudine-containing ART regimens and a longer duration of ART (≥1 year) was significantly associated with the occurrence of lipodystophy.

(Feleke, Fekade, and Mezegebu, 2012). A case control study that assessed adverse effects of long-term ART by Mercier et al., in Senegal reported that the prevalence of moderate to severe lipodystrophy among PLWHIV on zidovudine, stavudine and PIs was 31.1%, while the prevalence of mild to moderate lipodystrophy was 65.0%. The use of stavudine was also reported as a risk factor for developing lipodystrophy in this population (OR=2.8, CI: 1.4 -5.5). (Mercier, Ndeye, Cournil, Annick, Nane, Ibrahima, Dupuy, Cames, Papa, Ibra, Eric, and Simondon, 2009). A cross sectional study to determine the prevalence of HIV associated lipodystrophy and metabolic outcomes among patients on ART in Ethopia reported the prevalence of lipodystrophy to be 12.1% among PLWHIV on ART. Long term use of ART (>1 year) was also associated with the occurrence of HALS (AOR=3.59) (Tsegay, Alemishet, Fessahaye, Tilahun, Leja, Mehedi, and Kebede, 2012). One major limitation in these studies is the varying methods of diagnosis and evaluating lipodystrophy. Manickum and Suleman reported lipid abnormalities, lipodystrophy and gynaecomastia as separate events, rather than as types of lipodystrophy. (Manickum and Suleman, 2012). A study in Spain demonstrated that switching from stavudine to dolutegravir helped improve lipodystrophy markers. A strength of this study was the use of dual energy x-ray absorptiometry (DEXA) and other lipodystrophy severity grading scale to measure and assess lipodystrophy (Domingo et al., 2014).

A cross sectional study in Tanzania reported that the prevalence of lipodystrophy among HIV-infected children was 30%, with stavudine use and older age as risk factors for lipodystrophy. However, it is unsure whether the lipodystrophy was due to ART or due to the HIV infection itself.(Kinabo, Sprengers, Msuya, Shayo, van Asten, Dolmans, van der Ven, and Warris, 2013). A retrospective cross sectional analysis of ART-associated ADR reports in South-Africa reported that lipodystrophy accounted for 16.3% of reported ADRs. Female sex and age between 0-19 years

on stavudine-based regimens were more likely to report lipodystrophy (Manickum and Suleman, 2012). Tadessee et al., reported that 11.34% of treatment changes due to ADRs in a cross sectional study was due to lipodystrophy (Tadesse et al., 2014).

2.14 Peripheral Neuropathy

Peripheral neuropathy is a common adverse drug reaction among PLWHIV on ART. Like lipodystrophy, peripheral neuropathy is also associated with HIV disease itself as well as neurotoxic ART. Most studies that try to identify ART associated peripheral neuropathy focus on ART-naïve patients with no symptoms of peripheral neuropathy reported at baseline. This is in order to rule out neuropathy caused by advanced HIV disease (Kranick and Nath, 2012; S. R. Evans, Lee, Ellis, Chen, Wu, Bosch, and Clifford, 2012; Tumusiime et al., 2014).

There is a high prevalence of peripheral neuropathy among people on ART. This prevalence ranges from 11% to 59% in studies in Sub Saharan Africa(Luma, Doualla, Choukem, Temfack, Ashuntantang, Joko, and Koulla-Shiro, 2012; Kenneth A Agu et al., 2013; Tumusiime et al., 2014; Bassi et al., 2017). A cross sectional study in Cameroun showed that PN was the most common ADR reported by PLWHIV on ART, accounting for 21.2% of all ADRs, with a median onset of 9 months. It also accounted for 72.9% of treatment changes (Luma et al., 2012).

Risk factors for ART associated peripheral neuropathy include concomitant use of anti-tuberculosis drugs, use of Stavudine based ART regimen, older age, previous history of diabetes, protease inhibitor use and being of African ancestry (Pujades-Rodríguez, Dantony, Pinoges, Ecochard, Etard, Carrillo-Casas, and Szumilin, 2011; S. R. Evans, Ellis, Chen, Yeh, Lee, Schifitto, Wu, Bosch, McArthur, Simpson, Clifford, Ellis, and Chen, 2011; D. Evans, Takuva, Rassool, Firnhaber, and Maskew, 2012; Mcgrath, Njoroge, John-Stewart, Kohler, Benki-Nugent, Thiga,

Etang, and Chung, 2012; Tumusiime et al., 2014).A standard scale, the Brief Peripheral Neuropathy Screen is used to screen for peripheral neuropathy, however many studies relied on patient report of adverse drug reactions and clinical examinations to detect peripheral neuropathy(Mcgrath et al., 2012; Tumusiime et al., 2014).

Stavudine use has been reported as an independent predictor of peripheral neuropathy among patients on ART. In a cohort study of patients on ART in Nigeria, PN was responsible for 12.7% of adverse drug reaction reports after 20 months of active surveillance. PN was also associated with Stavudine-based therapy, as patients on Stavudine based therapy were 3 times more likely to report peripheral neuropathy. However, the researchers in this study did not use a standard instrument to screen for neuropathy, but relied on patients' reports of pain, numbness and tingling in the extremities(Kenneth A Agu et al., 2013). Phan et al reported that reported that peripheral neuropathy was common in patients treated with Stavudine in Cambodia (10.7%) and was a cause of treatment substitution. Peripheral neuropathy was also screened clinically in this study (Phan, Thai, Choun, Lynen, and Griensven, 2012). Peripheral neuropathy has also been associated with the use of Tenofovir. In an analysis of ADRs received from a spontaneous reporting system, Agu and Oparah also reported that PN was associated with Tenofovir use (Kenneth A Agu and Oparah, 2013).

The relationship between Stavudine and peripheral neuropathy appears to be dose related. Researchers in a multicenter cohort study reported that higher rates of peripheral neuropathy and shorter time to toxicity was reported among those who were treated with 40mg of Stavudine as compared with those treated with 30mg (Mcgrath et al., 2012).

Female sex is a predictor of peripheral neuropathy among patients on ART. In a cohort study of 150 patients on ART, Mehta et al reported that women were 9.6 times more likely to develop PN

than men (HR=9.6). A possible explanation may be that the prevalence of HIV among women is greater, as women made up a greater percentage (60%) of the cohort (Mehta et al., 2011).In South Africa, a retrospective cross sectional study reported that more females reported peripheral neuropathy than men (Manickum and Suleman, 2012).

Older age is reported as a risk factor for peripheral neuropathy among patients on ART. Evans and colleagues reported that older age was associated with peripheral neuropathy among patients on ART. The researchers analysed data from the AIDS Clinical Trial Group studies and demonstrated that older age was associated with peripheral neuropathy even after discontinuation of ART. This study also utilized a standard instrument for measuring peripheral neuropathy. However, about 22.6% of participants already had symptomatic peripheral neuropathy at baseline before commencement of the study (S. R. Evans et al., 2011). A cross sectional study in Rwanda also reported that older age was associated with peripheral neuropathy, with a one unit increase in odds ratio for every one unit increase in age (Tumusiime et al., 2014).

Concurrent anti-tuberculosis use has also been associated with peripheral neuropathy among patients on ART. Anti-tuberculosis drugs like Isoniazid have been reported to cause peripheral neuropathy, thus there may be a synergistic relationship between ART and anti-tuberculosis in the peripheral neuropathy pathway(D. Evans et al., 2012). In India, a cohort study reported that 37% of patients on both ART and anti-tuberculosis drugs experienced peripheral neuropathy. This may have been due to the synergistic toxicity between stavudine and other ATT drugs. However, it is unsure if the occurrence of PN was due to ART, ATT or a synergy of both.(Isaakidis et al., 2012)

2.15 Cutaneous/Skin and Appendages Adverse Drug Reactions

Rash, Stevens - Johnson syndrome and Toxic Epidermal Necrosis are reported cutaneous adverse reactions of ART. Rash is a common ADR experienced by people living with HIV on ART, but Steven Johnson's Syndrome (SJS) and toxic epidermal necrosis (TEN) are quite rare and have serious outcomes.

The incidence of rash among patients on ART ranges from 4.9% to 15%, in studies conducted in Africa and Europe (Knobel et al., 2008; Griensven et al., 2010; Shet et al., 2014; Masenyetse et al., 2015). In a cohort study investigating stavudine and nevirapine related toxicities in 2190 adults on ART in Rwanda, 4.9% of patients developed skin rash, with 93% occurring within the first six months. The incidence rate was 30 per 1000 person-years. However, there was no association between age, sex, baseline body weight, CD4 count and the occurrence of rash (Griensven et al., 2010). Shet and colleagues reported that the incidence of rash was 6.3% in a cohort of PLWHIV initiating first line ART in India. Rash was also reported to account for 10.1% of severe ADRs in this population. Although the study reported risk factors for the occurrence of any ADR, it did not report risk factors for the occurrence of rash in this cohort (Shet et al., 2014).

In Spain, that the incidence of skin rash among patients on ART was 11.3%. The study was a retrospective study of ADRs occurring among treatment-naïve PLWHIV initiating ART. The study. The study divided participants into two based on CD4 counts. The hazard of developing a rash among those with lower CD4 counts was 4 times higher than those with higher CD4 counts. Concomitant use of co-trimoxazole might have been responsible for the increased hazard (Knobel et al., 2008). In a retrospective study of ADR surveillance system in South Africa, rashes accounted for 15% of reported ADRs, but was not attributed to any specific regimen.(Masenyetse et al., 2015).

NNRTIs such as Nevirapine and Efavirenz are often associated with skin toxicities. In a Ghanaian cohort followed up for 7 ½ years, 82.4% of rash cases were NNRTI related, with 6% experiencing more than one episode. Cumulative incidence of rash was 7.0%; incidence of NVP-associated rash was 10.2%, while EFV-associated rash was 5.6%. The incidence rate of NNRTI-associated rash was 2.63 events per 100 person-years, with median time to development of 2 months. There was no difference in the severity between NVP-associated and EFV-associated rash. The study reported that NVP-based therapy, female gender and lower CD4 counts (<50 cells/mm^3) and WHO clinical stage were risk factors for the development of skin toxicities in the cohort.(Fred Stephen Sarfo, Sarfo, Norman, Phillips, and Chadwick, 2014).

In the 2NN clinical trial in Thailand, 34% of study participants developed rash due to NNRTIs at 24 weeks. The study randomized patients into any of four groups: NVP 200mg twice daily, NVP 400mg once daily, NVP400mg+EFV 800mg once daily and EFV 600mg once daily. Treatments with NVP+EFV had the highest risk of rash, followed by NVP with adjusted OR of 11.916 and 3.081 respectively (with EFV once daily as the reference group). There was no association between NVP twice daily and the occurrence of rash. Risk factors for the development of rash include NVP+EFV therapy, NVP once daily, females with CD4 >250×10^6 cells/L and high body mass index and increase in CD4 and alanine transferase levels (Ananworanich, Moor, Siangphoe, Chan, Cardiello, Duncombe, Phanuphak, and Ruxrungtham, 2005). As a randomized clinical trial, the study eliminated issues of confounding.

Skin rash has been quite common among PLWHIV in Nigeria. In studies carried out in Nigeria, incidence rates of rash have ranged from 8.1% to 65.5%(Eluwa et al., 2012; Oshikoya, Lawal, Oreagba, Awodele, Olayemi, Iroha, Ezeaka, Temiye, Akinsulie, and Opanuga, 2012; Kenneth A Agu et al., 2013; I A Oreagba et al., 2014). Reported risk factors for the development of rash in

Nigerian populations include NVP based regimens, use of concomitant medicines, and extremes of age (elderly and paediatric populations).

Stevens Johnson Syndrome and toxic epidermal necrosis are rare and often life threatening cutaneous adverse drug reactions. SJS and TEN are peculiar clinical syndromes as they are usually drug induced. They are characterised by skin and mucous membrane detachment, with less than 10% of skin detachment in SJS and greater than 30% in TEN (Dube, Adewusi, and Summers, 2013; Knight, Muloiwa, Dlamini, and Lehloenya, 2014; Knight, Todd, Muloiwa, Matjila, and Lehloenya, 2015). Although the incidence of SJS and TEN is very low worldwide, the incidence is increased among people on ART. (Knight et al., 2015). A systematic review reported that the pooled proportion of SJS was 0.7% among 7391 patents on NVP-based therapy(Shubber et al., 2013). The Nigerian National HIV Guidelines (2014) lists SJS as primary toxicities for NNRTIs

SJS and TEN have been reported among patients on Nevirapine (Dube, Adewusi and Summers, 2013), Efavirenz (Isaac Okoh Abah et al., 2015), Zidovudine and concomitant co-trimoxazole therapy (Knight et al., 2015). Reported risk factors for SJS include Nevirapine use and pregnancy. However, due to the rarity of these ADRs, many of the available literature are predominantly case reports(Paik, Sen, Era, Saha, and Tripathi, 2016; Saka, Akakpo, Bassowa, Dapam, Mahamadou, Teclessou, Mouhari-Toure, Laouali, Mensah, Kombaté, and Pitché, 2018; da Costa Vieira, Almeida Sarmento, Leite Ribeiro, Martins Netto, Brites, and Lins-Kusterer, 2019).

