ADVERSE DRUG REACTIONS TO ANTIRETROVIRAL DRUGS: EFFECT ON VIROLOGIC FAILURE IN A NIGERIAN COHORT OF HIV-INFECTED ADULTS ON FIRST-LINE ANTIRETROVIRAL THERAPY

ISAAC OKOH ABAH

A mini-thesis submitted in partial fulfilment of the requirements for the degree of Master of Public Health at the School of Public Health, University of the Western Cape, South Africa

Supervisor: Dr Hazel Bradley

Co-supervisor: Nondumiso Ncube

November 2017

KEYWORDS

Adverse drug reaction

Antiretroviral therapy

HIV medicines

Side effects

Toxicity

Pharmacovigilance

Treatment failure

Viral suppression

Regimen durability

Resource-limited setting

ABSTRACT

Background: Despite the prevalent nature of adverse drug reactions (ADRs) and its negative impact on treatment outcomes in patients on antiretroviral therapy (ART), the impact of ADRs on HIV treatment outcomes - including virologic failure, at Jos University Teaching Hospital HIV clinic have not been fully explored. Identifying ADRs and understanding their risk factors could aid early management and ultimately improve treatment outcomes.

Aim: The aim of the research was to investigate the frequency, types, and risk factors of clinical ADRs to antiretroviral medicines (ARVs) and assess if ADRs increased the risk of virologic failure in patients on ART.

Methodology: A retrospective cohort study design was utilized. Data of HIV-1 infected patients, ≥18 years of age, treatment naïve at enrolment and receiving first-line ART at Jos University Teaching Hospital HIV clinic between June 2004 and February 2012 were evaluated. The incidence and spectrum of ART-associated ADRs were described, and factors associated with ADRs were assessed by Chi-square analyses. A multivariate logistic regression model was fitted to identify independent predictors of ADRs. The association between ADRs and virological failure was assessed by multivariate logistic regression. All statistical tests were two-tailed and a *p*-value <0.05 was considered statistically significant. Stata (version 13) was used for the statistical analyses.

Results: A total of 12,115 patients with a mean age of 35.8 ± 9.1 years, and predominantly females (67%) were included in the analyses. The majority (76%) of the study participants initiated nevirapine-based ART, while zidovudine was the most frequently used nucleoside reverse transcriptase inhibitor (50.2%). In all, 918 incident ADRs were documented during a median (interquartile range) of 4 (1-7) years follow-up period; 45,034 person-years (py) of observation. The incident rate of ADRs was 20 (95% CI: 19 – 22) per 1000 py and was highest during the first year of ART (41 per 1000 py versus 14 per 1000 py, for ≤1 year and >1 of ART; crude incident rate ratio, 2.87 (95% CI: 2.53-3.24)). Compared to other grades of ADRs, the prevalence of severe ADRs was highest (4.5%), while 2.6% ADRs were moderate, and 0.8% were mild. The most common types of ADRs were lipodystrophy (2.6%) attributable mostly to the use of stavudine, and anaemia (1.9%) mainly due to zidovudine use. Others included skin rash and itching (0.7%), peripheral neuropathy (0.5%), and nightmares and insomnia (0.4%). The likelihood of ADRs increased by a factor of 2% for every one-year increment in age (OR, 1.02;

95% CI: 1.01-1.03; p<0.001). Among the nucleoside reverse transcriptase inhibitors, compared to tenofovir, ADRs were more likely with the following ARVs: abacavir (OR, 2.11; 95% CI: 1.23-3.61; p =0.007), zidovudine (OR, 2.22; 95% CI: 1.74-2.84; p <0.001), stavudine (OR, 15.9; 95% CI: 11.07-21.11; p <0.001), and didanosine (OR, 2.13; 95% CI: 1.25-3.63: p <0.006). The prevalence of virologic failure was 36% at 24 weeks of ART, 29% at 48 weeks, and 34% at 72 weeks of ART. Antiretroviral therapy-related anaemia increased the odds of virologic failure at 72 weeks by 74% (OR, 1.74; 95% CI: 1.2 - 2.51; p <0.001); adjusting for age, sex, baseline disease stage, pre-treatment CD4+ cell count, antiretroviral regimen, and year of ART initiation.

Conclusion and Recommendations: The incidence of reported ADRs in the studied population was low and occurred more frequently in the first year of therapy. The risk of ART-related ADRs increased with age. Of the ADRs experienced by patients in the studied population, anaemia significantly increased the risk of late virologic failure. Routine monitoring of haemoglobin levels and prompt management of anaemia in all patients on ART is recommended as a strategy to improve virologic success rates. In addition, close follow-up of patients, throughout the duration of ART, is recommended to track both early and late onset ADRs and to manage them promptly.

DECLARATION

I declare that **ADVERSE DRUG REACTIONS TO ANTIRETROVIRAL DRUGS: EFFECT ON VIROLOGIC FAILURE IN A NIGERIAN COHORT OF HIV-INFECTED ADULTS ON FIRST-LINE ANTIRETROVIRAL THERAPY** is my own work, that it has not been submitted for any Degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

ISAAC OKOH ABAH  November 2017

ACKNOWLEDGEMENTS

My gratitude first is to the almighty God by whose grace and mercies I was able to complete the Masters of Public Health (MPH) degree at the University of the Western Cape (UWC). My sincere appreciation and gratitude go to the Management, Academic and Support staff of the UWC for their generous assistance and support during the course of my studies. I would like to specifically acknowledge and thank my supervisor Dr Hazel Bradley for her patience, unflinching support, continuous guidance and encouragement that saw me to the end of this thesis. I am sincerely grateful to Nondumiso Ncube my co-supervisor. She was a great motivator who pushed me really hard to complete this thesis. I am equally grateful to Dr Lucia Knight, Ms. Corinne Carolissen, and Ms. Janine Kader, for the unstinting help and support they gave me during the planning, approval and implementation phases of my MPH mini-thesis. I am also grateful to Dr. Gavin Reagon who gave me a firm foundation in quantitative methods in public health research and data analysis. I am equally grateful to all the lecturers who taught me in the different modules of the MPH programme and built my capacity to undertake an independent research.

Going through the MPH programme at UWC impacted me positively as a public health practitioner and researcher beyond my expectations. I will not forget to acknowledge Professor Brian van Wyk and the entire Higher Degrees Committee for offering guidance and approval for my final proposal for the MPH mini-thesis research. In addition, I would like to thank both the internal and external reviewers of my mini-thesis report for their invaluable input and suggestions. My sincere appreciation also goes to my course mates; MPH 2015 set, they were all wonderful colleagues.

The management and staff of AIDS prevention in Initiative in Nigeria (APIN) Jos University Teaching Hospital (JUTH) were extremely supportive. In particular, I want to thank Professor Oche Agbaji for his understanding and support, as well as for granting permission for the use APIN JUTH facility for the study. I am grateful to Placid Ogoagu and Bola of the data Unit for assisting with the data extraction. I am equally grateful to the head of Department of Pharmacy Jos University Teaching Hospital Pharm. (Mrs) H.O Jimoh for

her encouragement and motivation to carry one with the studies despite its rigorous demands.

This research couldn't have been possible without the approval of the Harvard T.H. Chan School of Public who granted approval for the use of secondary data. I am particularly grateful to Professor Phyllis Kanki for supporting research efforts at APIN JUTH. Patients' care at APIN JUTH is funded, in part, by the U.S. Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and the Centers for Disease Control and Prevention (CDC) through a cooperative agreement with APIN (PS 001058).

Last but not the least I would like to pour out my deep-seated appreciation to my lovely and supportive wife Mercy Abah and my four boys; Ochayi, Oloha, Ochaba, and Olohi. When I started the MPH journey in 2015, I never envisaged the toll it was going to take on my family. Through the long period of absence, endless deadlines, and sleepless nights, the encouragement of my wife and children was overwhelming. I did not give up the pursuit of the MPH degree because you all stood by me. Thank God your patience paid off and I pray that you all will reap the benefits of your unflinching support in perpetuity.

ABBREVIATIONS

ABC	Abacavir (antiretroviral medicine)
AIDS	Acquired Immuno-Deficiency Syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
ARV	Antiretroviral
APIN	AIDS Prevention Initiative in Nigeria
ART	Antiretroviral Therapy
AZT	Zidovudine (antiretroviral medicine)
3TC	Lamivudine (antiretroviral medicine)
cART	Combination antiretroviral therapy
CD4	CD4 T-cells (T-lymphocytes bearing CD4 receptor)
CNS	Central Nervous System
ddI	Didanosine (antiretroviral medicine)
d4T	Stavudine (antiretroviral medicine)
DNA	Deoxyribonucleic Acid
DTG	Dolutegravir (antiretroviral medicine)
EFV	Efavirenz (antiretroviral medicine)
FMoH	Federal Ministry of Health
FTC	Emtricitabine (antiretroviral medicine)
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HIV	Human Immuno-Deficiency Virus
HSPH	Harvard School of Public Health
INSTI	Integrase Strand Inhibitor
IR	Incident Rate
IQR	Inter Quartile Range
JUTH	Jos University Teaching Hospital
LPV	Lopinavir (antiretroviral medicine)
LPV/r	Lopinavir/ritonavir (antiretroviral medicine)
RAL	Raltegravir (antiretroviral medicine)

NACA	National Agency for the Control of AIDS
NAFDAC	National Agency for Food, Drug, Administration, and Control
NPC	National Population Commission
NNARHS	Nigerian National HIV/AIDS & Reproductive Health Survey
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine (antiretroviral medicine)
STI	Sexually Transmitted Infection
TB	Tuberculosis
TDF	Tenofovir (antiretroviral medicine)
OR	Odds Ratio
PI	Protease Inhibitor (antiretroviral medicine)
PMTCT	Prevention of Mother to Child Transmission of HIV
PY	Person-years
RNA	Ribonucleic Acid
UMC	Uppsala Monitoring Centre
UNAIDS	Joint United Nations Programme on HIV and AIDS
VL	Viral load
WHO	World Health Organization

DEFINITIONS OF KEY CONCEPTS AND TERMS

Except indicated otherwise, the terms are from Edwards and Aronsom (2000), WHO (2006), (AIDSinfo, 2015), and WHO (2012).