A case control study in South Africa reported that pregnant women were 14 times more likely to develop SJS. However, the sample size utilized in this study was small (6 cases and 30 controls), resulting in a wide confidence interval (1.54 - 131.82). A study in Nigeria reported the incidence of SJS as 1.7% in a cohort on EFV-based therapy(Isaac Okoh Abah et al., 2015)

Although rare, SJS and TEN are very important ADRs due to ART. This is because the reaction sequalae is often poor, resulting in mortality, significant disability and fetal abortions. Recent studies in South Africa by Knight *et.al* reported that 10% of HIV patients with SJS experienced mortality, while 11% of pregnant women had intrauterine deaths, with some experiencing genital erosions and vaginal tears. (Knight et al., 2014, 2015). There have also been reports of fatality among elderly patients with SJS (Paik et al., 2016).In Ghana, Sarfo et al reported that death of 13% of patients who developed grade three cutaneous drug reactions. The patients died from NVP-associated SJS(Fred Stephen Sarfo et al., 2014).

2.15 Anaemia

Anaemia is a common adverse effect of antiretroviral therapy, particularly among those on Zidovudine and HIV/TB co-infected patients on concurrent ATT therapy. This is particularly a concern in developing countries where there already is a high prevalence of anaemia prior to the start of ART(Subbaraman et al., 2007). ART-associated anaemia has a prevalence ranging fom 3.8% to 47.3% among patients on ART (Luma et al., 2012; Pulagam et al., 2012; Shet et al., 2014). Anaemia often presents as a serious ADR, often requiring hospitalization and leading to ART discontinuation (Pulagam et al., 2012; Phe, Thai, Veng, Sok, Lynen, and Van, 2013). HIV disease itself causes significant anaemia, thus, it is important to rule out baseline anaemia in order to differentiate between HIV-induced anaemia and ART associated anemia. Studies in Uganda and Ethopia measured anaemia at baseline and after ART initiation, thus ascertaining temporality and association with ART (Parkes-ratanshi, Katende, Levin, Wakeham, Heiner, Kamali, and Lalloo, 2015; Zemenu, Tamir, Alemu, and Tsegaye, 2018).

Most studies report Zidovudine use as an independent risk factor for anaemia in patients on antiretroviral therapy. A retrospective analysis of ART-associated ADRs in a tertiary centre in

India showed that anaemia developed in 2.82% of patients. Patients developed anaemia within 6 months of therapy, with a median time to onset of 105 days. Anaemia was strongly associated with zidovudine use in this population, with an aOR of 29.3 (Anwikar, Bandekar, Smrati, Pazare, Tatke, and Kshirsagar, 2011).

A cohort study in India also reported that the prevalence of ADR-associated anaemia was 47.3%. 15.7% were cases of leucopenia, 21% pancytopenia, 5.2% of eosinophilia and 10.5% of bicytopenia, with about 50% of participants requiring hospitalization. The highest prevalence of anaemia was among those on zidovudine-based regimens. Although the study utilized a small sample size (70), patients were actively followed up to measure these ADRs (active surveillance) (Pulagam et al., 2012).

In a retrospective cohort study by Abah et al., in Nigeria, the prevalence of ADR-anaemia was 1.97%. The occurrence of anaemia in this cohort also predicted the odds of virologic failure at 24 and 72 weeks of treatment, with an AOR of 1.74. A strength of the study was the large sample size (over 10,000 study participants) (Isaac O Abah, Ncube, Bradley, Agbaji, and Kanki, 2018). Another cohort study by Eluwa et al reported an incidence of 4%, exclusive to patients on zidovudine-containing regimens. (Eluwa et al., 2012). Agu et al., also reported that anaemia in Nigerian cohorts was also significantly associated with the use of concomitant medicines such as cotrimoxazole, which is used to prevent pneumocystic pneumonia in PLWHIV (Kenneth A Agu and Oparah, 2013).

Shet et al., reported that a cumulative incidence of 37.1% in a prospective cohort on ART. They reported that the risk factors for the development of anaemia as Zidovudine use (RR=22), cotrimoxazole use (RR=1.75), with no relationship between anaemia and BMI or gender. Of the

patients who were hospitalized for anaemia, 7 received blood transfusions and 1 died(Shet et al., 2014).

Although Zidovudine use is widely reported as a risk factor for anaemia, a recent cohort study in the US reported that use of INSTI such as Dolutegravir and raltegravir are also significantly associated with the development of anaemia.

2.17 METABOLIC DISTURBANCES AND CVD SIDE EFFECTS

HAART has been associated with the metabolic syndromes, which are risk factors for adverse cardiovascular events. More importantly, studies have demonstrated that HAART can contribute to the development of insulin resistance and diabetes, independent of lipodystrophy.(Gazzola, Tincati, and D'Arminio Monforte, 2010).

In the APROCO study, (Duval et al., 2004) reported that 13.6% of reported serious adverse dug events were metabolic and cardiovascular events. Cardiovascular events are also a concern in aging HIV patients due to increased HIV survivorship(Gebo and Justice, 2009; Gleason et al., 2013).

In a nationwide, prospective cohort study in Denmark, Obel et al., reported a higher risk of myocardial infarction among HIV patients on regimens that included abacavir. (RR=2.0) The study also showed that the incidence of hospitalization due to myocardial infarction increased from 2.4/1000 person-years to 5.7/1000 person-years after initiation of abacavir. (Obel et al., 2010).

Results from the AIDS Clinical Trial Group A5142 study showed that an increase in median cholesterol and triglyceride levels associated with antiretroviral therapy. In the A5142 clinical trial, patients were randomized equally into three different treatment arms-lopinavir/ritonavir(boosted lopinavir)+efavirenz, two NRTIs +lopinavir/ritonavir and two

NRTIs+efavirenz. Study participants were followed up for 96 weeks. 16% of study participants developed hyperlipidemia and were placed on a lipid lowering agent, while lipoatrophy occurred in 32% of participants in the efavirenz+NRTI arm, 17% of paricipants in the lopinavir/ritonavir+ NRTI arm and 9% in the lopinavir/ritonavir(boosted lopinavir)+efavirenz arm (Haubrich, Riddler, Dirienzo, Komarow, Haas, Mellors, Havlir, Clinical, and Group, 2010).

From the Data Collection on Adverse Events of Anti-HIV drugs (D:A:D), Worm et al., reported an increased risk of myocardial infarction with PIs and NRTIs. However, the increased risk of myocardial infarction was not associated with an increased risk of dyslipidemia, but with longer exposure to ART, with RR of 1.12 and 1.13 for indinavir and boosted lopinavir respectively.(Worm, Sabin, Weber, Reiss, El-Sadr, Dabis, De Wit, Law, D'Arminio Monforte, Friis-Møller, Kirk, Fontas, Weller, Phillips, and Lundgren, 2010)

2.18 Other ADRs

Other ADRs reported with the use of ART include immune reconstitution inflammatory syndrome (IRIS), nephrotoxicity and gastro-intestinal effects.(Dimie Ogoina, Victor Adekunle, Reginald Obiako, Abdulaziz Umar, Michael Akolawole, 2011; Eluwa et al., 2012; Quesada et al., 2015; Hill, Mitchell, Hughes, and Pozniak, 2018). In a four-year retrospective review in Nigeria, Ogoina et al., reported that IRIS was responsible for 42.1% of deaths among hospitalized HIV patients on ART (Ogoina, Obiako, Muktar, Adeiza, Babadoko, Hassan, Bansi, Iheonye, Iyanda, and Tabi-ajayi, 2012).

2.2 Determinants of Adverse Drug Reactions To Antiretroviral Therapy

2.21 Age

There have been divergent reports on the association between age and the occurrence of ADRs. Some studies have reported the association between age, particularly older age and the occurrence of ADRs, while others have reported no association. Some studies, however, have reported an association between age and the development of specific ADRs.

A cross sectional chart review of adult HIV patients on ART study by Luma et al in Cameroun found no association between age and the occurrence of ADRs.(Luma et al., 2012). Similarly, it was reported that mean age was not associated with the development of rash in HIV patients randomized to four different NNRTI regimens in the 2NN trial in Thailand investigating the incidence, characteristics, severity and treatment of rash and the outcome after use of NNRTI based therapy (Ananworanich et al., 2005). In another study investigating the incidence and risk factors for NVP associated hepatotoxicity, Chu and colleagues reported a null association between age and development of NVP associated early hepatotoxicity. (Chu et al., 2010)

In a prospective cohort study among HIV patients in Rwanda on stavudine and nevirapine based ART, Griensven et al., showed that patients older than 35 years had a higher risk of nevirapine-related hepatotoxicity and stavudine-related late neuropathy as compared with patients younger than 35 years (adjusted hazard ratio=2.6 and 2.7 respectively).(Griensven et al., 2010) On the contrary, increasing age (every 10 years) was reported as a weak protective factor for ART associated lipoatrophy among patients randomized into 3 different regimens, with an OR of 0.72(Haubrich et al., 2010).

Domingo et al. found an association beteween median age and limb fat gain in a study to investigate the effects of switching from stavudine to raltegravir in HIV-infected patients on ART. However, the study reported median age, rather than individual ages. (Domingo et al., 2014)

In Nigeria, while some studies have found no association between age and the development of ADRs, other studies have reported age as a risk factor for the development of ADRs. In a retrospective cohort study to investigate incidence and types of ADRs associated with ART reported in Nigeria, researchers reported that age was not associated with the development of ADRs in that cohort.

In another retrospective cohort in Jos, Nigeria, it was reported HIV patients older than 40 years on efavirenz had a higher risk of developing neuropsychiatric ADRs as compared with patients below 40 years (adjusted HR=2.59). The study also reported that the proportion of reported ADRs decreased with an increase with age. However, age was categorized into <30, 30-39, 40-49 and ≥50, with the highest proportion among those <30 years old.(Isaac Okoh Abah et al., 2015)

Obiako et al., reported an association between age and occurrence of ART related ADRs in HIV infected patients on ART. Results from the cohort study investigating ART associated ADRs in Zaria, showed that age 16-59 years had an association with the occurrence of ADRs. However, this is contrary to the hypothesis that elderly people are at a higher risk of adverse drug reactions (Gebo and Justice, 2009; Obiako O et al., 2012; Edelman et al., 2013). A possible explanation may be that the majority of PLWHIV in Nigeria are patients aged 15-49 years.(UNAIDS, 2019). Similarly, results from a study on spontaneous reporting of ART associated ADRs showed that different age groups were associated with different ADRs. Fever, hearing difficulty, dystonia, cough and restlessness were associated with age less than 15 years. Headache, abdominal pain, fatigue and arthralgia were associated with age greater than 24 years.

2.22 Sex

Most adverse drug reactions are significantly associated with female sex. Women have varying pharmacokinetic profiles from men, which could affect ARV tolerability. Pregnancy and the use of contraceptives also affect ARV safety and increase the occurrence of ARV associated ADRs.(Clark, 2005)

In a prospective cohort study investigating the incidence and risk factors of ADRs among Kenyan patients initiating ART, it was reported that women had a 9.6 times increased risk of developing peripheral neuropathy than men (RR=9.6). It was also reported that women were more anaemic than men (median hemoglobin level, 9.3 vs 11 g/dL; p< .0001). However, the study did not report the risk independently for pregnant women, although 3% of study participants were pregnant at ART initiation. The study however showed that the hazard ratio for peripheral neuropathy reduced from 9.6 to 7.4 when haemoglobin levels were controlled for.(Mehta et al., 2011)

In a cohort study to investigate stavudine and nevirapine associated toxicities, it was reported that women on ART are almost ten times more likely to develop ART associated lipoatrophy than men, with an adjusted hazard ratio of 9.7. The possible causes are unknown, as no inferences were made as this was an observational study. Similarly, in the 2NN trial, there was an increased risk of ART associated rash among women with CD4 counts >250×10^6 cells per litre.(Ananworanich et al., 2005; Griensven et al., 2010).

In a Nigerian cohort, HIV-infected women on efavirenz-based regimens had 10 times higher risk for adverse neuropsychiatric events than men. The risk for pregnant women was also not independently reported, as pregnancy has been shown to affect the occurrence of ADRs.(Isaac Okoh Abah et al., 2015). Women may also be a higher risk of lactic acidosis and NVP-associated hepatotoxicity (Subbaraman et al., 2007).

2.23 Use of Concomitant Medicines

The use of concomitant medicines, and by extension, polypharmacy greatly increases the risk of ADRs among HIV-infected patients. HIV-infected patients also have varying co-morbidities, ranging from infectious diseases to non-communicable diseases.(Gebo and Justice, 2009; Gleason et al., 2013). The use of concomitant medicines among PLWHIV is quite common and synergistic interactions occur between ART and other prescribed medicines. In addition, the high prevalence of tuberculosis among PLWHIV in developing countries presents a risk of overlapping toxicities between ARVs and anti-tuberculosis drugs.(Subbaraman et al., 2007; Moore, Mao, and Oramasionwu, 2015)

In the PAART study in an Australian cohort, the use of concomitant medicines in addition to ART among HIV-infected patients was significantly associated with adverse drug reactions, with an odds ratio of 2.6. Polypharmacy was also significantly associated with adverse dug reactions in the cohort. Use of concomitant medicines was significantly associated with sleep disturbances, lipodystrophy and myalgia in this cohort with odd ratios of 2.6, 6.0 and 2.1 respectively. However, the researchers did not state if the ADRs reported were due to the synergistic effects of the medications(Siefried, Mao, Cysique, Rule, Giles, Smith, McMahon, Read, Ooi, Tee, Bloch, De Wit, and Carr, 2018).

A prospective cohort study in Ethopia among patients among patients on concomitant HAART and ATT medicine reported that concomitant ART and ATT therapy increased the risk of liver toxicities by 10 times, as compared to those on anti-tuberculosis medications alone. The study participants were divided into four groups, based on ART regimen and TB regimen. The incidence of drug-induced liver toxicity was highest among those on rifampicin-based and EFV-based

therapy.(Yimer, Gry, Amogne, Makonnen, Habtewold, Petros, Aderaye, Schuppe-Koistinen, Lindquist, and Aklillu, 2014)

In another prospective cohort study in Ethopia investigating hepatotoxicity from first line ARVs, concurrent HAART and ATT use increased the risk of grade 2-4 transaminitis by 16 times ($p<0.01$) (Kalyesubula et al., 2011)

2.24 Type of ART Regimen:

In literature, many adverse drug reactions have been associated with particular regimens, thus necessitating substitution or withdrawal. In Africa, many antiretroviral regimens are available in fixed dose combinations (FDCs) of two or more drugs, so it is often difficult to ascertain the exact, causative drug(Miller et al., 2012).

Zidovudine based ART regimens have been associated with haematologic reactions in both adults and children (Pulagam et al., 2012; Phe et al., 2013; Parkes-ratanshi et al., 2015; Zemenu et al., 2018; Thanh, Nguyen, Kobbe, Schulze-sturm, Blohm, Hollwitz, Hertling, Becker, Oommen, Martignoni, Olah, Schmidtke, Kreuels, Vasconcelos, and Neubert, 2019). Nevirapine based regimens have been associated with hepatotoxicity, rash, Stevens-Johnson syndrome and toxic epidermal necrosis (Gao et al., 2010; Kalyesubula et al., 2011; Fred Stephen Sarfo et al., 2014; Knight et al., 2015). These adverse reactions have caused the WHO to relegate regimens containing Zidovudine and Nevirapine to alternative first line regimens especially among pregnant women (World Health Organization, 2016). Neuropsychiatric adverse events are commonly associated with Efavirenz use, however there have been reports of neuropsychiatric events with zidovudine and other ARVs. (Fred S. Sarfo et al., 2016; Treisman and Soudry, 2016). Tenofovir use is associated with renal toxicity, cutaneous adverse drug reactions and Fanconi syndrome.

Fanconi syndrome is a rare adverse drug reaction involving the proximal renal tubule. (Jain, 2013; Kapadia, Shah, Desai, Desai, Patel, Shah, and Dikshit, 2013; Casado, 2016). There have also been reports of Tenofovir-associated neuropsychiatric disorders, either alone or as an interaction with Efavirenz(Allavena, Moal, Michau, Chiffoleau, and Raffi, 2006; Dalwadi et al., 2018).

Stavudine use has been associated with peripheral neuropathy, lipodystrophy and metabolic adverse effects . In 2009, the WHO recommended the removal of Stavudine from ART, due to drug safety concerns. However, Stavudine is still in use in some resource-limited settings due to cost considerations (Pujades-Rodríguez et al., 2011; World Health Organization, 2013, 2016; Kiwuwa-Muyingo, Kikaire, Mambule, Musana, Musoro, Gilks, Levin, and Walker, 2014). Protease inhibitors such as Lopinavir-ritonavir and atazanavir are often associated with gastrointestinal side effects and multiple interactions with other drugs (Reust, 2011). There are very few reports of adverse reactions to Lamivudine in the literature. As lamivudine is always used as a backbone in all antiretroviral regimen and is never given solely, it is difficult to ascertain any adverse effect to lamivudine.

2.3 Classification of Adverse Drug Reactions to Antiretroviral Therapy.

The WHO Adverse Reaction Terminology is used to describe and code ADRs reported through either spontaneous reporting or active pharmacovigilance. It was first developed in 1968.. The coding is based on a hierarchical system that is divided into four categories: System Organ Class, High Level Term, Preferred Term and Included Term. (Sills, 1989; Wallberg, 2009)

Included terms are the lowest level and are terminologies similar to the preferred terms.Preferred terms are the main terms for coding and presentation of ADRs. High level terms refer to a group of similar preferred terms. The system organ class refers to a group of preferred terms relating to

the same body organ. There are 3607 included terms, 2158 preferred terms, 184 high level terms and 32 system organ class (Nahler, 2009; Wallberg, 2009).

2.4 Outcomes of Adverse Drug Reactions to Antiretroviral Therapy

Outcomes of adverse drug reactions refer to the sequalae of events after the occurrence of the ADRs. The outcomes of the ADR refers to the degree of resolution of the signs and symptoms of the ADR(Ibrahim A. Oreagba, Oshikoya, Ogar, Adefurin, Ibrahim, Awodele, and Oni, 2017). Based on the ADR reporting form, the outcomes of ADRs are described as recovered fully, recovered with disability, congenital abnormality, life-threatening or death.

Fatal ADRs have been well described in literature. Fatal ADRs are often an important, yet overlooked cause of mortality among patients on ART. In South Africa, Mouton and colleagues reported that 65% of patients who died from ADRs were on ART. HIV patients on ART had increased odds of ADR associated mortality (Mouton, Mehta, Parrish, Wilson, Stewart, Njuguna, Kramer, Maartens, Blockman, and Cohen, 2015). In Uganda, a cohort study reported a fatality rate of 7.3% associated with ART-associated anaemia (Parkes-ratanshi et al., 2015).

Severe cutaneous adverse reactions (Steven-Johnson Syndrome and Toxic Epidermal Necrolysis) are often associated with an increased risk of mortality. This is particularly important as Steven-Johnson Syndrome and Toxic Epidermal Necrolysis are only drug-induced. Paik and colleagues reported a case of mortality following Nevirapine associated Steven-Johnson Syndrome (Paik et al., 2016). Knight et al reported an ADR-associated mortality rate of 9% among patients on ART, with Nevirapine as the offending agent (Knight et al., 2014). In Nigeria, Ogoina et al observed ADR-associated mortality among hospitalized HIV patients in a tertiary hospital (Ogoina et al., 2012). They also reported mortality due to ART-associated immune reconstitution syndrome in

another study (Dimie Ogoina, Victor Adekunle, Reginald Obiako, Abdulaziz Umar, Michael Akolawole, 2011). In the Swiss HIV cohort, Keiser et al reported an association with laboratory-confirmed ADRs and mortality, with an adjusted hazard ratio of 1.3 (Keiser, Fellay, Opravil, Hirsch, Hirschel, Bernasconi, Vernazza, Yerly, et al., 2007).Steinman et al postulate that ADR-associated mortality may be diminished by early detection of drug related problems(Steinman, Handler, Gurwitz, Schiff, and Covinsky, 2011).

Many patients recover from ADRs, particularly after treatment discontinuation. Hoffman et al reported that patients with neuropsychiatric symptoms recovered after discontinuation of the offending drug (Hoffmann, Welz, Sabranski, Kolb, Wolf, Stellbrink, and Wyen, 2017). In South Africa, pregnant women with nevirapine associated toxicity recovered after discontinuation of Nevirapine (Dube et al., 2013). In a Ghanaian cohort, it was reported that a quarter of patients who developed rash due to Nevirapine stopped their medications(Fred S. Sarfo et al., 2016). Hsu et al also reported recovery in patients after treatment discontinuation(Hsu, Fusco, Henegar, Mounzer, Wohlfeiler, Vannappagari, Aboud, Curtis, and Fusco, 2018).

2.5 Pharmacovigilance and Post Marketing Surveillance

Pharmacovigilance is defined as the "science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug related problems." Pharmacovigilance encompasses post-marketing surveillance, adverse drug reactions, adverse drug effects, medication errors, counterfeit medications, inefficacy of medications, abuse/misuse of medicines and drug-drug interactions. (World Health Organization, 2002). Post-marketing is considered the final phase of clinical and vaccine trials.

Spontaneous reporting of adverse drug reactions is the basis of pharmacovigilance globally and in Nigeria. A spontaneous report is a voluntary report of an adverse drug event that occurs in a patient taking a medication, who is not involved in a study(Pal, Duncombe, Falzon, and Olsson, 2013; Pal, Olsson, and Brown, 2015). Health professionals, patients or pharmaceutical manufacturers usually report suspected adverse drug reactions to a coordinating centre. Spontaneous reporting systems are quite robust and can capture large amounts of adverse drug events with less cost. Spontaneous reporting systems are also able to capture rare ADRs, usually not captured in clinical trials or drug safety studies. However, as patients are not followed up to record the occurrence of ADRs, spontaneous systems have a limitation of underreporting, thus underestimating the true incidence of these ADRs.

In Nigeria, the spontaneous reporting system of adverse drug reactions is coordinated by the National Agency for Food and Drug Administration and Control (NAFDAC). NAFDAC has a National Pharmacovigilance Centre which collates adverse drug reaction reports, investigates these reports and forwards them to the WHO-Uppsala Monitoring Centre. (Pal *et al.*, 2013; NAFDAC, 2020; Awodele *et al.*, 2018; Lee Ventola, 2018)

CHAPTER THREE

METHODOLOGY

3.1 Study Setting:

Nigeria has a population of about 1 million people currently accessing highly active antiretroviral therapy. These ART services are accessed across various secondary and tertiary health facilities, through various donor funded programmes in partnership with the Federal Ministry of Health and its allied parastatals. Spontaneous reporting of adverse drug events is coordinated by the National Agency for Food and Drug Administration and Control (NAFDAC) and is carried out using a standardized form called the 'Yellow Form'. The form contains patient's socio demographic information, description, duration and outcome of the ADR, hospitalization due to the ADR, suspected drug(s), drug indication, concomitant medicines used and source of report.

ART providers are expected to report cases of adverse drug reactions using the yellow form. Each filled yellow form is called an Individual Case Safety Report (ICSR). The ICSRs are submitted to the NAFDAC state offices or zonal offices. The ICSRs are then forwarded to the National Pharmacovigilance Centre of NAFDAC. These reports are then investigated by the National Drug Safety Advisory Committee and signals generated are forwarded to the WHO-Uppsala Monitoring Centre.

Oyo State has a HIV prevalence of 0.9%. It is a state in South-west Nigeria, with a population of about 5.6 million people. PMTCT and ART services are provided at various health facilities at both secondary and tertiary level, and adverse drug reaction reports are sent to the NAFDAC State Office in the state capital.

3.2 Study Site: Key Informant Interviews were carried out at the Adeoyo Maternity Teaching Hospital, Yemetu

3.3 Study population: Patients on antiretroviral therapy with adverse drug reactions and healthcare providers (doctors, pharmacists and nurses) that provide antiretroviral therapy and counselling to patients.