Terms related to negative effects of drugs

Adverse [drug] reaction (ADR): An adverse [drug] reaction (ADR) is an adverse response to a medicine, which is noxious and unintended and which occurs at doses normally recommended for use in humans.

Adverse event or experience: An adverse event or experience is any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship to the treatment.

Avoidable (preventable) adverse reactions: Avoidable adverse reactions are those that can be predicted and that can, therefore, be prevented from happening.

Classification and coding of ADRs

Adverse reactions may be described and coded in terms of the body's systems and organs by using the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Long-term ADR: A long-term ADR occurs after the passage of a reasonably long period of time (months or years) after the administration of a medicine.

Side effect: A side effect is an unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the drug.

Serious adverse events are those that:

- are life-threatening
- cause or prolong hospital admission
- cause persistent incapacity or disability
- are sometimes caused by misuse or dependence on a particular drug

Severity of ADR: The severity of an adverse reaction denotes the intensity of the effect, which may be mild, moderate or severe.

Short-term ADR: A short-term ADR occurs within a reasonably short interval after administration (such as minutes or days after the administration of a medicine).

The seriousness of ADRs: The seriousness of adverse drug reactions is based on the seriousness of the outcome or harm caused to the patient.

Type A and B adverse effects

Type A adverse effects*:* Type A adverse effects are those that are caused by the heightened (exaggerated) pharmacological effects of a drug. They are fairly common, predictable, dose-related, and are avoided by using doses that are better tolerated by an individual patient.

Type B adverse effects*:* Type B adverse effects are generally rare, unpredictable and may be serious. They may be immunological or non-immunological and occur in patients with often unknown predisposing conditions.

Rare adverse event: A rare adverse event is an event with a probability frequency of between 1 in 10,000 and 1 in 1,000.

Spontaneous reporting system: A spontaneous reporting system is a system whereby case reports of suspected adverse drug events are voluntarily submitted by health professionals, patients and pharmaceutical manufacturers to the national drug regulatory authority.

Unexpected adverse reaction: An unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with domestic labelling or marketing authorization, and which is not expected from the characteristics of the drug.

Terms related to antiretroviral therapy

First-line antiretroviral therapy: A treatment that is accepted as best for the initial treatment of a condition or disease. The recommended first-line HIV treatment regimens include antiretroviral (ARV) drugs that are safe, effective, and convenient for most people with HIV who have never taken ARVs before.

Regimen backbone: The two nucleoside reverse transcriptase inhibitors (NRTIs) upon which an initial HIV regimen is built. To complete the HIV regimen, the two NRTIs are combined with a third antiretroviral HIV drug from either the non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) drug class.

Salvage therapy: therapy given when the standard treatment for a disease or condition is no longer effective and when treatment options are limited. People with HIV who have experienced toxicity and/or developed resistance to many HIV drugs receive salvage therapy.

Terms related to outcome of antiretroviral therapy

Clinical failure: new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 conditions) after 6 months of effective treatment (World Health Organization (WHO), 2016a).

Immunological failure: CD4 count at or below 250 cells/mm3 following clinical failure or persistent CD4 levels below 100 cells/mm^3(World Health Organization (WHO), 2016a).

Viral load (VL): the amount of HIV in a sample of blood. Viral load (VL) is reported as the number of HIV RNA copies per millilitre of blood. An important goal of antiretroviral therapy (ART) is to suppress a person's VL to an undetectable level—a level too low for the virus to be detected by a VL test.

Viral suppression: when antiretroviral therapy (ART) reduces a person's viral load (HIV RNA) to an undetectable level.

Virologic failure: viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months; with adherence support following the first viral load test, after at least 6 months of antiretroviral therapy (World Health Organization (WHO), 2016a)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 Global and national epidemiology of HIV

Since 1981 when acquired immunodeficiency syndrome (AIDS) was first described (Centers for Disease Control (CDC), 1981) and the discovery of the Human Immunodeficiency Virus (HIV) (Barré-Sinoussi et al., 1983), more than 70 million people have been infected with the HIV virus and about 35 million people have died of HIV (UNAIDS, 2016). Despite the concerted global effort to combat the HIV epidemic, the 2016 report of the Joint United Nations Programme on HIV/AIDS (UNAIDS) shows that HIV is still a major public health problem affecting an estimated 36.7 million people globally at the end of 2015 (UNAIDS, 2016). The report indicated that there were about 2.1 million new HIV infections and 1.1 million AIDS-related deaths globally by the end of 2015. Sub-Saharan Africa is the region worst affected by the HIV epidemic, with an estimated 25.5 million HIV-infected persons living in the region (69% of global HIV cases) (UNAIDS, 2016).

Available data indicate that Nigeria bears the second highest burden of HIV-infected persons globally, after South Africa, with an estimated 3.5 million people living with the virus, which is about 10% of all persons living with HIV globally in 2013 (UNAIDS, 2014). Although HIV prevalence in Nigeria is relatively stable at 3.4% (National Agency for the Control of AIDS (NACA), 2015), there is wide variability in the prevalence across states and zones in Nigeria as shown in Figure 1.1 below; ranging from as low as 0.2% in a South Western State to as high as 15.1% in a South-South State (Federal Ministry of Health (Nigeria), 2013). Generally, the 2012 Nigerian National HIV/AIDS and Reproductive Health Survey (NARHS) report revealed that the HIV prevalence by zone was highest in the South-South geopolitical zone, followed by North Central zone, and lowest in the South East zone. Across demographic groups, HIV prevalence was highest among those aged 35 to 39 (4.4%), and lowest among the 15-19 age group (2.9%), while the prevalence for males aged 35 to 39 years was highest at 5.3%, and women aged 30 to 34 years was 4.2% (Federal Ministry of Health (Nigeria), 2013).

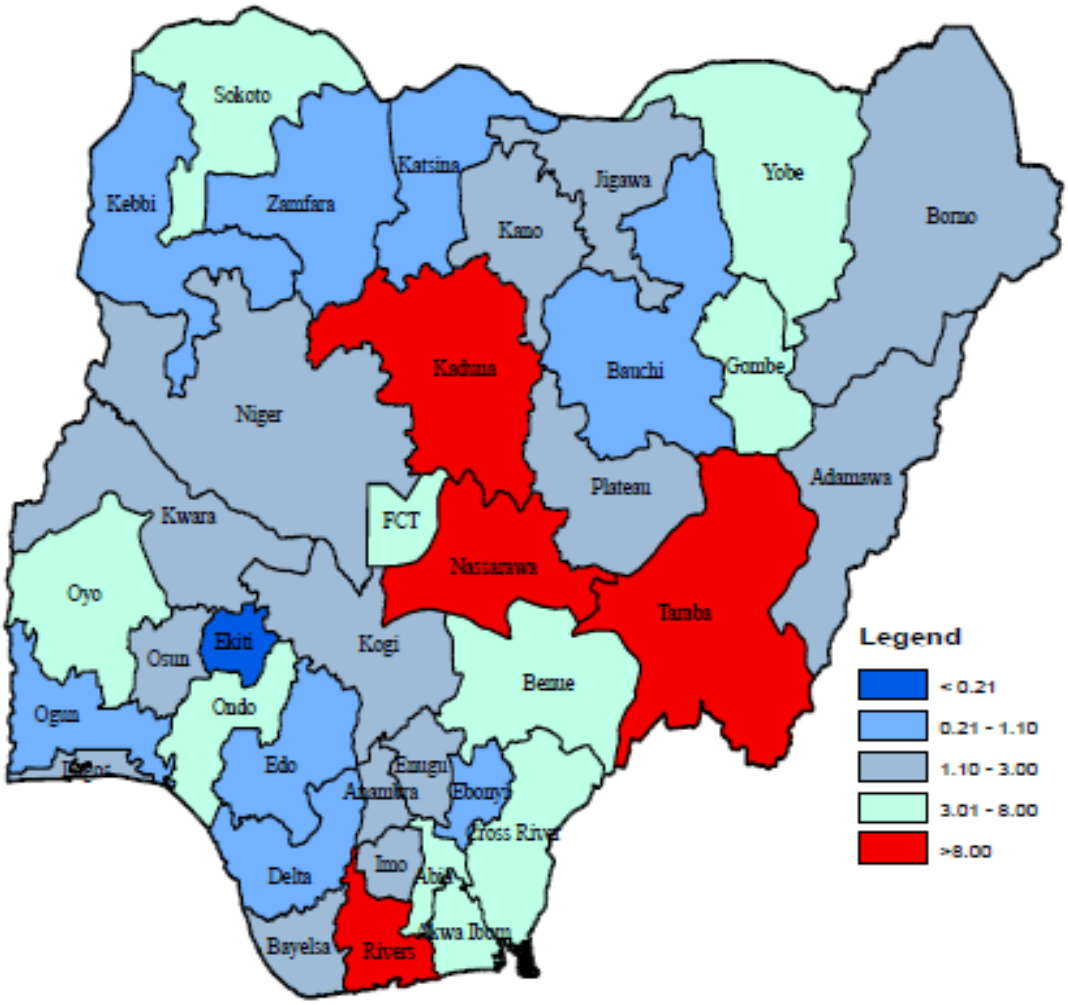


Figure 1.1: Distribution of HIV prevalence by states in Nigeria, 2012

Source: (National Agency for the Control of AIDS (NACA), 2015, p. 40)

Key drivers of the HIV epidemic in Nigeria include low personal risk perception, multiple concurrent sexual partnerships, transactional and intergenerational sex, ineffective and inefficient services for sexually transmitted infections (STIs), and inadequate access to quality healthcare services (National Agency for the Control of AIDS (NACA), 2015).

1.1.2 Global and national response to HIV/AIDS epidemic

Considerable progress has been made in combating the HIV epidemic globally. As depicted in Figure 1.2, the 2016 UNAID estimates show a reversal in the HIV epidemic curve in the number

of new infections (UNAIDS, 2016). According to the UNAIDS, 2016 report, since the 2000s, the number of new infections declined steadily by about 6%, with the greatest decrease in HIV incidence observed among children, which has been reduced by 50% since 2010.