3.4 Study Design: A mixed method study design was used. A retrospective descriptive analysis of ICSRs due to antiretroviral medicines submitted to the National Pharmacovigilance Centre between 2014 and 2018 was conducted. Facility based key informant interviews were conducted and among healthcare providers involved in the provision of ART care and counselling.

3.5 Study Sample: All ICSRs suspected to be due to any highly active antiretroviral therapy regimen between 2014 to 2018. The following data were extracted using a pro forma form.

i. Socio-demographic information
ii. Adverse drug reactions reported
iii. ART regimen
iv. Concomitant medicines
v. Outcome of the Adverse drug reactions: recovered/recovering, ongoing, fatal, unknown
vi. Seriousness of ADR
vii. Duration of ADR (days).

For the qualitative study, healthcare providers directly involved in the provision of ART were interviewed.

3.6 Variables:

Dependent Variables: Reported adverse drug reactions. Reported ADRs were classified using the WHO System-Organ Classification

Independent variables:

i. Socio-demographic information (Age, sex, weight)
ii. ART regimen
iii. Concomitant medicines

3.7 Operational Definitions:

i. Adverse drug reactions: a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function
ii. ART regimen: Antiretroviral therapy regimen, a combination of antiretroviral therapy used
iii. Concomitant medicines: Any other medications, including herbal preparations and over-the-counter medicines taken within 3 months of occurrence of ADR.
iv. Outcome of ADR: Recovered, ongoing or fatal
v. Seriousness of ADR: If the ADR was fatal, life-threatening, causes permanent disability, congenital abnormality or prolonged hospitalization

3.8 Sample Size Determination: For quantitative analysis, the Leslie-Kish formula of single proportions was used. In the qualitative study, key informant interviews were conducted until data saturation and data redundancy occurred.

For quantitative analysis, the Leslie-Kish formula of single proportions was used:

$$n=\frac{z_{\alpha}^{2}pq}{}$$

d^2

where

p= the estimate of the population prevalence of ADRs (53.4%), as reported by Bassi et al, 2017

q= 1-p=46.6%

Zα= the standard normal estimate when level of significance, α, is 5% and level of confidence is 95%. Z=1.96

d= the level of precision, set at 5% or 0.05

n=382.

To account for a non-response rate of 10%, a minimum of 425 case safety reports was calculated. However, all ICSRs due to antiretroviral medicines were collected for analysis.

3.9 Sampling Technique: Study participants for the qualitative study were purposively selected from the Adeoyo Maternity Teaching Hospital.

3.10 Inclusion Criteria:

i. Healthcare providers (doctors, pharmacists and nurses) who are directly involved in the provision of ART to patients living with HIV/AIDS.

3.11 Exclusion Criteria:

i. Healthcare providers who have less than one year experience of providing ART services

3.12 Statement of confidentiality:

To ensure confidentiality, no names were recorded during data extraction and during the interviews. However, ICSRs and respondents were identified by codes for ease of sorting and transcription.

3.13 Data Collection techniques:

A proforma form was used to extract the data from the ICSRs submitted to the National Pharmacovigilance Centre, NAFDAC. Key Informant Interviews were conducted by the researcher and one research assistant who was trained prior to data collection. Both the benefits and possible problems were explained to research participants. Permission to carry out the study was sought from the management of NAFDAC and the management of the facilities.

3.14 Data Analysis and Management:

Serial numbers were written on the data extraction tool. After data extraction; cleaning, recording and coding of the data for analysis was carried out. The data from the quantitative analysis was cleaned and stored in a password protected computer system. The key informant interviews weretranscribed and the data was extracted and stored in a password protected computer. The collected and coded data was carefully entered into statistical software and analysed based on the different specific objectives. The themes of the key informant interviews were extracted. The data analysis matrix is shown below:

Data Analysis Matrix

S/N	Specific Objective	Dependent Variable	Independent Variable	Test Statistic
1	To determine the pattern of occurrence of adverse drug reactions among people living with HIV on highly active antiretroviral therapy	Pattern of occurrence of Adverse drug reactions		Descriptive Statistics, frequencies and percentages
2	To investigate determinants of adverse drug reactions among people living with HIV on highly active antiretroviral therapy.	Occurrence of Adverse drug reactions	Factors such as age, sex, use of concomitant medicines, type of ART regimen	Chi-squareand binary logistic regression
3	To investigate the determinants of serious of adverse drug reactions to antiretroviral therapy among people living with HIV.	Serious adverse drug reactions	Factors associated with serious adverse drug reactions	Chi-square, binary logistic regression
4	To determine the outcomes of adverse drug reactions to antiretroviral therapy among people living with HIV.	Outcomes of adverse drug reactions		Descriptive statistics, frequencies and percentages

3.15 Ethical issues/Considerations: Ethical approval was obtained from the Research Ethics Review Committee of the Oyo State Ministry of Health, with approval number AD/13/479/1768. The ethical principles of Helsinki that applies to human health research were strictly adhered to.

i. **Informed Consent:** Written informed consent or assent as the case may be was obtained from all respondents.

ii. **Voluntary participation:** The respondents were told that participation is voluntary and they can withdraw at any time.

iii. **Confidentiality:** To ensure confidentiality, no names was recorded on the data extraction forms and during the interviews. Filled data extraction forms and interview recordings were kept in a safe place, only accessible to members of the research team.

iv. **Non-maleficence:** There was no medically invasive procedures or tests. Study participants were not made to divulge any information that they are not comfortable with.

v. **Beneficence:** Respondents were informed that there are no special benefits for participating in the research. However, the results of this study will be useful in designing pharmacovigilance programmes and drug safety monitoring of antiretroviral therapy.

CHAPTER FOUR

RESULTS

4.1 Baseline Characteristics of Individual Case Safety Reports

A total of 3,398 reports were received between 2014 and 2018. Over two-thirds of the reports were from female patients (n=2429, 71.5%). The mean age of patients with ADRs was 34.7 ± 11 years. Majority of reports were from patients aged 16-50 years (n=3052, 89.8%). Patients were on a combination of two NRTIs and either an NNRTI or a PI. Almost half of patients were on Tenofovir/Lamivudine based regimens and Efavirenz based NNRTI. Over half of patients were on concomitant Co-trimoxazole prophylactic therapy. Other concomitant medicines used by patients included herbal medicines, antitubercular medicines, antimalarial medicines, other antivirals, anti-inflammatory medicines, haematinics and multivitamins.

Table 4.1: Baseline Characteristics of ADR Reports due to Antiretroviral Therapy

Variables	Frequency	Percentage (%)
Sex		
Male	969	28.5
Female	2429	71.5
Age groups		
≤15	85	2.5
16-35	1899	55.9
36-50	1153	33.9
51-87	261	7.7
ART regimen		
ZLN	1247	36.7
TLN	187	5.5
SLN	402	11.8
TLE	1348	39.7
ZLE	151	4.4
SLE	42	1.2
TLL	2	0.3
ZLL	9	0.3
NRTI backbone	1546	45.5
Tenofovir/Lamivudine		
Zidovudine/Lamivudine	1407	41.4
Stavudine/Lamivudine	445	13.1
NNRTI/PI regimen		
Efavirenz	1541	45.4
Nevirapine	1836	54.0
Lopinavir/Ritonavir,	21	0.6
Concomitant Medicine Use		
Cotrimoxazole	2289	67.4
Other concomitant medicines	359	10.6
No concomitant medicine use	750	22.0
Total	3398	100

ZLN: Zidovudine/Lamivudine/Nevirapine; TLN: Tenofovir/Lamivudine/Nevirapine; SLN: Stavudine/Lamivudine/Nevirapine; TLE: Tenofovir/Lamivudine/Efavirenz; ZLE: Zidovudine/Lamivudine/Efavirenz; SLE: Stavudine/Lamivudine/Efavirenz; TLL: Tenofovir/Lamivudine/Lopinavir.ritonavir; ZLL: Zidovudine/Lamivudine/Lopinavir.ritonavir

4.11 Pattern of Adverse Drug Reactions to Antiretroviral Therapy

A total of 6145 ADRs were reported in the 3398 reports, giving an average of 1.81 ADRs per report. Of the 3398 reports, 50.1% reported one ADR, 28.9% reported two ADRs, 14.0% reported three ADRs, 5.1% reported four ADRs,1.2% reported five ADRs and 0.7% reported 7-13 ADRs. The most common adverse drug reactions reported were dizziness(n=820), fatigue(n=702) ,rash(n=554), headache(n=539), pain (n=375), pruritus(n=367), vomiting(n=244), nausea(n=242), anaemia(n=193), nightmares (n=184), neuropathy(n=177), insomnia (n=161), anorexia (n=133), diarrhea (n=121) and fever (n=91). Other ADRs reported include abnormal vision, numbness, cough, hallucination, malaise, dry mouth, oedema, abnormal pigmentation, Stephen Johnson Syndrome, loss of appetite, polyuria, gynaecomastia, amenorrhoea, myalgia, palpitations, drowsiness, lipidosis, abdominal discomfort, dyspnea, weight loss, depression, and jaundice.

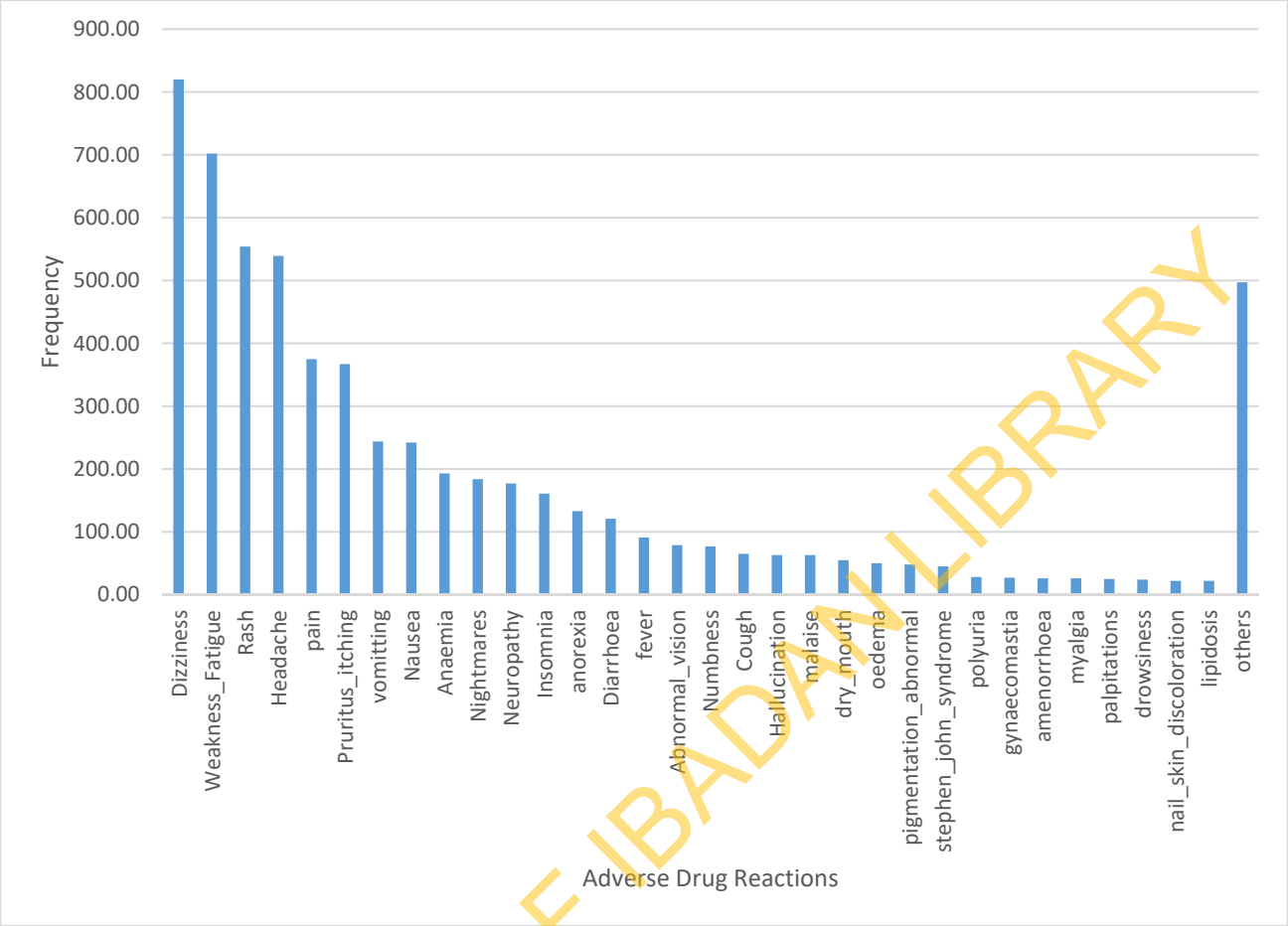


Fig. 1: Pattern of Adverse Drug Reactions to Antiretroviral Therapy in Nigeria

The adverse drug reactions were grouped according to the WHO System-Organ Classification, and are presented in the table below. Neuropsychiatric disorders, skin and appendages, systemic disorders, musculoskeletal disorders, gastrointestinal disorders and anaemia were the most commonly reported categories of adverse drug reactions.