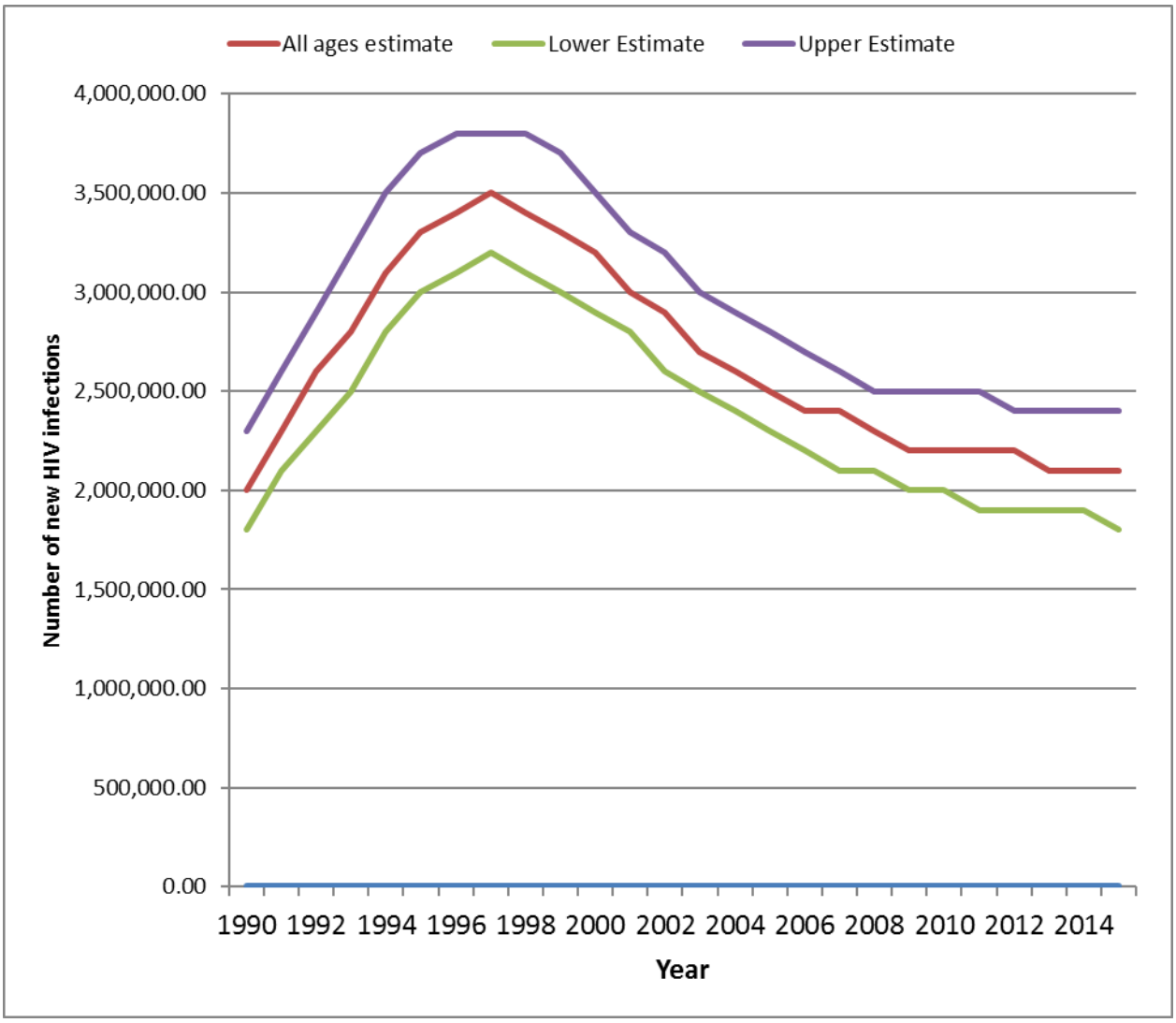


Figure 1.2: Trend in the number of persons newly infected with HIV from 1990 to 2015

Source: UNAIDS estimates 2016

The achievement of maximum effect at the population level in the reduction of HIV transmission in specific settings has been possible through a combination of prevention strategies involving the application of several evidence-based interventions such as a combination of biomedical, behavioural, and structural strategies in a highly focused public health approach (UNAIDS,

2010). The UNAIDS Prevention Reference Group in December 2009 agreed on the operational definition of combination prevention programmes as:

... rights-based, evidence-informed, and community-owned programmes that use a mix of biomedical, behavioural, and structural interventions, prioritized to meet the current HIV prevention needs of particular individuals and communities, so as to have the greatest sustained impact on reducing new infections. (UNAIDS, 2010, p. 8)

According to the 2009 UNAIDS prevention reference group report, well-designed combination prevention programmes should be carefully tailored to national and local needs and conditions. Importantly, resources should be focused on a mix of programmatic and policy actions required to address both immediate risks and underlying vulnerability. In addition, they should be thoughtfully planned and managed to operate synergistically and consistently at multiple levels such as individual, relationship, community, and society levels over an adequate period of time. Furthermore, such programmes should mobilize the community, private sector, government and global resources in a collective undertaking, as well as require and benefit from enhanced partnership and coordination. Mechanisms for learning, capacity building and flexibility to permit continual improvement and adaptation to the changing environment are essential components of combination prevention programmes. (UNAIDS, 2010)

Obviously, combination prevention programmes are working; reflected in the declining new HIV infections rates (UNAIDS, 2016). It is projected that putting combination prevention programmes into practice will help ensure that HIV responses outpace the epidemic in every country, and will move the world closer to the UNAIDS' global vision to reduce new HIV infections to fewer than 500 000 globally by 2020 (United Nations, 2016).

1.2 The use of antiretroviral therapy to combat HIV epidemic

Among the strategies that have been deployed to combat the HIV epidemic, the introduction of combination antiretroviral therapy represents one of the most significant interventions that changed the landscape of HIV-related mortality (Montaner et al., 1998). Antiretroviral therapy substantially modified the natural history of HIV infection and changed it from an end of life event to a manageable chronic condition (Deeks, Lewin, & Havlir, 2013). In both high and low-income countries combination antiretroviral therapy has resulted in improved health,

prolongation of life and a significant reduction in the risk of HIV transmission (Deeks et al., 2013). The life expectancy of HIV-infected persons who are optimally treated is now measured in decades and may approach that observed in uninfected population (Johnson et al., 2013).

The global gains attributable to ART has been largely due to improved access to life-saving ART (UNAIDS, 2016). The UNAIDS 2016 global HIV/AIDS update indicates that access to ART has been on a fast-track trajectory with a steep rise in the number of people accessing life-saving antiretroviral therapy increased from below 5 million in 2000 to about 17million as of December 2015. As shown in Figure 1.3 below, after a peak in 2005, there has been a consistent decline in AIDS-related deaths corresponding to increased global access to ART. Available data suggest that the gains in treatment contributed significantly to about 26% decline in AIDS-related deaths globally since 2010, from an estimated 1.5 million in 2010 to 1.1 million in 2015 (UNAIDS, 2016). It has been suggested that with Advances in treatment and prevention, it is projected that expanded access to treatment in some settings could eventually lead to the elimination of HIV (Granich et al., 2015).

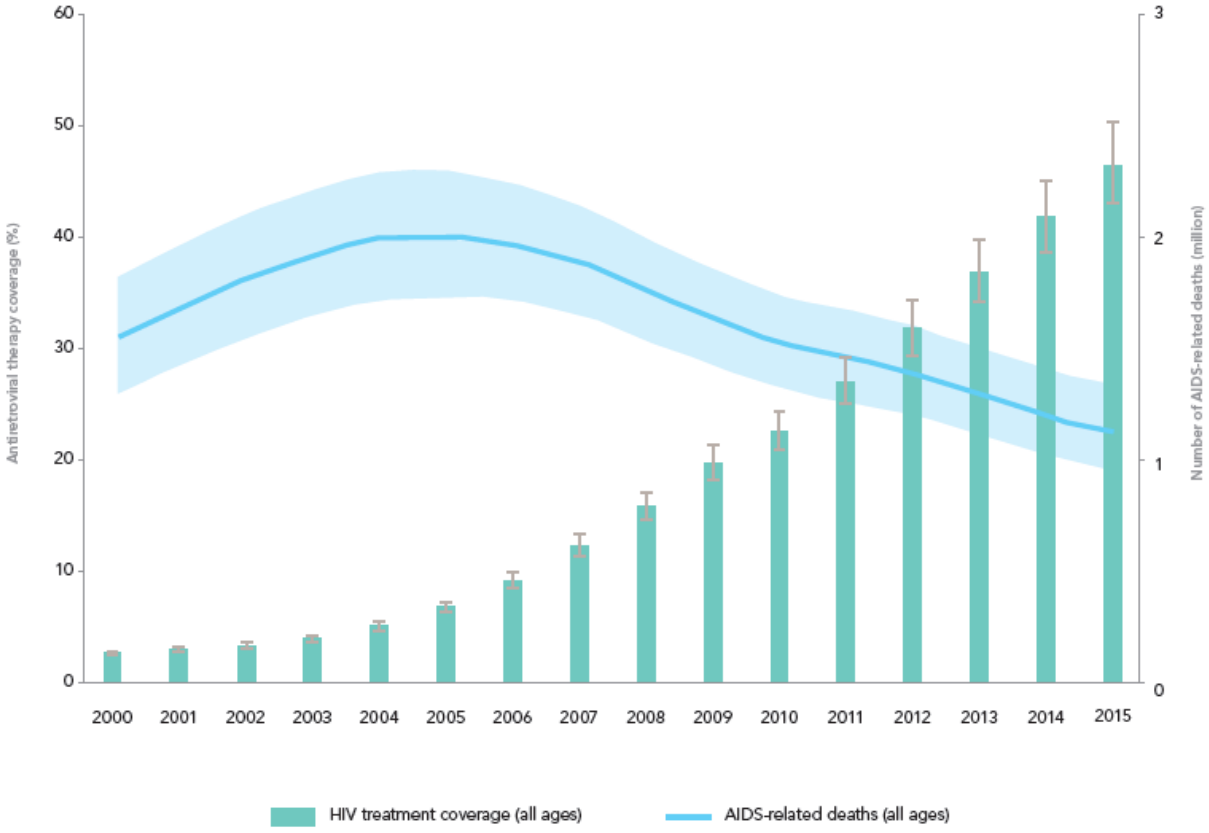


Figure 1.3: Antiretroviral therapy coverage and number of AIDS-related deaths, global, 2000–2015

Source: GARPR 2016; UNAIDS 2016 estimate: p5

Nigeria is not left out in the global response to HIV. The Nigerian National Agency for the Control of AIDS (NACA) 2015 estimates show that new infections declined by 24% within a decade from an estimated 316,733 in 2003 to 239,155 in 2013 and AIDS-related deaths declined by 17% from 210,031 deaths in 2013 to 174,253 in 2014 (National Agency for the Control of AIDS (NACA), 2015). According to the NACA, 2015 report, Nigeria has witnessed an upsurge in the number of HIV-infected persons accessing life-saving ART since 2002. Coverage of ART services increased from 25 health facilities in the year 2002 to 820 in 2013, and from 2009 to 2014, the number of persons receiving ART more than doubled, from 302,073 to 747 382, respectively.

1.2.1 Challenges of antiretroviral therapy

Despite the benefits of ART, it is not without challenges. The initial objectives of the introduction of combination antiretroviral therapy was focused on reduction in HIV-1-associated mortality and morbidity, but issues such as drug toxicity, resistance and compliance with treatment began to emerge as these objectives were being accomplished (Moreno et al., 2010; Murphy, Sunpath, Kuritzkes, Venter, & Gandhi, 2007). Adverse drug reactions (ADRs) associated with the use of ARVs can rapidly reverse the gains of ART resulting in poorer health outcomes (Syed, Sulaiman, Hassali, & Lee, 2015) and increased mortality (Keiser et al., 2007). Acute toxicities may lead to dose interruption and discontinuation of therapy. Some studies have reported treatment discontinuation rates ranging from 4% to 46% related to neuropsychiatric adverse effects of antiretroviral therapy (Bartlett, Chen, & Quinn, 2007; Spire, Carrieri, Garzot, L'henaff, & Obadia, 2004). Cumulative toxicities from exposure to antiretroviral drugs for decades may result in clinically relevant metabolic disturbances and end-organ damage (Johnson et al., 2013).

Antiretroviral therapy associated ADRs increases the cost (Rajesh, Vidyasagar, Muralidhar, & Guddattu, 2012) and complexity of managing HIV (Moreno et al., 2010). Direct costs associated with ADRs include the cost of treating ADRs, the cost of laboratory investigations, and cost of hospitalization stay (Rajesh et al., 2012). Other indirect costs such as disability, work productivity losses related to absenteeism and other financial costs are also associated with ADRs (Kingston-Riechers, 2011).

1.2.2 Risk factors for adverse drug reactions to antiretroviral therapy in developing countries

The burden of ART-associated ADRs seems to be higher in developing countries compared to developed countries (Subbaraman, Chaguturu, Mayer, Flanigan, & Kumarasamy, 2007). According to Subberaman et al. (2007), the reason for the disparity between developed and developing countries in the burden of ART-related ADRs are: 1) economic constraints which limit the repertoire of accessible antiretroviral medications to a handful older and more toxic agents responsible for most of the observed toxicity; 2) prohibitory laboratory monitoring costs

may delay the identification of specific toxicities, thereby increasing their severity; 3) high prevalence of comorbid conditions like anaemia, malnutrition, tuberculosis, initial presentation with advanced immunosuppression (Agaba et al., 2014); 4) concomitant antituberculosis therapy; 5) the use of herbal medications practices which may influence the incidence of adverse effects; and 6) genetic factors - which is an important factor in individual variability to drug response. For instance, the incidence of neuropsychiatric ADRs associated with the use of the antiretroviral drug efavirenz has been shown to be higher in African compared to Caucasians and Asian (Barrett et al., 2002; Pfister et al., 2003).

1.2.3 Prevalence of antiretroviral therapy-related adverse drug reactions

Adverse drug reactions to ART is common, with reported prevalences ranging from 30% to as high as 90% (Lartey et al., 2014; Shet et al., 2014; Subbaraman et al., 2007; Syed et al., 2015). Published reports on ART-related ADRs in Nigeria are sparse despite ADRs being common among patients on ART. The few available studies in Nigeria estimate the incidence of ART-related ADRs to be between 4.6% to 10.4% among individuals receiving ART (Abah, Akanbi, et al., 2015; Agu et al., 2013; Eluwa, Badru, & Akpoigbe, 2012; Reginald et al., 2012). A high prevalence of self-reported ADRs of 73% was documented among patients on ART in a Government health facility in Benin City (Balogun & Adeleye, 2014). However, this was a cross-sectional study based on patient-reported ADR and is limited in estimating the true prevalence of ADR in the setting. Although some studies suggest that acute toxicities associated with antiretroviral medicines may lead to dose interruption and discontinuation of therapy (Leutscher, Stecher, Storgaard, & Larsen, 2013; Prosperi et al., 2012) which is a risk factor for virologic failure (Keiser et al., 2007), reports on the association between ART-associated ADRs and virologic failure are sparse.

1.2.4 Global and national prevalence of virologic failure among patients on ART

The UNAIDS set an international goal for 2020 termed the "90–90–90 target," which aims to increase the number of persons living with HIV (PLWH) who know their serostatus to 90%; among those who are diagnosed, to increase the percentage who are prescribed ART to 90%; and for 90% of persons on ART to achieve and maintain viral suppression (UNAIDS, 2017). One of

the strategies to achieve the viral suppression target, apart from the promotion of adherence, is the use of an ART regimen that is well tolerated to promote maximal viral suppression and immune reconstitution (Margolis, Heverling, Pham, & Stolbach, 2014). Estimates of viral suppression rates after 12 months of antiretroviral therapy in low- and middle-income countries, depending on the HIV RNA thresh hold, range from 50% to as high as 90% (McMahon, Elliott, Bertagnolio, Kubiak, & Jordan, 2013). Data on HIV treatment cascade in Nigeria are scarce. One Nigerian study reported that only 50% of patients on standard care attained undetectable viral load of <400 copies per ml after one year of antiretroviral therapy (Taiwo et al., 2010). The low rate of viral suppression among patients on ART in Nigeria is a challenge which requires a critical evaluation to understand the factors that underpin poor treatment response to ART.

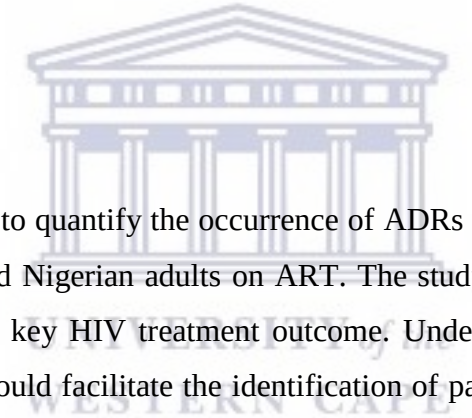
1.3 Research problem

In Nigeria and other sub-Saharan Africa countries, where limited medicine options are common due to limited resources and providers are constrained to operate with a limited formulary, ART regimen durability takes on an important role (Murphy et al., 2007). Failure of first-line ART regimens resulting from ADRs creates the need for more expensive and difficult-to-implement second-line regimens, often unaffordable in most resource-constrained countries who are largely donor dependent for their ART programs (Renaud-Théry et al., 2007). The initial ART regimen affords the best opportunity to attain maximal viral suppression. Despite the prevalent nature of ADRs among patients on ART and their negative impact on treatment outcomes, the impact of ADRs on HIV treatment outcomes including virologic failure among patients accessing ARVs at JUTH HIV clinic has not been fully explored. JUTH HIV clinic has one of the largest HIV treatment cohorts in Nigeria; with over 20,000 patients enrolled in care (Agaba et al., 2014). Previous studies that evaluated treatment outcomes among patients on first-line ART at JUTH HIV clinic showed a high level of treatment modification of 83% (Abah, et al., 2015), treatment discontinuation of 28% (Agbaji et al., 2015) and virologic failure of 49% (Taiwo et al., 2010) among patients receiving standard care. However, the impact of ADRs on virologic failure was not evaluated. The research questions for this study are: how common are ADRs due to ART in our study setting? What are the common types of ADRs? What are the risk factors for ART-related ADRs? What is the impact of ADRs on virologic failure? In summary, are patients who

experience an ADR at greater risk of virologic failure compared to those who do not experience an ADR?

1.4 The setting: a Federal Tertiary Healthcare Facility in Jos, North-central Nigeria

The study was carried out at JUTH HIV clinic; a Federal Tertiary Healthcare Facility located in the cosmopolitan city of Jos in North-central Nigeria. Jos University Teaching Hospital HIV clinic is an outpatient specialist clinic and is one of the largest HIV treatment centres providing comprehensive HIV care services in Nigeria. The clinic serves as a referral centre for health facilities within and outside Jos including local government areas of Plateau state and other states in the region. In the 2006 census, the population of Plateau State was 3,206,531, with the capital city of Jos having a population of approximately 900,000 (National Population Commission (NPC) Nigeria, 2006).



1.5 Study significance

The purpose of this study was to quantify the occurrence of ADRs and identify its risk factors in a clinic cohort of HIV-infected Nigerian adults on ART. The study also evaluated the effect of ADRs on viral suppression, a key HIV treatment outcome. Understanding the risk factors for ADRs in a given population could facilitate the identification of patients at risk of ADRs which could result in appropriate steps such as the use of alternative regimens or closer monitoring of patients for early detection and management of ADRs when they occur. This will contribute to the improved durability of first-line regimens (Perović-Mihanović et al., 2013). In addition, understanding the association between ADRs and viral suppression could be exploited in the rational selection of ARV regimens to achieve maximal and durable viral suppression as well as foster retention of patients on treatment (Perović-Mihanović et al., 2013). Furthermore, data derived from within the country or region may have greater relevance and educational value and may encourage national regulatory decision-making (World Health Organization (WHO), 2002).