Table 4.2: System Organ Classification of Adverse Drug Reactions to Antiretroviral Therapy

System Organ Class	Frequency	Percentage (%)
Neuropsychiatric disorders	1831	29.8
Skin and appendages disorders	1056	17.1
Systemic disorders	869	14.1
Gastrointestinal disorders	761	12.4
Musculoskeletal disorders	413	6.7
Peripheral nervous system disorders	265	4.3
Red blood cells disorders (Anaemia)	193	3.1
Lipodystrophy disorders	49	0.8
Respiratory disorders	73	1.2
Sensory disorders	155	2.50
Others	480	8.0
Total	**6145**	**100**

4.2 **Determinants of Adverse Drug Reactions.**

4.2.1 **Determinants of Neuropsychiatric disorders**

A total of 1382 patients reported 1831 neuropsychiatric ADRs. Of those that reported neuropsychiatric ADRs, 1020 patients reported one ADR, 281 patients reported two neuropsychiatric ADRs, 77 patients reported three neuropsychiatric ADRs, two patients reported four ADRs and two patients reported five ADRs. The four patients who reported more than three ADRs were females. Patients who reported five ADRs were on Tenofovir-Lamivudine-Efavirenz and the patients who reported four ADRs were on Zidovudine-Lamivudine-Nevirapine. Table 4.2.1 shows the association between sex, age group, ART regimen and concomitant medicine use with neuropsychiatric adverse drug reactions. In chi-square analysis, only sex, age group, ART regimen and use of other concomitant medicines were associated with neuropsychiatric disorders.

Table 4.3 Determinants of neuropsychiatric disorders

Factors	Neuropsychiatric Disorders reported n(%)	No Neuropsychiatric Disorders reported n(%)	χ^2	p-value
Sex				
Male	333(34.4)	636(65.6)	22.423	<0.001
Female	1049(43.2)	1379(56.8)		
Age groups				
≤15	12(14.1)	73(85.9)	54.604	<0.001
16-35	854(45.0)	1044(55.0)		
36-50	405(35.1)	748(64.9)		
51-87	111(42.5)	150(57.5)		
NRTI regimen				
Tenofovir/Lamivudine	928(60.0)	618(40.0)	443.404	<0.001
Zidovudine/Lamivudine	362(25.7)	1045(74.3)		
Stavudine/Lamivudine	92(20.7)	352(79.3)		
NNRTI regimen				
Efavirenz	991(64.3)	550(35.7)	650.004	<0.001
Nevirapine	386(21.0)	1450(79.0)		
PI regimen				
Lopinavir/ritonavir	5(25.0)	15(75)	2.046	0.153
No PI	1376(40.8)	2000(59.2)		
Concomitant medicine use	949(41.5)	1340(58.5)	1.752	0.186
Co-trimoxazole use	443(39.6)	675(60.4)		
No cotrimoxazole use				
Other concomitant medicines	125(34.9)	233(65.1)	5.515	0.019
	1257(41.4)	1782(58.6)		
No concomitant medicine				
Total	**1382**	**2015**		

After logistic regression, sex, age groups, NRTI class and Efavirenz use remained significantly associated with the occurrence of neuropsychiatric ADRs. Patients aged 16-35, 36-50 and >50 were 3.3, 2.3 and 2.8 times more likely to develop neuropsychiatric symptoms than those aged less than 15 respectively. Female patients had a higher odds of developing neuropsychiatric symptoms compared to male patients (OR=1.439). Patients on tenofovir and zidovudine based regimens had higher odds of developing neuropsychiatric symptoms than those on stavudine based regimens (OR=1.627, 1.392) respectively. Patients on Efavirenz based regimen had five times higher odds of developing neuropsychiatric symptoms than those on nevirapine based regimens.

Table 4.3 Logistic regression analysis of determinants of Neuropsychiatric ADRs

		95% CI		
	Odds ratio	Lower	Upper	p-value
Age				
≤15	1			
16-35	3.320	1.708	6.453	<0.001
36-50	2.321	1.189	4.532	0.014
>50	2.757	1.353	5.617	0.005
Sex				
Male	1			
Female	1.439	1.206	1.718	0.030
NRTI regimen				
Stavudine/Lamivudine	1			
Tenofovir/Lamivudine	1.627	1.188	2.227	0.002
Zidovudine/Lamivudine	1.352	1.031	1.772	0.029
NNRTI regimen				
Nevirapine	1			
Efavirenz	5.573	4.411	7.041	<0.001
Use of other concomitant Medicines				
No	1			
Yes	0.836	0.646	1.082	0.173

4.2.2 Anaemia

Of 3398 ADR reports, 193 patients had anaemia. Three-quarter of the reports were from female patients (74.6%) and over half were from patients aged 16-35(58%). Over 90% of patients who reported anaemia were on Zidovudine based regimen and 52.3% had concomitant Co-trimoxazole use. On bivariate analysis, sex and use of other concomitant medicines was not associated with the occurrence of anaemia. Table 4.32 shows the association between the independent variables and anaemia. Age group, use of co-trimoxazole and ART regimens were associated with the occurrence of anaemia.

Table 4.4 Determinants of anaemia among patients on antiretroviral therapy

Factors	Anaemia reported n(%)	No anaemia reported n(%)	χ^2	p-value
Sex				
Male	49(5.1)	920(94.9)	0.987	0.322
Female	144(5.9)	2284(94.1)		
Age groups				
≤15	11(12.9)	74(87.1)	10.043	0.018
16-35	112(5.9)	1786(94.1)		
36-50	56(4.9)	1097(95.1)		
51-87	14(5.4)	247(94.6)		
NRTI regimen				
Tenofovir/Lamivudine	11(0.7)	1535(99.3)	226.729	<0.001
Zidovudine/Lamivudine	180(12.8)	1227(87.2)		
Stavudine/Lamivudine	2(0.5)	442(99.5)		
NNRTI regimen				
Efavirenz	13(0.8)	1528(99.2)	120.291	<0.001
Nevirapine	175(9.5)	1661(90.5)		
PI regimen				
Lopinavir/ritonavir	5(25)	15(75)	14.005	0.004*
No Lopinavir/ritonavir	188(5.6)	3188(94.4)		
Concomitant medicine use	101(4.4)	2188(95.6)		
Co-trimoxazole use	92(8.3)	1016(91.7)	21.092	0.00
No cotrimoxazole use				
Other concomitant medicines	24(6.7)	334(93.3)	0.781	0.398
Other concomitant medicines	169(5.6)	2870(94.4)		
No concomitant medicine				
Total	193	3204		

*Fisher's exact test

On logistic regression analysis, only zidovudine use and nevirapine use remained significantly associated with the occurrence of Anaemia. Patients on Zidovudine based regimen were 32 times more likely to report anaemia (OR=32.052) than those on stavudine/lamivudine based therapy. Patients on Nevirapine based regimen were 4 times more likely to report anaemia than those on Efavirenz based regimen. However, Co-trimoxazole use was protective of the occurrence of Anaemia. Patients on concomitant Co-trimoxazole therapy were 1.72 times less likely to report anaemia.

Table 4.5: Logistic regression analysis of determinants of anaemia among patients on antiretroviral therapy

		95% CI		
	Odds ratio	Lower	Upper	p-value
Age				
≤15	1			
16-35	0.809	0.409	1.600	0.506
36-50	0.575	0.283	1.169	0.126
>50	0.829	0.350	1.962	0.586
NRTI regimen				
Stavudine/Lamivudine	1			
Tenofovir/Lamivudine	4.241	0.989	22.908	0.052
Zidovudine/Lamivudine	32.566	8.038	131.946	<0.001
NNRTI regimen				
Efavirenz	1			
Nevirapine	4.181	2.094	8.369	<0.001
Cotrimoxazole use				
No	1			
Yes	0.582	0.427	0.793	0.001

4.2.3 **Determinants of Skin and appendages disorders**

A total of 807 patients reported 1056 skin related ADRs. Of 807 reports, 578 patients reported only one skin related ADR, 210 patients reported two skin ADRs, 18 patients reported three skin ADRs and one patient reported four skin ADRs. In chi-square analysis, only age groups and ART regimens were significantly were significantly associated with skin and appendages disorders.

Table 4.6: Determinants of skin and appendages disorders among patients on antiretroviral therapy

Factors	Skin disorders reported n(%)	No skin disorders reported n(%)	χ^2	p-value
Sex				
Male	226(23.3)	743(76.7)	0.140	0.721
Female	581(23.9)	1847(76.1)		
Age groups				
≤15	40(47.1)	45(52.9)	36.406	<0.001
16-35	404(21.3)	1494(78.7)		
36-50	304(26.4)	849(73.6)		
51-87	59(22.6)	202(77.4)		
NRTI regimen				
Tenofovir/Lamivudine	252(16.3)	1294(83.6)	97.414	<0.001
Zidovudine/Lamivudine	447(31.8)	960(68.2)		
Stavudine/Lamivudine	108(24.3)	336(75.7)		
NNRTI regimen				
Efavirenz	204(13.2)	1337(86.8)	175.401	<0.001
Nevirapine	601(32.7)	1235(67.3)		
PI regimen				
Lopinavir/ritonavir	2(10)	18(90)	2.104	0.191
No Lopinavir/ritonavir	805(23.8)	2571(76.2)		
Concomitant medicine use				
Co-trimoxazole use	552(24.1)	1737(75.9)	0.500	0.492
No cotrimoxazole use	255(23.0)	853(77.0)		
Other concomitant medicines				
Other concomitant medicines	92(25.7)	266(74.3)	0.833	0.359
No concomitant medicine	715(23.5)	2324(76.5)		
Total	807	2590		

After logistic regression analysis, being older than 15 years was associated with decreased odds of reporting skin ADRs. Patients aged 16-35 years were 2.56 times less likely to report skin ADRs. Patients aged 36-50 years were 1.97 times less likely to develop skin ADRs and patients older than 50 years were 2.25 times less likely to develop skin ADRs than patients aged less than 15 years. Patients on tenofovir and zidovudine based therapy were 1.6 and 1.4 times more likely to develop skin disorders than those on stavudine-based therapy. Patients on Nevirapine based regimen were 3.7 times more likely to develop skin and appendages disorders than those on Efavirenz based NNRTI.

Table 4.7: Logistic regression of factors associated with skin and appendages disorders

		95% CI		
	Odds ratio	Lower	Upper	p-value
Age				
≤15	1			
16-35	0.390	0.248	0.614	<0.001
36-50	0.508	0.321	0.804	0.004
>50	0.444	0.261	0.757	0.003
NRTI regimen				
Stavudine/Lamivudine	1			
Tenofovir/Lamivudine	1.660	1.195	2.305	0.002
Zidovudine/Lamivudine	1.449	1.131	1.896	0.003
NNRTI regimen				
Efavirenz	1			
Nevirapine	3.698	2.818	4.851	<0.001

4.2.4: **Determinants of Musculoskeletal disorders.**

Of 410 patients who reported musculoskeletal ADRs, 407 reported one ADR while three patients reported two ADRs. About two-thirds of the ADR reports were from females (72.2%) and over half were from those aged 16-35 (56.6%). Almost half of the musculoskeletal ADR reports were from patients on Zidovudine based regimen (49.1%). In chi-square analysis, only ART regimen was statistically associated with the development of musculoskeletal disorders. Sex, age and use of concomitant medicines did not have any significant association with the occurrence of musculoskeletal disorders.

Table 4.8: Factors associated with musculoskeletal disorders

Factors	Musculoskeletal disorders reported n(%)	No musculoskeletal disorders reported n(%)	χ^2	p-value
Sex				
Male	114(11.8)	855(88.2)	0.112	0.771
Female	296(12.2)	2132(87.8)		
Age groups				
≤15	4(4.7)	81(95.3)	4.494	0.213
16-35	232(12.2)	1666(87.8)		
36-50	141(12.2)	1012(87.8)		
51-87	33(10.3)	288(89.7)		
NRTI regimen				
Tenofovir/Lamivudine	124(8.1)	1422(91.9)	51.331	<0.001
Zidovudine/Lamivudine	201(14.3)	1206(85.7)		
Stavudine/Lamivudine	85(19.1)	359(80.9)		
NNRTI regimen				
Efavirenz	121(7.9)	1420(92.1)	46.608	<0.001
Nevirapine	285(15.5)	1551(84.5)		
PI regimen				
Lopinavir/ritonavir	4(20)	16(80)	1.191	0.291*
No PI	406(12.1)	2970(87.9)		
Concomitant medicine use				
Co-trimoxazole use	268(11.7)	2021(88.3)	0.863	0.369
No cotrimoxazole use	142(12.8)	966(87.2)		
Other concomitant medicines				
Other concomitant medicines	49(13.7)	309(86.3)	0.987	0.345
No concomitant medicine	361(11.9)	2678(88.1)		
Total	410	2987		

*Fisher's exact test

After logistic regression analysis, only stavudine use and nevirapine use was significantly associated with musculoskeletal disorders (OR=1.959, 1.563). Patients on Stavudine based regimens were two times more likely to have musculoskeletal disorders than those on tenofovir-based therapy, and those on Nevirapine based therapy were 1.6 times more likely to develop musculoskeletal disorders than those on Efavirenz based therapy.

Table 4.9: Logistic regression analysis of determinants of musculoskeletal disorders among patients on antiretroviral therapy

		95% CI		
	Odds ratio	Lower	Upper	p-value
NRTI regimen				
Tenofovir/Lamivudine	1			
Zidovudine/Lamivudine	1.388	0.976	1.974	0.054
Stavudine/Lamivudine	1.959	1.315	2.919	0.001
NNRTI regimen				
Efavirenz	1			
Nevirapine	1.563	1.108	2.203	0.011

4.2.5 Determinants of Peripheral Nervous System disorders.

On chi-square analysis, only age, NRTI regimen and NNRTI regimen were associated with the occurrence of peripheral nervous system disorders (p=<0.001 respectively). Sex and use of concomitant medicines had no association with the occurrence of peripheral nervous system disorders.

Table 4.10 Determinants of Peripheral Nervous System disorders

Factors	Peripheral Nervous System disorders reported n(%)	No Peripheral Nervous System disorders reported n(%)	χ2	p-value
Sex				
Male	84(8.7)	885(91.3)	2.227	0.151
Female	174(7.2)	2254(92.8)		
Age groups				
≤15	2(2.4)	83(97.6)	37.006	<0.001
16-35	103(5.4)	1795(94.5)		
36-50	125(10.8)	1028(89.2)		
51-87	28(10.7)	233(89.3)		
NRTI regimen				
Tenofovir/Lamivudine	46(3.0)	1500(97.0)	282.341	<0.001
Zidovudine/Lamivudine	93(6.6)	1314(93.4)		
Stavudine/Lamivudine	119(26.8)	325(73.2)		
NNRTI regimen				
Efavirenz	57(3.7)	1484(96.3)	61.674	<0.001
Nevirapine	200(10.9)	1636(89.1)		
Concomitant medicine use				
Co-trimoxazole use	169(7.4)	2120(92.6)	0.449	0.534
No cotrimoxazole use	89(8.0)	1019(92)		
Other concomitant medicines				
Other concomitant medicines	33(9.2)	325(90.8)	1.502	0.220
No concomitant medicine	225(7.4)	2814(92.6)		
Total	258	3139		

After logistic regression, patients aged 36-50 and on zidovudine and stavudine based regimen had increased odds of developing peripheral nervous system disorders. Patients on Zidovudine based regimens were two times more likely to develop peripheral nervous system disorders than those on Tenofovir based regimens. Patients on Stavudine based regimens were 10 times more likely to develop peripheral nervous system disorders. Patients aged 36-50 were 4 times more likely to develop a peripheral nervous system disorder than those aged less than 15.

Table 4.11 Logistic regression of determinants of Peripheral nervous system disorders

		95% CI		
	Odds ratio	Lower	Upper	p-value
Age				
≤15	1			
16-35	2.164	0.514	9.116	0.293
36-50	4.724	1.124	19.857	**0.034**
>50	4.373	0.984	19.438	0.053
NRTI regimen				
Tenofovir/Lamivudine	1			
Zidovudine/Lamivudine	2.069	1.243	3.442	**0.005**
Stavudine/Lamivudine	10.621	6.383	17.674	**<0.001**
NNRTI regimen				
Efavirenz	1			
Nevirapine	1.235	0.787	1.939	0.359

4.2.6 Determinants of Systemic disorders

On chi-square analysis, age, use of cotrimoxazole and ART regimens were associated with the occurrence of systemic disorders. Sex and use of other concomitant medicines were not associated with the occurrence of systemic ADRs.

On logistic regression analysis, patients' age was not significantly associated with systemic disorders. Use of cotrimoxazole also increased the odds of experiencing a systemic ADR by 58.7%. Patients on Tenofovir/Lamivudine and Zidovudine based regimens had their odds of experiencing systemic ADRs increased by 111% and 57.2% respectively. Nevirapine based regimens was protective of systemic ADRs. Patients on Nevirapine based regimens 2.81 times less likely to develop systemic ADRs.

Table 4.12 Determinants of Systemic Disorders among patients on antiretroviral therapy

Factors	Systemic disorders reported n(%)	No systemic disorders reported n(%)	$\chi 2$	p-value
Sex				
Male	245(25.3)	724(74.7)	0.970	0.325
Female	575(23.7)	1853(76.3)		
Age groups				
≤15	12(14.1)	73(85.9)	21.657	**<0.001**
16-35	513(27.0)	1385(73.0)		
36-50	242(21.0)	911(79.0)		
51-87	53(20.3)	208(79.7)		
NRTI regimen				
Tenofovir/Lamivudine	558(36.1)	988(63.9)	226.004	**<0.001**
Zidovudine/Lamivudine	216(15.4)	1191(84.6)		
Stavudine/Lamivudine	46(10.4)	398(89.6)		
NNRTI regimen				
Efavirenz	575(37.3)	966(62.7)	266.044	**<0.001**
Nevirapine	242(13.2)	1594(86.8)		
Concomitant medicine use				
Co-trimoxazole use	625(27.3)	1664(72.7)	38.403	**<0.001**
No cotrimoxazole use	195(17.6)	913(82.4)		
Other concomitant medicines				
Other concomitant medicines	80(22.3)	278(77.7)	0.702	0.434
No concomitant medicine	740(24.4)	2299(75.6)		
Total	820	2577		

Table 4.13 Logistic regression of determinants of systemic disorders among patients on antiretroviral therapy

		95% CI		
	Odds ratio	Lower	Upper	p-value
Age				
≤15	1			
16-35	1.674	0.880	3.186	0.116
36-50	1.243	0.648	2.384	0.513
>50	1.123	0.552	2.283	0.749
NRTI regimen				
Stavudine/Lamivudine	1			
Tenofovir/Lamivudine	2.116	1.446	3.097	**<0.001**
Zidovudine/Lamivudine	1.572	1.116	2.213	**0.010**
NNRTI regimen				
Efavirenz	1			
Nevirapine	0.355	0.273	0.460	**<0.001**
Cotrimoxazole Use				
No Cotrimoxazole use	1			
Cotrimoxazole use	1.587	1.313	1.918	**<0.001**

4.2.7 Determinants of Gastrointestinal Disorders among patients on antiretroviral therapy

Age, NRTI, NNRTI and PI regimens and use of other concomitant medicines were the only factors associated with the occurrence of gastrointestinal disorders after chi-square analysis. Sex and concomitant use of cotrimoxazole were not associated with the occurrence of gastrointestinal symptoms.

Table 4.14 Determinants of gastrointestinal symptoms.

Factors	Gastrointestinal symptoms reported n(%)	No gastrointestinal symptoms reported n(%)	χ2	p-value
Sex				
Male	147(15.2)	822(84.8)	1.431	0.232
Female	409(16.9)	2017(83.1)		
Age groups				
≤15	13(15.3)	72(84.7)	19.641	**<0.001**
16-35	356(18.8)	1541(81.2)		
36-50	159(13.8)	993(86.2)		
51-87	28(11.2)	233(92.8)		
NRTI regimen				
Tenofovir/Lamivudine	238(15.4)	1307(84.6)	12.738	**0.002**
Zidovudine/Lamivudine	264(18.8)	1142(81.2)		
Stavudine/Lamivudine	54(12.2)	390(87.8)		
NNRTI regimen				
Efavirenz	228(14.8)	1312(14.8)	4.442	**0.035**
Nevirapine	321(17.5)	1514(82.5)		
Concomitant medicine use				
Co-trimoxazole use	390(17.0)	1898(83.0)	2.289	0.138
No cotrimoxazole use	166(15.0)	941(85.0)		
Other concomitant medicines				
Other concomitant medicines	73(20.4)	284(79.6)	4.721	**0.030**
No concomitant medicine	483(15.9)	2555(84.1)		
Total	556	2839		

After logistic regression analysis, patients on Tenofovir and Zidovudine based regimens were 48% and 66% more likely to develop gastrointestinal disorders. Efavirenz use was protective of gastrointestinal disorders, but this association was not statistically significant.

Table 4.15 Logistic regression of determinants of gastrointestinal disorders

		95% CI		
	Odds ratio	Lower	Upper	p-value
Age				
≤15	1			
16-35	1.467	0.799	2.692	0.217
36-50	0.963	0.518	1.788	0.905
>50	0.787	0.385	1.608	0.511
NRTI regimen				
Stavudine/Lamivudine	1			
Tenofovir/Lamivudine	1.481	1.002	2.191	0.049
Zidovudine/Lamivudine	1.663	1.211	2.282	0.002
NNRTI regimen				
Nevirapine	1			
Efavirenz	0.818	0.611	1.095	0.177
Other concomitant medicines				
No concomitant medicine	1			
used	1.379	1.044	1.821	0.024
Concomitant medicine used				

4.3 Determinants of Serious Adverse Drug Reactions

Patients with serious ADRs were those who ADRs were life threatening, fatal, disabling, required prolonged hospitalization or had other medically important conditions. Out of 3398 reports, 84 (2.5%) were serious. Of the patients that reported serious ADRs, 71.4% were female and 66.7% were aged 16-35.Over half of serious ADRs were life-threatening (52.3%), and one-third required prolonged hospitalization (35.6%). Serious ADRs were reported by 2.5% of the ICSR reports. Over half of patients who reported serious ADRs were on Zidovudine/Lamivudine/Nevirapine regimen, and this association was statistically significant. Cotrimoxazole was used concomitantly by 52% of patients with serious ADRs. On chi square analysis, ART regimen and cotrimoxazole use were associated the occurrence of serious ADRs. Sex and age were not associated with the occurrence of serious ADRs.

Table 4.16 Pattern of Serious ADRs

Types	Frequency(n=84)	Percentage (%)
Life-threatening	48	57.2
Prolonged hospitalization	30	35.7
Disabling	4	4.7
Other medically important condition	2	2.4

Table 4.17 Determinants of serious ADRs

Factors	Serious ADRs reported n(%)	No serious ADRs reported n(%)	χ2	p-value
Sex				
Male	23(2.4)	946(97.2)	0.903	0.055
Female	61(2.5)	2367(97.5)		
Age groups				
≤15	4(4.7)	81(95.3)	7.107	0.057*
16-35	56(3.0)	1842(97.0)		
36-50	20(1.7)	1133(98.3)		
51-87	4(1.5)	257(98.5)		
NRTI regimen				
Tenofovir/Lamivudine	17(1.1)	1529(98.9)	25.351	<0.001
Zidovudine/Lamivudine	56(4.0)	1351(96.0)		
Stavudine/Lamivudine	11(2.5)	433(97.5)		
NNRTI regimen				
Efavirenz	17(1.1)	1524(98.9)	21.695	<0.001
Nevirapine	66(3.6)	1770(96.4)		
Concomitant medicine use				
Co-trimoxazole use	44(1.9)	2245(98.1)	8.794	0.003
No cotrimoxazole use	40(3.6)	1068(96.4)		
Other concomitant medicines	12(3.4)	346(96.6)	1.283	0.257
Other concomitant medicines	72(2.4)	2967(97.6)		
No concomitant medicine				
Total	84	3313		

*Fishers Exact test

After logistic regression analysis, only Zidovudine use was associated with the occurrence of a serious ADR. Patients on Zidovudine/Lamivudine therapy were 2 times more likely to develop a serious ADR than those on Tenofovir/Lamivudine based therapy. Conversely, concomitant cotrimoxazole use was protective of a serious ADR. Patients on concomitant cotrimoxazole therapy were 1.7 times less likely to develop a serious ADR.