CHAPTER 2

LITERATURE REVIEW

2.1 Principles of antiretroviral therapy

The discovery of antiviral drugs, which can suppress HIV-1 replication to undetectable levels has been the most significant advance in the medical management of HIV-1 infection (Arts & Hazuda, 2012). As described in Arts & Hazuda (2012), antiretroviral drugs act by interfering with the replication of the HIV-1 virus by different molecular mechanisms. Based on their molecular mechanism and resistance profiles they are distributed into six distinct classes: (1) nucleoside-analog reverse transcriptase inhibitors (NRTIs), (2) non–nucleoside reverse transcriptase inhibitors (NNRTIs), (3) integrase inhibitors (INSTI), (4) protease inhibitors (PIs), (5) fusion inhibitors, and (6) coreceptor antagonists.

The goal of ART includes the achievement of sustained virologic, immunologic, clinical, and epidemiologic control of HIV (World Health Organization (WHO), 2016b). It is expected that under optimal conditions, the use of ART should lead to rapid and sustained suppression of viral load down to < 400 copies /ml after 24 weeks and <50 copies/ml after 48 weeks of initiation of therapy (Federal Ministry of Health Abuja, 2016). With effective ART immune functions recovery is expected; with a progressive increase in CD4+ cell count at a rate of 50 to 100 cells/µL /year. Additionally, there should be a significant improvement in clinical outcomes with reduced occurrence of morbid conditions and improved clinical indices (Federal Ministry of Health Abuja, 2016).

The World Health Organization (WHO) approach to ART recommends the use of less toxic, more convenient and simplified ARV regimens, with a limited number of preferred first-line options that may be used across a range of populations (World Health Organization (WHO), 2016). According to the WHO consolidated ART treatment guidelines for adults and adolescents, first-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI) (World Health Organization (WHO), 2016). The guidelines recommend efavirenz (EFV) + tenofovir (TDF) + either lamivudine (3TC) or emtricitabine (FTC) as a fixed-dose

combination as the preferred option to initiate ART (World Health Organization (WHO), 2016). WHO 2016 consolidated ART treatment guidelines for adults and adolescents also recommends that ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count. However, as a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count=350 cells/mm^3.

2.2 Nigeria ART treatment guidelines

In March 2017, the government of Nigeria adopted the WHO 2016 ART treatment guidelines for adults and adolescents. The key recommendations of the Nigerian ART guidelines 2016 (Federal Ministry of Health Abuja, 2016) are summarized in Table 1.1 below. They include initiation of ART in all persons who test positive for HIV including children, adolescents, adults, pregnant and breastfeeding women, regardless of clinical and immunological stages of the disease. Other recommendations in the new guidelines cover the retesting of patients prior to initiation of ART, adoption of pre-exposure prophylaxis for individuals at high risk of acquiring the infection and addition of dolutegravir, efavirenz 400 mg and darunavir/ritonavir to the pool of approved antiretroviral drugs.

Table 2.1: Key recommendations of the Nigerian national guidelines for HIV prevention, treatment and care 2016

Target population	Recommendations
What is new for HIV-positive adults and adolescents	• Initiate ART in all adults and adolescents with a diagnosis of HIV. This is regardless of the clinical stage of the disease and also regardless of CD4+ cell count. • Dolutegravir (DTG) and Efavirenz (EFV) 400mg are new alternative options in first-line ART regimens.
What is new for HIV-positive pregnant and breastfeeding women.	• Initiation of ART for all HIV-positive and pregnant, post-partum and breastfeeding women, regardless of CD4+ cell count • Use of maternal ART throughout pregnancy and breastfeeding to reduce MTCT. This ART treatment is for life • Repeat HIV testing for HIV-negative pregnant women in the last trimester • Viral load testing for pregnant women in the last trimester of pregnancy
What is new for HIV-exposed infants	• Infants born to mothers with HIV who are at high risk of acquiring HIV should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life, whether they are breastfed or formula fed • Breastfed infants who are at high risk of acquiring HIV, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis)
What is new in prevention	Pre-exposure prophylaxis is recommended for most at risk persons with special emphasis on serodiscordant couples and key populations

Source: (Federal Ministry of Health Abuja, 2016, p. 43)

2.2.1 Recommended ART Regimen for Adults, Adolescents and Children

According to the Nigerian ART guidelines 2016 (Federal Ministry of Health Abuja, 2016), ART regimens are generally classified as first, second and third line. The first line regimens are used

in ARV-naive patients while second and third line regimens are used in individuals who have failed first and second line regimens respectively. Summary of antiretroviral regimen recommendations in the 2016 Nigerian ART guidelines is presented in Table 2.2 below.

Table 2.2: Recommended first-line ART regimens for adults, adolescents, pregnant, breastfeeding women and children based on Nigerian 2016 ART guidelines

First-line ART	Preferred first-line regimen	Alternative first-line regimens
Adults	TDF + 3TC (or FTC) +EFV	• TDF + 3TC (or FTC) + *DTG • AZT + 3TC + NVP (or EFV) • TDF + 3TC (or FTC) + *EFV400 • ABC +3TC +EFV • TDF + 3TC (or FTC) + NVP
Pregnant/breastfeeding women	TDF + 3TC (or FTC) +EFV	• AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents (10-19 years)	TDF + 3TC (or FTC) +EFV	• TDF + 3TC (or FTC) + *DTG • TDF + 3TC (or FTC) + EFV400 • AZT + 3TC + NVP or EFV • ABC + 3TC (or FTC) + *DTG • ABC + 3TC + (or FTC) +*EFV400 • TDF + 3TC (or FTC) + NVP • ABC + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	• ABC + 3TC + NVP • AZT + 3TC + EFV (or NVP) • TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC + 3TC + LPV/r AZT+3TC+LPV/r	• ABC + 3TC + NVP • AZT + 3TC + NVP • AZT+3TC+RAL

TDF, tenofovir; 3TC, lamivudine; FTC, emtricitabine; EFV, efavirenz 600mg; EFV400, efavirenz 400mg, DTG, dolutegravir; NVP, nevirapine;ABC, abacavir; LPV/r,lopinavir/ritonavir; RAL, raltegravir

Source: (Federal Ministry of Health Abuja, 2016, p. 47)

2.3 Pharmacovigilance of antiretroviral medicines in low and middle-income countries

It is now required that pharmacovigilance should be an integral part of every public health programme that uses medicines in order to optimize the use of scarce health resources and prevent potential medicine related harm (World Health Organization (WHO), 2006). Pharmacovigilance is defined as *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems"* (World Health Organization (WHO), 2006, p. 7). The major aim of pharmacovigilance is to safeguard public health by identifying medicine related risks and the risk factors in the shortest possible time so that harm can be avoided or minimized. When such information is communicated effectively, it can be utilized for the intelligent, evidence-based use of medicines and has the potential for preventing many adverse reactions.

The use of antiretroviral medicines (ARVs) is associated with significant safety concerns including serious ADRs, with both short- and long-term effects. The practice of pharmacovigilance is well-established in most high-income countries, such as the United States' Food and Drug Administration (FDA) Adverse Event Reporting System (U.S. Department of Health and Human Services. U.S. Food and Drug Administration (FDA), 2014) but the practice is limited and variable in low and middle-income countries (Strengthening Pharmaceutical Systems Program, 2011). The need for a robust pharmacovigilance system is particularly important in settings of rapid scale-up of new medications, as is the case of ART scale-up across many resource-limited settings, which has mostly involved the use of generic ART drug combinations that are not available in well-resourced settings (Gilks et al., 2006; Rosen, Fox, & Gill, 2007). Other conditions and factors in in low and middle-income countries which increase the safety concerns of ARVs *"include the existence of comorbid conditions such as a high prevalence of tuberculosis (TB), malaria and other infections of all types; malnutrition; reliance on traditional and/or alternative therapies; insufficient numbers of trained doctors and pharmacists; irrational use of prescription medicines; and likelihood of medicine interactions"* (Coulter, 2013, p. 4). Furthermore, due to shortage of trained manpower, some local systems for the delivery of healthcare may rely on people who have limited training, knowledge or expertise. Additionally, medicine regulatory systems in some low and middle-income countries are either

rudimentary or non-existent and are not adequately equipped to deal with medicine safety issues (Coulter, 2013).

2.4 Pharmacovigilance of antiretroviral medicines in Nigeria

An overview of pharmacovigilance activities in Nigeria as documented in the Global HIV/AIDS Initiative Nigeria (GHAIN) pharmacovigilance training manual (HUCE/PACE & NAFDAC, 2009) indicates that the history of pharmacovigilance in Nigeria dates back to 1981. This essentially was the training of some staff of the federal ministry of health in pharmacovigilance at Uppsala Monitoring Centre (UMC) in Sweden. After that, some pockets of pharmacovigilance activity started in 1996; albeit on a very weak starting. In Sept 2004, the National Pharmacovigilance Centre (NPC), NAFDAC Nigeria was granted full membership as a 74th member country of the WHO International Drug Safety Monitoring Programme.

There is a huge gap in drug safety reporting, including on ARVs, in Nigeria. For instance, between 2004 and 2009, the Nigerian NPC received only 879 individual case reports, of which 78 (8.9%) were attributable to antiretroviral medicines. The Uppsala Monitoring Centre indicates that adequate reporting translates to 200 reports/million inhabitants/year. For Nigeria, this means that in any given year, we would expect to get 28,000 individual case reports but this is not the case (HUCE/PACE & NAFDAC, 2009).

Recently, however, there has been an improvement in ADRs reporting due increase awareness created by NAFDAC and the involvement of public health programmes such as antiretroviral programmes in ADR reporting. A recent report on the patterns of adverse drug reaction signals in the Nigerian National Agency for Food, Drug, Administration and Control (NAFDAC) pharmacovigilance activities from September to November 2014 showed that a total of 100 individual case safety reports were received within a period of three months. Out of this ART-associated ADRs accounted for 24.3% of the case reports; which is a pointer that ART centres have been alerted to report ADRs in addition to suggesting that ADRs are common among patients on ART in Nigeria (Awodele, Ibrahim, & Orhii, 2016). This report brings to the fore the need to strengthen pharmacovigilance activities in antiretroviral programmes in Nigeria.

2.5 Specific adverse drug reaction reported with combination antiretroviral therapy

Antiretroviral medicines (ARV), like most pharmaceutical agents, can result in ADRs that in some cases may be severe or life-threatening, especially if they are not recognized and managed on time (Mouton et al., 2015; Shet et al., 2014). Adverse drug reaction to ART are common and may occur immediately (soon after an antiretroviral medicine has been administered), early (within the first days or weeks of treatment) or late (after months of treatment), and vary in severity from mild to severe to life-threatening (Hawkins, 2010; Tadesse, Mekonnen, Tesfaye, & Tadesse, 2014). An ADR may be specific to the medicine or generic to the class of medicines used on a patient (Hawkins, 2010). The spectrum of ADRs according to the medicine classes are described below.

2.5.1 Nucleoside Reverse-Transcriptase Inhibitors (NRTIs) related ADRs

The majority of adverse events (AE) associated with NRTIs are due to mitochondrial toxicity with differences in the ability of different NRTIs to affect mitochondrial function (Subbaraman et al., 2007). Stavudine (d4T) and didanosine (ddI) are worse than zidovudine (AZT) while lamivudine (3TC) and abacavir (ABC) have the least toxicity of all (Subbaraman et al., 2007). Mitochondrial toxicities result in high rates of peripheral neuropathy, lipoatrophy, lactic acidosis, and pancreatitis (Subbaraman et al., 2007). The prevalence of these adverse events are presented below.

***Peripheral neuropathy (PN)*:** This is a distal sensory neuropathy resulting from decreased mitochondrial function (Calmy, Hirschel, Cooper, & Carr, 2009). About 10% to 21% of persons exposed to d4T developed peripheral neuropathy in developed countries (Van-Oosterhout et al., 2005). However, 56% of patients in a Malawian cohort developed peripheral neuropathy while receiving d4T therapy (Van-Oosterhout et al., 2005). A PN prevalence of 63% was reported among patients on first-line ART in Zimbabwe (Nemaura et al., 2012), while studies in Nigeria reported prevalence ranging from 12.7% to 30% (Agu et al., 2013; Bassi et al., 2017; Eluwa et al., 2012). Symptoms usually resolve after prompt discontinuation of d4T therapy but may be persistent in a subset of patients. Currently, d4T is not recommended as part of the first line

regimen (World Health Organization (WHO), 2016b).

***Lipodystrophy and metabolic complications*:** Lipoatrophy is characterized by loss of subcutaneous fat in the extremities, buttocks, and face (Murphy, Sunpath, Kuritzkes, Venter, & Gandhi, 2007). Although AZT sometimes causes lipodystrophy, d4T is more strongly associated with this adverse effect (Subbaraman et al., 2007). Prevalence of d4T-associated lipodystrophy as high as 50% to 63% has been reported in western studies (Subbaraman et al., 2007). African studies have reported lower prevalence: 0.8% in a Nigeria cohort (Agu et al., 2013), 24.8% of patients in a Rwandan cohort (Van-Griensven et al., 2010), and 38% in Zimbabwe (Nemaura et al., 2012). The diagnosis of stavudine-associated lipodystrophy might be complicated by malnutrition which commonly presents as lipoatrophy (i.e., fat loss in the cheeks, arms, and buttocks) (Murphy et al., 2007).

Lactic acidosis: Lactic acidosis is a rare (0.85 – 2.7 per 1,000 person-years) but life-threatening condition, which clinically manifests as subacute onset of nausea, fatigue, weight loss, abdominal pain, dyspnoea and eventual circulatory collapse (Calmy et al., 2009). Rates as high as 20% have been described in southern Africa (Wester et al., 2007). Factors associated with lactic acidosis are older age, female sex, high body mass index, lipoatrophy, low CD4 and T-cell count, hypertriglyceridemia and use of d4T and ddi; although this AE has been described with all NRTIs except ABC (Bonnet et al., 2005; Wester et al., 2007).

***Myelosuppression*:** Anemia is an important early AE primarily associated with AZT-containing regimens and typically develops in the first six months of therapy and can be severe, particularly when AZT is introduced in individuals with advanced immunosuppression (Murphy et al., 2007). Studies from Coˆte d'Ivoire, Haiti, and India have found rates of AZT-related anaemia of 3% – 12% (Subbaraman et al., 2007). In Nigeria, the reported prevalence ranged from 2.2% to 7% among patients on first-line ART (Agu et al., 2013; Reginald et al., 2012). Risk factors for anaemia include high AZT dosage, increased treatment duration, low CD4 cell count, and preexisting anaemia (Murphy et al., 2007).

2.5.2 Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) related ADR

Toxic effects frequently associated with NNRTIs such as nevirapine (NVP) and efavirenz (EFV) include hypersensitivity reaction, hepatotoxicity, neuropsychiatric disorders and immune reconstitution syndrome (Subbaraman et al., 2007).

***Hypersensitivity reaction*:** most commonly reported with NVP and may be characterized by a rash, fever, symptomatic hepatitis, and eosinophilia (Murphy et al., 2007). This AE most commonly occurs in the first 16 weeks of therapy and can occasionally progress to fulminant, fatal liver failure (Murphy et al., 2007). Risk factors for hypersensitivity reaction include a high baseline CD4 cell count of >250 cells/mm^3 as well as female sex (Murphy et al., 2007). Prevalence of the hypersensitivity rash of between 3% to 26% has been reported in studies from developed and developing countries (Subbaraman et al., 2007). The reported prevalence in Nigerian cohorts ranged from 16% to 26% (Agu et al., 2013; Eluwa et al., 2012; Reginald et al., 2012).

***Hepatotoxicity*:** this is characterized by transaminase level elevation and symptomatic hepatitis and is most frequently associated with NVP than EFV (Murphy et al., 2007; Sanne et al., 2005). Incidence of drug-related hepatitis in the United States (US) and European studies ranges from 1% to 10% (Pollard, Robinson, & Dransfield, 1998; Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, 2003), while a higher incidence of 17% was reported in a South African study (Sanne et al., 2005). The incidence of hepatotoxicity in Nigerian patients is poorly described but a study reported a jaundice prevalence of 4% (Reginald et al., 2012).

Neuropsychiatric disorder: Neuropsychiatric disorders including psychosis-like behavior, suicide, severe delusions, dizziness, insomnia, impaired concentration, irritability, nervousness, somnolence, abnormal dreams, and hallucinations are usually classified as CNS symptoms are the most common and significant adverse effects associated with EFV therapy (Abah et al., 2015; Subbaraman et al., 2007). In US and European cohorts, 50% of patients have neuropsychiatric symptoms after initiating EFV therapy, but these symptoms usually resolve within one month (Subbaraman et al., 2007). A study from Cote d'Ivoire found a high neurotoxicity rate of 69% after initiation of therapy with EFV (Danel et al., 2003), while the

incidence rate in a Nigerian study was 30 per 1000 person-years of ART (Abah et al., 2015). Risk factor for EFV-related neurotoxicity includes female gender, age < 40 years, advanced HIV disease (WHO stage 3 or 4 diseases), and use of EFV with AZT or d4T (Abah et al., 2015). Some studies suggest that people of African ancestry with a variant of hepatic enzyme CYP2B6 may experience slower clearance of EFV from plasma and increased neurotoxicity (Barrett et al., 2002; Haas et al., 2004; Pfister et al., 2003; Sarfo et al., 2014).

2.6 Effect of adverse drug reactions on key HIV treatment outcomes

2.6.1 Adverse drug reactions and medication adherence

A sufficiently high level of adherence (>90%) to combination antiretroviral therapy is required to achieve and sustain viral suppression and to prevent disease progression and death in HIV-infected patients (Bangsberg et al., 2000; Lucas et al., 1999; Oreagba et al., 2014; Paterson et al., 2000). Studies have shown that achieving and sustaining the high level of adherence required for optimal virologic control is a major challenge to many HIV-infected patients (Adeyemi, Olaogun, & Adesola, 2008; Bärnighausen et al., 2011; Monjok, Smesny, Okokon, Mgbere, & Essien, 2010; Ostrop, Hallett, & Gill, 2000). Medication side effect has been consistently reported in several studies as one of the factors that negatively impact on treatment adherence (Shet et al., 2014; Syed et al., 2015; Tadesse et al., 2014). Although Nigerian studies on the effect of ADRs on treatment adherence are scarce, in one Nigerian study, 76% of patients indicated medication side effect as reasons for not taking their medication (Uzochukwu et al., 2009).

2.6.2 Adverse drug reaction and regimen modification/discontinuation

In resource-limited settings, regimen durability is critical to treatment success due to limited treatment options (Murphy et al., 2007). A study conducted at Jos University Teaching Hospital ART Centre reported a high rate of regimen modification of 83% and a significant association between regimen modification and ADRs (Abah, et al., 2015). In another study at the same hospital, drug toxicity/side was the most frequent (34%) reason for modification of first-line regimen (Falang et al., 2008). In agreement with the finding of Falang et al., 2008, several other

studies have reported ADRs as the most frequent reason for regimen modification/discontinuation among patients on combination antiretroviral therapy. The proportion of regimen modification /discontinuation due to ADRs was 27% in south Indian adults (Sivadasan et al., 2009), 30% in Ethiopians (Teklay, 2013), 60% among Scandinavians (Leutscher, Stecher, Storgaard, & Larsen, 2013), 66% in Western Kenya (Inzaule et al., 2014), and as high as 95% in Rio de Janeiro, Brazil (Torres, Cardoso, Velasque, Veloso, & Grinsztejn, 2014). What is not very clear from these studies is the impact of the regimen modification on virologic outcomes.