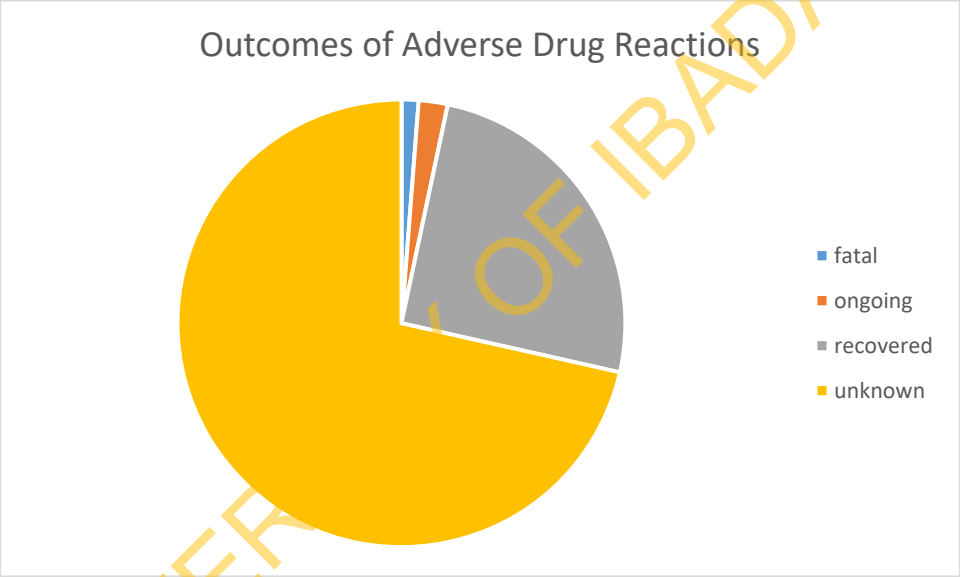
Table 4.18 Logistic regression of determinants with serious ADRs

		95% CI		
	Odds ratio	Lower	Upper	p-value
NRTI regimen				
Tenofovir/Lamivudine	1			
Zidovudine/Lamivudine	2.325	1.062	5.090	**0.035**
Stavudine/Lamivudine	1.376	0.529	3.578	0.513
NNRTI regimen				
Nevirapine	1			
Efavirenz	0.524	0.246	1.119	0.095
Cotrimoxazole use				
No cotrimoxazole use	1			
Cotrimoxazole use	0.577	0.369	0.903	**0.016**

4.4 Outcomes of ADRs

The outcome of the ADR referred to the sequelae of the ADR. The outcomes were grouped into recovered, ongoing and fatal. However, 71.5% of outcomes were unknown at the time of report, 25.2% recovered, 2.1% were ongoing as at the time of report and 1.2% of outcomes were fatal.

After reclassifying the outcomes into recovered and fatal, factors associated with outcomes are shown below:



4.5 KEY INFORMANT INTERVIEWS

1. **Cadre and duration of work in the facility:** Chief Nursing Officer, Matron and Assistant Director, Pharmacy.
2. **Duration of work**: 2-12 years
3. **Meaning of ADRs:** The respondents could define ADRs, however one respondent wrongly defined ADRs as side effects.

"They are side effects of a drug, adverse reactions are side effects of any drug"- Respondent 2

4. **Experience with ADRs:** All participants responded that they have had patients with ADRs to ART in the course of their practice. Commonly reported ADRs include oedema, renal toxicities, hepatotoxicity, rashes, weight gain due to Dolutegravir, blisters, jaundice. One participant responded that she had had patients with anaemia due to Zidovudine, CNS side effects due to EFV, weight gain due to TLD, hepatotoxicity with NVP and GI side effects due to PIs.

"*Yes, I have seen quite a lot during my practice here. I have seen series of ADRs reported. Some ADRs are peculiar to certain kinds of drugs, that patients on that particular regimen report. Anaemia is common among patients on Zidovudine, although it does not come up immediately, but after some time. Patients with EFV in their regimen present with CNS side effects like hallucinations, funny dreams. Patients on Protease Inhibitors like Lopinavir and Atazanavir, also complain of diarrhea, nausea and vomiting, both in children and in adults. There are also some patients whose side effects have to be assessed by laboratory investigations, like hepatotoxicity with Nevirapine. These unwanted effects do occur in overdose too, when patients do not comprehend the dosage and are taking more than the required dose. Lately, with the switch to*

Dolutegravir, there are a lot of reports of weight gain with Dolutegravir, loss of appetite, insomnia, and some weight loss, although there have been more reports of weight gain, hyperglycemia. Side effects with ARVs are common, however most times, they are transient, mostly when patients are just initiating therapy, they experience changes with their body adjustments, some adjust while some have to be taken off the drug and they have to be managed in order to correct the ADR"- Respondent 3.

5. **Risk factors for the occurrence of the ADRs**: The respondents did not think that habits such as smoking or drinking could affect the occurrence of ADRs. One respondent replied that she thinks smoking and drinking does not affect the occurrence of ADRs as women who do not drink and smoke as much as men experience more ADRs. One participant also mentioned that use of concomitant use of medicines, particularly herbal medicines is common in the society and may increase the risk of ADRs.

6. **Management of ADRs:** Treatment switching, treatment substitution, hospitalization and referral for specialist care are some of the management strategies for ADRs.

"*It was TLD (Tenofovir/lamivudine/dolutegravir) so in such a case we had to change the patient back to TLE. Initially investigations done on the patient such as liver function test, urea etc revealed that the patient had fatty liver and we recommended he stopped taking the drugs for a week. We observed that after that all the blowing up stopped, there now changed him back to TLE(Tenofovir/Lamivudine/Efavirenz). Actually the patient was on TLE before he was changed to TLD because of the directive to change all our patients to TLD, but after the patient experienced that reaction, the drug was reversed back to TLE, and since then there was no such complain anymore, with no need for hospitalisation. In fact immediately the drugs were reversed everything*

subsided, even the patients with ascites and swollen legs experienced similar outcome when the drugs were reversed." Respondent 1.

7. **Reporting of ADRs**: All participants reported the use of toxicity forms initiated by the HIV/AIDS programme and the use of the standard reporting form-the Yellow Form by NAFDAC.
8. **Trainings on ADRs**: The respondents noted that trainings on ADRs were incorporated with other trainings organized by the programme donors. However, one respondent had not participated in any trainings on ADRs.

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMMMENDATION

5.0 DISCUSSION

This chapter presents the discussion of the findings of this research. It highlights the significance of the findings in public health with a view to make practical recommendations for public health action.

5.1.1 Baseline Characteristics of Individual Case Safety Reports

A total of 3,398 reports were received between 2014 and 2018, of which majority (71%) were from female patients. A possible explanation may be that there is a higher prevalence of HIV among females in Sub-Saharan Africa, particularly in Nigeria, thus more females are on ART, as compared to males. This is similar to what was obtained in the study of Eluwa, et al, where 64% of ADRs were reported by females (Eluwa et al., 2012). This is also similar to a studies in South Africa and Kenya that reported more females (70.8%, 94%) significantly reported ADRs in tertiary hospitals in both countries. (Mehta et al., 2011; Graan, Viljoen, Rheeders, Motara, and Africa, 2018). Mehta et al also reported that 98% of patients on ART were females. Females are also more likely to get tested for HIV and placed on care when positive compared to males (Taylor-Smith, Tweya, Harries et al., 2010). Another reason may be that females are more likely to experience ADRs due to higher plasma concentrations of ARVs and smaller body mass, when compared with men (Clark, 2005; Umeh and Currier, 2006; Greig and Anderson, 2014)

The mean age of patients with ADRs was 34.7 ± 11 years. Majority were from patients of age range of 16-50 years. This age range is similar with the age range of people living with HIV, and thus on ART. This presents a concern, as young people within their productive ages have

comordities and toxicities due to antiretroviral therapy. This is also similar to the study of Agu, and Oparah, (2013) had a similar result with this current study with a mean age of 35.3 years. Almost half of patients were on Tenofovir/Lamivudine based regimens and Efavirenz based NNRTI. In the 2014 National HIV guidelines, (Federal Ministry of Health, 2014), Tenofovir/Lamivudine/Efavirenz was recommended as the first-line regimen for adolescents aged 10-19 years, adults and pregnant women on ARV therapy. Reports from Stavudine based therapy were had the lowest number (13%), as Stavudine based therapy was being phased out in 2014. Two-thirds of patients were on concomitant Co-trimoxazole prophylactic therapy, to reduce the risk of opportunistic infections.

5.1. 2 Pattern of Adverse Drug Reactions to Antiretroviral Therapy among Patients

Multiple ADRs were reported by 49.9% of patients with ADRs. The occurrence of multiple ADRs may increase the risk of co-morbidities, which in turn may lead to non-adherence and increase the risk of resistance and virologic failure (Monjok, Smesny, Okokon, Mgbere, and Essien, 2010; Li et al., 2017). The occurrence of multiple ADRs can also lead to a decrease in the quality of life. As HIV therapy is life long, the occurrence of multiple ADRs in one patient may lead to non-adherence, increased healthcare costs, and further risk of polypharmacy (Gleason et al., 2013; Fred Stephen Sarfo et al., 2014). Healthcare providers should routinely screen and monitor for ADRs to prevent loss to follow up and non-adherence.

The WHO System-Organ Classification was used in grouping the ADRs reported. Neuropsychiatric disorders and skin disorders were the most common groups of ADRs reported (28%). This was similar to a study by Abah et al, which reported occurrence of neuropsychiatric

disorders in 29% of the observed cohort in Nigeria but lower than that reported by and Mugusi et al (56%) of the cohorts in Tanzania (Isaac Okoh Abah et al., 2015; Mugusi et al., 2018). However, this contrasts with studies by Masenyetse et al and Bassi et al, which did not report neuropsychiatric ADRs among patients (Masenyetse et al., 2015; Bassi et al., 2017). As this is a nationally representative study, it is more likely that the National Pharmacovigilance Centre may have received reports from ART centres that have not been reported in the literature.

Specifically, dizziness and headache were the most commonly reported ADRs. Other studies have reported dizziness as a common ADR among patients on ART (Ford, Shubber, Pozniak, Vitoria, Doherty, Kirby, and Calmy, 2015b; Birbal et al., 2016; Valeriano, Carvalho-Silva, Coelho, Moura, Arraes, Brandão, Crovella, and Guimarães, 2020). However, this is contrast to findings by Mukonzo et al, which reported sleep disorders and hallucination as commonest type of neuropsychiatric disorders (Mukonzo, Okwera, Nakasujja, Luzze, Sebuwufu, Ogwal-Okeng, Waako, Gustafsson, and Aklillu, 2013).

Skin and appendages disorders was the second most frequent group of ADRs reported (17%). Rash was the most frequent type of ADR, accounting for 9.3%. This is consistent with previously reported studies (Griensven et al., 2010; Fred Stephen Sarfo et al., 2014; Shet et al., 2014; Masenyetse et al., 2015). However, it was lower than the incidence of rash in the 2NN trial in Thailand, which reported an incidence of 34%. Although rash may be a mild ADR, it is often associated with more serious hypersensitivity reactions (Wu, Cheng, Liu, Lee, Yang, Tsai, Cheng, Lin, Lin, Wang, Lee, Sun, Tang, and Hung, 2017) Although Steven-Johnsons Syndrome accounted for only 0.7% of ADRs reported, it is still an important ADR as it has the potential to be fatal or life threatening. Cutaneous ADRs have serious implications, as they not only affect the quality of

life of patients, but they can lead to treatment discontinuation, serious complications and death (Knight et al., 2014, 2015; Paik et al., 2016).

5.1. 2. 2 Healthcare Providers' Perspectives on ADRs to Antiretroviral Therapy

The qualitative aspect of this study assessed healthcare providers' perspectives focused on their knowledge about ADRs, their experience in encountering patients with ADRs, reporting of ADRs, training on ADRs and management of ADRs.

Majority of healthcare providers assessed in this study were able to correctly define ADRs and identified the risk factors that predisposed the patients. This aspect of the findings is in contrast with other studies(Danekhu, Shrestha, Aryal, and Shankar, 2019; Kassa Alemu and Biru, 2019; Gidey, Seifu, Hailu, Asgedom, and Niriayo, 2020) that reported poor knowledge of healthcare professionals on ADRs. This may be because these other studies used quantitative study instruments, whereas, this study assessed based on a qualitative interview.