2.6.3 Adverse drug reactions and virological failure

One of the goals of ART is to achieve maximal and durable viral suppression. Attaining an undetectable viral load is a major indicator of treatment success. The WHO recommends viral load testing as the preferred monitoring approach to diagnose and confirm ARV treatment failure (World Health Organization (WHO), 2016). In an earlier single institutional Nigerian study, Taiwo et al (2010) found that up to 50% of patients do not achieve undetectable viral load in one year of ART. In contrast to the earlier Nigerian study (Taiwo et al., 2010), a recent multicenter cohort study involving 70,002 patients in Nigeria reported that a high proportion (85%) of patients on ART achieved viral suppression (Meloni et al., 2016), with 69% of the patients achieving suppression within six months of ART. The differences in the viral suppression rates reported across different studies in Nigeria highlights the importance of continuous monitoring of virologic outcome in a cohort of patients on ART, as the virologic success rates might change over time and may be influenced by several factors. The impact of ADRs on viral suppression is poorly described in the literature. This is despite that ADRs is a significant prognostic factor for poor adherence; an independent predictor of virologic failure. An Indian study evaluated the effect of ADR on treatment success among Indians and found no significant association between the occurrence of severe ADR and the attainment of undetectable viral load at 12 and 24 months of ART (Shet et al., 2014). However, the study did not evaluate the effect of mild ADRs on viral suppression, despite that mild ADRs were very common in the study. The relationship between ADRs and viral suppression has not been sufficiently described and requires further exploration. This is particularly important considering the high proportion of patients on ART who

experience an ADR as described above.

2.6.4 Prevention and management of adverse effects of antiretroviral therapy

Available evidence already described above shows that adverse events are common with all available antiretroviral agents. Therefore, it is critical to anticipate, recognize, and manage them promptly when providing primary care for HIV-infected patients to mitigate the possibility of negative outcomes. Patients should be informed of potential side effects during consideration of the first regimen, and possible management strategies in case of adverse events. Known profile of adverse events associated with ARV medicines should be considered in the initial treatment decision. For instance, if the medication is associated with CNS side effects which may impact psychomotor function, as in the case of EFV, it may be risky to initiate patients whose job demand high mental alertness on the medicine. Also, medications associated with a high risk of diarrhoea may not be the best option for patients who are experiencing diarrhoea or HIV-related wasting. Considering the impact of ADRs on medication adherence and the unforgiving nature of HIV infection with regards to adherence, it is essential to establish the patient's readiness for HAART before the first prescription, including knowledge of, and treatment for possible adverse events (Max & Sherer, 2000). Similarly, adherence is not a "one-shot" problem and ADRs can occur anytime in the course of therapy; repeated monitoring, education, and interventions are therefore required throughout the period of ART (Max & Sherer, 2000).

2.6.5 Conceptual framework for studying effect of adverse effects on virologic failure

Available evidence suggests that acute and chronic toxicities associated with antiretroviral medicines may lead to dose interruption and discontinuation of therapy (Leutscher et al., 2013; Prosperi et al., 2012). Poor adherence to treatment and treatment discontinuation are risk factors for treatment failure, and development and selection of drug-resistant virus (Keiser et al., 2007). The development of drug resistance has public health implications of transmission of drug-resistant HIV viruses and the need to implement treatment with much more expensive second-line and salvage therapies. This could be a major threat to ART programme success and sustainability in sub-Saharan Africa where most of the programmes are donor dependent (Keiser et al., 2007; Max & Sherer, 2000; Moreno et al., 2010). Drug refill adherence was used as a proxy for medication intake in this study since poor adherence to therapy is on the causal pathway of virologic failure.

Although it is expected that poor adherence due to ART-associated ADRs would result in poor viral response owing to the significant prognostic effect of poor adherence on treatment failure, studies on the impact of ADRs on viral outcomes are scarce. Key factors to be considered while studying the magnitude of ADRs and the association between ADRs and virologic failure are shown in the conceptual framework in Figure 2.1 below.

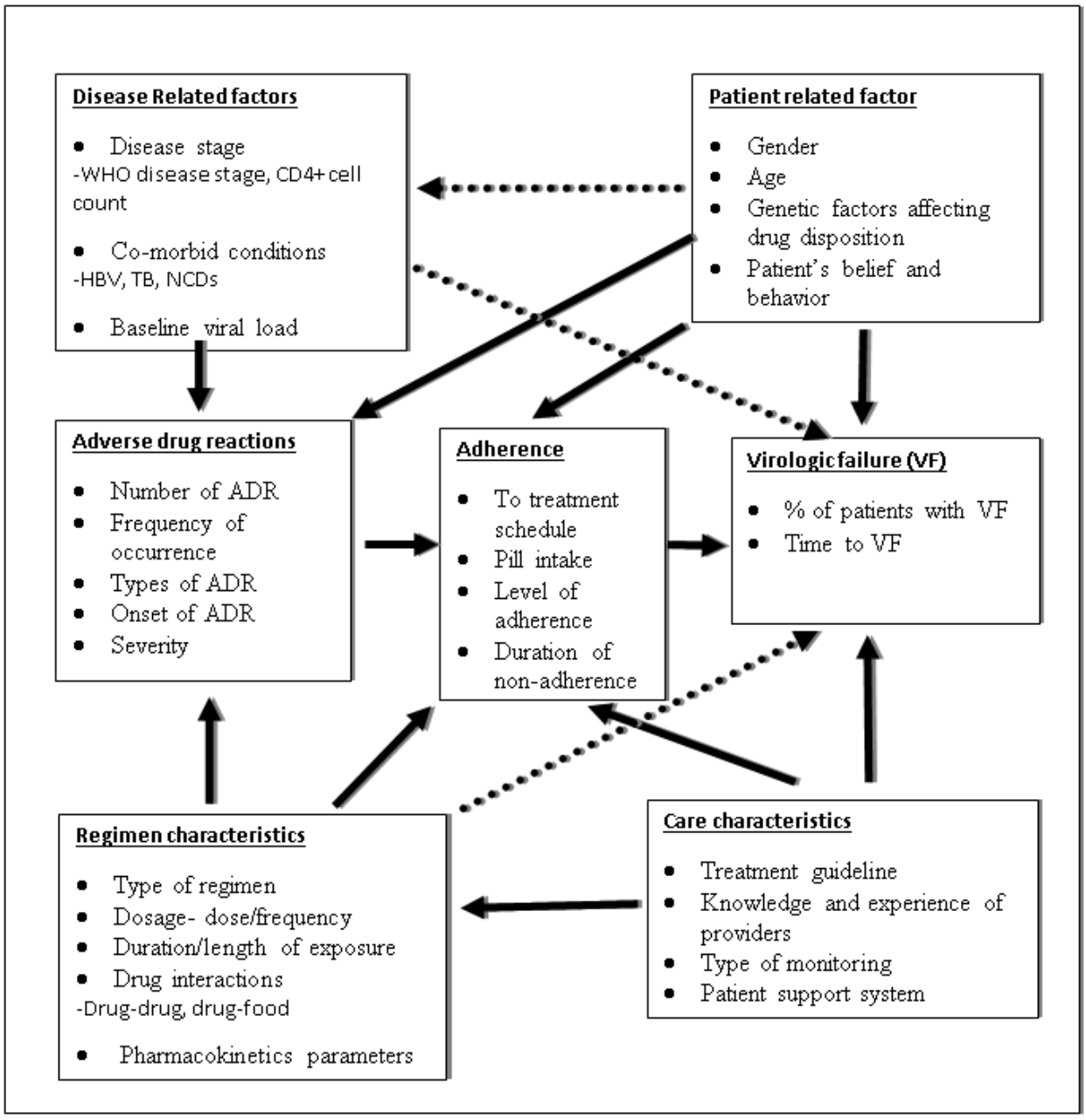


Figure 2.1: Conceptual framework for studying antiretroviral medicine related ADR and its effect on virologic failure

In conclusion, ADRs related to ART are common; however, the magnitude of ADRs and their impact on treatment success particularly durable or sustained viral suppression in patients on ART in Nigeria have not been fully explored. This study utilized longitudinal data to describe the incidence and spectrums of ADRs associated ARVs and evaluate the impact of ADRs on the achievement of sustained HIV suppression.

CHAPTER 3

AIMS AND OBJECTIVES

3.1 Aims

The aim of the research was to describe the frequency, types, and risk factors for clinical ADRs due to ART, and to assess the effect of ADRs on virologic failure among patients on ART at Jos University Teaching Hospital (JUTH) HIV Clinic.

3.2 Objectives:

1. To describe the incidence of clinical ADRs in a clinic cohort of adults on ART at the study site
2. To describe the types of clinical ADRs among adults on ART at the study site
3. To assess the association between patients' pre-ART demographic, clinical, and regimen characteristics and the risk of clinical ADRs due to ART
4. To identify baseline demographics, clinical, and regimen characteristics that independently predict the risk of virologic failure among patients on ART
5. To measure the likelihood of developing virologic failure in patients who experience clinical ADRs due to ARVs

CHAPTER 4

METHODOLOGY

4.1 Study design

A retrospective cohort study design was utilized to address the study aim. Utilizing longitudinal data stored in an electronic medical record system, it was possible to describe the incidence rate and profile of ARV medicine-related clinical adverse reactions in our patient cohort as well as retrospectively assess the risk factors for ADRs. The use of retrospective data also made it possible to examine the association between two time-varying variables such as ADR and virologic failure. The chosen approach offered the advantage of being cheap and quick to implement, as data had already been collected. Also, it was more efficient for measuring time-varying exposures such as ADRs and outcomes like virologic failure with variable induction and latency periods. Additionally, the study design was suitable for studying rare exposures and outcomes. Furthermore, the design made it possible to study a large number of participants and with a long history of follow up (Bonita, Beaglehole, & Kjellström, 2006). The introduction of an electronic medical record system at the study site in 2004 resulted in significant improvements in the quality of data which was used to address the research questions.