Their experience with the patients showed that the common reported ADRs are oedema, renal toxicities, hepatotoxicity, rashes, weight gain due to Dolutegravir, blisters, jaundice. One participant responded that she had had patients with anaemia due to Zidovudine, CNS side effects due to EFV, weight gain due to TLD, hepatotoxicity with NVP. This account of the patients provided by the healthcare providers is similar with the study report conducted by Güner and Ekmekci in Turkey (Güner and Ekmekci, 2019), where nearly 70% of the healthcare providers assessed also reported that they encountered patients that report ADRs. The study also reported that the participants assessed used pharmacovigilance form as part of their ADR reporting and

monitoring system when interacting with their patients. This is also similar to the Yellow Form used by the participants in this study.

On the management of the ADRs reported by the patients, treatment substitution and referrals for specialist care were methods used in the management of patients with ADRs. This management approach used by switching the regimen was in line with the National Guidelines WHO (2018) recommendation in the Workshop on management and reporting of adverse drug reactions related to ARVs on 26 June 2018, in Gaborone, Botswana.

5.1.3 Determinants of ADRs:

5.1.3.1 Neuropsychiatric Disorders:

Older age (being older than 15 years), female sex and Efavirenz based therapy were strongly associated with neuropsychiatric disorders. Being on Efavirenz based therapy increased the odds of Neuropsychiatric disorders by five times. This result is similar to studies reported in Nigeria and other parts of the world (Isaac Okoh Abah et al., 2015; Fred S. Sarfo et al., 2016; Sumari-de Boer et al., 2018). This finding has implications in clinical and programmatic settings. Clinicians should take special note of neuropsychiatric ADRs when placing adult, female patients on Efavirenz-based therapy, or consider other regimens in patients with existing mental illnesses. In this study, Tenofovir and Zidovudine were associated with neuropsychiatric disorders. It is unclear whether Tenofovir and Zidovudine independently mediated the neuropsychiatric disorders, or whether they had a synergistic effect with Efavirenz. This finding is similar to a report by Margalida et al, where it was reported that Tenofovir influenced neuropsychiatric properties of Efavirenz (Margalida, Sara, Hansjakob, Laurent, Thierry, and Amalio, 2007). Tenofovir and

Zidovudine are used in other regimens, thus clinicians should also screen for neuropsychiatric disorders in patients on these regimens.

5.1.3.2 Skin and Appendages Disorders

Findings from this study indicate that being younger than 15 years and Nevirapine based therapy increased the odds of developing skin and appendages disorders. This is similar to findings of other studies (Dziuban, Hughey, Stewart, Blank, Kochelani, Draper, and Schutze, 2013; Wu et al., 2017; Saka et al., 2018). This holds important implications, as Nevirapine is prescribed for children born to HIV positive mothers as part prevention of mother to child transmission (PMTCT) guidelines, (Federal Ministry of Health, 2016). Clinicians, nurses and mothers should be alert to identify skin disorders in children on NVP based therapy, especially as skin disorders may be a marker of underlying hypersensitivity.

5.1.3.3 Anaemia

Zidovudine and Nevirapine use were strongly associated with the occurrence of Anaemia. However, co-trimoxazole therapy reduced the odds of developing anaemia. A possible explanation may be that co-trimoxazole reduces the risk of opportunistic infections that may contribute to the occurrence of anaemia in patients on ART. Zidovudine has been associated with the occurrence of anaemia in previous studies (Pulagam et al., 2012; Phe et al., 2013; Shet et al., 2014). The adjusted OR of developing anaemia with zidovudine therapy reported in this study (32) is slightly higher than studies conducted by Shet et al and Anwikar et al, which reported odds ratios of 22 and 29.3 respectively. (Anwikar et al., 2011; Shet et al., 2014). This study, together with previous studies give strong evidence of the association between Zidovudine and the occurrence of anaemia in patients on ART. Thus, clinicians, pharmacists and healthcare workers involved in ART/ARV care

should consider supplementing iron intake as part of routine care for those on Zidovudine based therapy. HIV/AIDS programme managers and funders should consider providing haematinics as part of HIV programmes and projects in Nigeria.

5.1.3.4 Musculoskeletal Disorders and Peripheral Nervous System Disorders:

Stavudine based therapy was significantly associated with the occurrence of musculoskeletal and peripheral nervous system disorders. Several studies have reported Stavudine-associated peripheral neuropathy among patients on ART (Mcgrath et al., 2012; Kiwuwa-Muyingo et al., 2014; Birbal et al., 2016). This study found no association between female sex and peripheral neuropathy, unlike studies in Kenya and South Africa However, based on WHO guidelines in 2014, Stavudine use has been discontinued in Nigeria, and many countries as well (World Health Organization, 2013).

5.1.4 Pattern and Determinants of Serious Adverse Drug Reactions To Antiretroviral Therapy

Over half of serious ADRs reported were life-threatening, with one-third requiring prolonged hospitalization. Although serious ADRs are rare, and were only reported by 2.5% of ICSRs in this study, they are a significant source of morbidity and mortality among patients on ART(Manickum and Suleman, 2012; Edelman et al., 2013; Ibrahim A. Oreagba et al., 2017). In this study, Zidovudine use was strongly associated with the occurrence of serious ADRs. Antiretroviral therapy providers should incorporate the risk associated with serious ADRs when considering Zidovudine based therapy for patients on ART.

5.1.5 Outcomes of ADRs among patients

About three-quarters of outcomes of ADRs among patients were unknown at the time of this study. As ADR reporting in Nigeria is based on a spontaneous/passive reporting system, there is no follow up to determine the eventual outcomes of ADRs. About 1.2% of reported outcomes were fatal. Similar findings were also reported by Agu and Opara (2013), where 66.8% of patients who reported ADRs had unknown outcomes.

5.2 Conclusion

This study assessed the determinants and outcomes of adverse drug reactions among HIVpositive individuals on highly active ART in Nigeria. Retrospective analysis of ICSRs submitted to the National Pharmacovigilance Centre, and qualitative interviews among ART providers were carried out.

A wide range of ADRs were reported. Neuropsychiatric disorders were the most common ADRs reported (29%). Skin and appendages disorders, Musculoskeletal disorders, Anaemia, peripheral nervous system disorders and systemic disorders were the more common disorders reported.

Female sex, older age (>15) and Tenofovir/Efavirenz based therapy were associated with neuropsychiatric disorders. Younger age (<15) and Zidovudine based therapy was associated with the occurrence of Skin and appendages disorders. Zidovudine based therapy was associated with the occurrence of anaemia and serious ADRs (prolonged hospitalization, life-threatening, fatal or causing disability). Stavudine based therapy was associated with musculoskeletal disorders and peripheral nervous system disorders.

New and previously unreported associations were reported in this study, such as the association between Tenofovir and neuropsychiatric disorders.

Healthcare providers were able to properly define ADRs, and narrate different ADRs seen in patients. They reported the use of the Yellow form to report ADRs. Treatment switching and referral for specialist care were some of the protocols of managing ADRs in patients.

Over half of patients had unknown outcomes to ADRs, however, 22% recovered, with mortality of 1.2%.

A strength of this study was that it captured all ADRs reported in the country, from 2014-2018. However, as an observational study, it cannot measure risk and causality.

5.3 Recommendations

From the findings of this research, the following recommendations are suggested:

1. It is important for healthcare providers to ensure that HIV-patients are well-informed about ARV adverse drug reactions before they begin treatment.
2. Healthcare providers should ensure regular active surveillance of ADRs among patients on Antiretroviral Therapy for early detection of ADRs early and follow the recommended management protocol.
3. Female patients on Efavirenz based therapy are at higher risk for Neuropsychiatric disorders, and thus should be monitored and followed up as required.
4. Routine provision of haematinics in patients on Zidovudine based therapy to prevent the occurrence of anaemia.
5. Children on Nevirapine based therapy in PMTCT programmes should be closely monitored for the occurrence of skin disorders.
6. Further research on the neuropsychiatric effects of Tenofovir is recommended.

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APPENDIX

Data Collection Instruments

Proforma Form

Age	
Sex	
Weight	
ADRs reported	
Seriousness(Yes/No)	
Outcome of ADR (underline the one that applies)	**recovered, ongoing, fatal, unknown**
ART regimen	
Duration of ADR	
Concomitant medicines	

Key Informant Interview Guide (Healthcare Provider)

Interview with ART Doctor, Pharmacist or Nurse

Introductions: Thank you very for agreeing to participate in this study. The responses we get from this study will help provide a better understanding of factors associated with adverse drug reactions experienced by people living with HIV on antiretroviral therapy. I will need to tape record your responses. Your responses will be kept confidential and it will linked to you in any way.

Themes	Questions
A	1. Profession, cadre and period of time spent in facility 2. Please tell us what ADRs are. 3a. Have you ever had patients with ADRs to Antiretroviral therapy? b. Probe: What do you think caused the ADRs? Risky behaviours, smoking, drinking? 1. What ART regimen was the patient on? 2. How was it managed? Probe: What was the severity of the ADR? 3. What was the outcome? Probe: Patient is alive/well, alive with disability, dead
B	1. What standard system of identifying adverse drug reactions does this facility operate? 2. What standard reporting system for ADRs does this facility operate? 3. Please show me the reporting protocol?
C	1. How often are trainings on ADRs or that include ADRs conducted? 2. What category of staff attend these trainings? 3 1. Are there standard reporting available for reporting ADRs?
D	1. What are the barriers to ADR reporting in general? 2. What are suggestions for improvement?

Thank you for participating

NATIONAL PHARMACOVIGILANCE CENTRE (NPC) NIGERIA

National Agency for Food and Drug Administration & Control (NAFDAC), Headquarters Office
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Tel: 08086899571 or Fax: 09-5241108

FORM FOR REPORTING OF SUSPECTED ADVERSE DRUG REACTIONS

IN STRICT CONFIDENCE

1. * PATIENT'S DETAILS

Full Name or Initials: _____ Patient Record No: _____

AGE/DATE OF BIRTH: _____ SEX: M ☐ F ☐ WEIGHT (kg): _____

HOSPITAL/Treatment Centre: _____

2. * ADVERSE DRUG REACTION (ADR)

A. DESCRIPTION

DATE Reaction Started	DATE Reaction Stopped

C. OUTCOME OF REACTION
TICK AS APPROPRIATE

☐ Recovered fully ☐ Recovered with disability (Specify) _____

☐ Congenital Abnormality (Specify) _____ ☐ Life Threatening (Specify) _____

☐ Death ☐ Others (specify) _____

B. Was Patient Admitted Due to ADR Yes ☐ No ☐

If Already Hospitalized, Was it Prolonged Due to ADR Yes ☐ No ☐

Duration of Admission (days) _____

Treatment of Reaction: _____

3. * SUSPECTED DRUG (Including Biologicals Traditional/Herbal Medicines & Cosmetics)

A. DRUG DETAILS (State name and other details if available / Attach product label / Sample (if available)

Brand Name: _____ Generic Name: _____ Batch No: _____

NAFDAC No: _____ Expiry Date: _____

Name & Address of Manufacturer: _____

B. Indications for Use	Dosage	Route of Administration	Date Started	Date Stopped

4. * CONCOMITANT MEDICINES (All medicines taken within the last 3months including herbal and self medication)

Brand or Generic Name	Dosage	Route	Date Started	Date Stopped	Reason for Use

5. * SOURCE OF REPORT:

Name of Reporter: _____

Address: _____

Profession: _____

Signature: _____ Tel No/E-mail: _____

*: MANDATORY FIELDS

INFORMED CONSENT FORM

My name is ETUK, Victoria Peter, a postgraduate student of the Department of Epidemiology and Medical Statistics, Faculty of Public Health, College of Medicine, University of Ibadan, Ibadan, Nigeria. I am interviewing healthcare providers providing ARV therapy in order to find out your experiences with adverse drug reactions to antiretroviral therapy. I will need to ask you some questions and record your answers. Please be assured that your answers will be kept very confidential. Your name will not be recorded and will not be used in connection with any information you give. The information you and other people give will help to make antiretroviral drugs safer for patients.

You are free to refuse to participate in this research. You have a right to withdraw at any time if you choose to. I will greatly appreciate your help in taking part in the study.

Consent: Now that the study has been well explained to me and I fully understand the content of the process, I am willing to take part in the study.

……. ……

Signature/thumbprint of participant Interview date