4.2 Study Setting

Jos University Teaching Hospital (JUTH) is a Federal Tertiary Healthcare Facility located in the cosmopolitan city of Jos in North-central Nigeria. The HIV treatment facility was established by the Federal Government of Nigeria in January 2002 as part of an expanded response to care and support for people living with HIV (PLWHA) (National Agency for the Control of AIDS (NACA), 2014). Rapid scale-up of ART services at JUTH started in 2004 through collaboration between JUTH, the University of Jos and the Harvard School of Public Health (HSPH)/AIDS Prevention Initiative in Nigeria (APIN) program, which was supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) grant.

Services at JUTH adult HIV clinic are provided by a complement of over 100 health and non-health professionals including doctors, pharmacists, nurses, laboratory scientists, dieticians, medical social workers. Non-health professionals include administrative officers, accountants,

secretaries, clerks, and cleaners. Services provided at the clinic include HIV counselling and testing, prevention of mother to child transmission of HIV (PMTCT), paediatric HIV care, and treatment and support for PLWHAs. At the time of this study, all services including clinical, pharmacy and laboratory services are offered free to patients.

4.3 Study population

The study population included HIV-infected adults ≥18 years of age accessing treatment at the treatment site between June 2004 and February 2012. The clinic population was drawn mostly from the North Central geopolitical zone of Nigeria and included various tribes and socio-economic strata in the society. Also, the cosmopolitan nature of Jos makes the population reflect the various ethnic nationalities in Nigeria.

***Inclusion criteria*:** HIV-infected patients' ≥18 years of age who were enrolled in the HSPH/APIN program, treatment naïve at enrolment and receiving first-line ART at JUTH for a minimum of 12 months' duration between June 2004 and February 2012. The starting period of June 2004 was chosen as the study starting point as it coincides with the introduction of electronic medical record in the treatment program, while February 2012 was used as the study endpoint because it marked a major transition period of transition in the HIV treatment program at JUTH. Hence, the study period of June 2004 and February 2012 assured access to usable and accurate data. Treatment naïve patients on first-line therapy were included as the initial ART regimen affords the best opportunity to attain maximal viral suppression (Asboe et al., 2012; Booth et al., 2014).

Exclusion criteria: Those who picked up ARVs only once at the pharmacy and those with insufficient baseline data such as missing the first ARV dispensing date were excluded.

4.4 Sample size

A total of 12,115 patients who met the inclusion criteria were included in the study. The availability of an electronic medical record system made it possible to select eligible participants.

4.5 Sampling procedure

All patients enrolled in care at the study site who met the inclusion criteria were included in the analyses. For ART-naïve patients, eligibility for ART in the HIV treatment program followed the Nigerian National Guidelines (Federal Ministry of Health (FMoH) [Nigeria], 2010; Federal Ministry of Health (FMoH) Nigeria, 2007) which closely mirrored the World Health Organization (WHO) Guidelines at the time of patient enrollment (Gilks et al., 2006; World Health Organization (WHO), 2010, 2013, 2016b). Beginning in 2004, patients were considered eligible for ART if their CD4+ cell counts dropped below 200 cells/mm^3 or if symptomatic with CD4+ cell counts below 350 cells/mm^3; from 2010 CD4+ cell counts eligibility was below 350 cells/mm^3 regardless of symptoms. The first line therapy was based on the Nigerian National Adult ART Guidelines (Federal Ministry of Health (FMoH) Nigeria, 2007, 2010) and involves combination antiretroviral therapy consisting of two nucleoside backbone of either AZT (AZT)/lamivudine (3TC), stavudine (d4T)/3TC, ABC (ABC)/3TC, (DDI)/3TC or Tenofovir (TDF)/3TC in combination with either NVP or efavirenz (EFV).

4.6 Data collection and processing

Patients' demographic, clinical, laboratory and prescription records were maintained in an electronic database developed for use in the HSPH/APIN program (FileMaker Pro, v10; FileMaker, Inc, Santa Clara, California, USA). The facility data manager carried out the data extraction with the aid of a data extraction form (Appendix I). A data extraction form was utilized to ensure that data on all required variables were extracted. The extracted data were exported to Microsoft Excel for data cleaning.

Independent variables (exposure): baseline or pre-treatment demographic (age, sex, education, employment status, marital status, and enrollment year), clinical (ART regimen, WHO clinical stage, TB co-infection, HBV and/or HCV co-infection, CD4+ cell count, viral load), adverse drug reactions, and drug refill adherence.

CD4 cell count, viral load data were obtained at baseline and at 24, 48, and 72 weeks of ART, while adherence was measured at 24, 48, and 72 weeks of ART. Age, CD4 cell count, viral load,

duration of ART, adherence to drug refill schedules were measured on a continuous scale. Duration of ART was determined from the first ARV dispensing date and the date of last drug refill, while adherence to ART determined using drug refill adherence. Drug refill adherence was calculated automatically by a computerized pharmacy appointment system which utilized the total number of days that the patient was behind for the drug- refill visits. Percentage of cumulative adherence was estimated by the following formula: The total number of days behind schedule divided by the total number of days the patient was assumed to be exposed to ART given the dispensed number of pills multiplied by 100 (Abah et al., 2014; El-Khatib et al., 2011).

Dependent variables (outcome): The main outcome measure was virologic failure defined as plasma viral load above 1000 copies/mL based on 2 consecutive viral load measurements after 6 to 12 months of ART initiation (World Health Organization (WHO), 2016). Viral load is the recommended preferred monitoring approach to diagnose and confirm treatment failure in patients on ART (World Health Organization (WHO), 2016). To evaluate the risk factors for ADRs, clinical ADRs will also be treated as an outcome measure.

Definitions of exposures and outcomes

Adverse drug reactions (ADRs)- defined as clinical ADRs documented on the ADR report form or toxicity form using International Classification of Diseases 10 (ICD-10) classification for ADRs (Hohl, Karpov, Reddekopp, & Stausberg, 2014). If a clinical ADR was identified, clinicians completed a program-specific toxicity form, which included detailed information about the suspected medication-related toxicity. The toxicity form contains an extensive checklist of symptoms categorized by body system. ADRs were graded on a four-point scale using the WHO severity grading (World Health Organization (WHO), 2005); Grade 1 was classified as “mild” and no limitation of daily activities; Grade 2 classified as “moderate” with mild to moderate limitation of activities; Grade 3 classified as “severe” with marked limitation of activities and Grade 4 classified as “life-threatening” with extreme limitation of activities and significant medical intervention.

Baseline: the time of ART initiation. Baseline clinical assessments or laboratory evaluations for naïve patients were the closest measurements to, and up to six months before or 0.5 months after, their first ART pick-up date.

Early virologic failure: for the purpose of this study, early virologic failure was defined as having an HIV viral load of >1000 copies/Ml after ≥6 months (24 weeks) of ART (Federal Ministry of Health Abuja, 2016).

Late virologic failure: for the purpose of this study, late virologic failure was defined as having an HIV viral load of >1000 copies/Ml after ≥ 18 months (72 weeks) of ART

4.7 Data analysis

Descriptive analyses, including frequencies and proportions, were reported for categorical variables. An initial exploratory analysis of continuous variables was conducted to examine their distribution. Normally distributed continuous variable such as age was reported as mean with standard deviation, while CD4 cell count and viral load which were skewed were reported as median with interquartile range (IQR). To calculate the incident rate of ADRs, patients were censored at the first occurrence of an ADR, discontinuation of ART (defined as failure to pick ARV for any reason for duration ≥12 months) or the end of the observation period, defined as the end of February 2012. The incidence rate of ADRs was determined by dividing the number of incident events by the total observation time contributed by patients. Each patient contributed observation time from baseline (defined as the start date of ART) to censor date. The total time of observation contributed by each patient was summed up to obtain the total person-years of observation. Bivariate analysis of factors associated with ADRs was performed using Pearson Chi-Square. For the bivariate analysis, age, CD4 cell count, and viral load were categorized. Age was categorized based on age quartiles, CD4 cell count based on WHO immunological disease staging (Gilks et al., 2006; World Health Organization (WHO), 2010, 2013, 2016b), while viral load was categorized according to a strata used in a previous study in a similar setting (Meloni et al., 2016). Baseline characteristics that were significantly associated with ADRs in the bivariate analysis ($p < 0.05$), as well as those that are clinically relevant or have biological plausibility to affect ADRs, were included in a multivariable logistic regression model to identify independent predictors ADRs. Age was included in the model as a continuous variable. A multivariable

logistic regression model was used instead of a time to event analysis to assess independent predictors of ADRs due to the limitations of the study design; the study is not a well-controlled longitudinal, follow up study in a dynamic cohort. Factors associated with virologic failure at 24 and 72 weeks of ART were assessed by chi-square analysis. The time point of 24 and 72 weeks was chosen for analysis of early and late virologic failure to provide sufficient internal between points of analysis of early and late virologic failure. The association between major ADRs identified in previous studies such as lipodystrophy, anaemia, peripheral neuropathy, and skin disorders (Kenneth A Agu et al., 2013; Awodele et al., 2016; Ogwuche et al., 2014) and virologic failure was examined by chi-square analysis. A multivariable logistics regression analysis was performed to adjust for the effect of confounders on virologic failure. Only variables that were significantly associated with virologic failure to a p <0.05 were included in the multivariate model. All statistical tests were two-tailed and a p-value <0.05 considered statistically significant. Stata version 13 (College Station, TX) was used for the statistical analyses.

4.8 Validity

To ensure validity, standard definitions for the outcomes and exposures were used. A virologic failure (the primary outcome measure) was defined using WHO definition for virologic failure – a viral load above 1000 copies/mL based on two consecutive viral load measurements in three months; with adherence support following the first viral load test, after at least six months of antiretroviral therapy (World Health Organization (WHO), 2016). Viral load measurement at different time points was utilized for the analysis since viral load is a time-varying covariate.

Clinical ADRs were documented by clinicians using case definition of ADR (Coulter, 2013), Adherence to ART, an important confounder of virologic failure, was measured and documented at JUTH HIV clinic by means of medication refill adherence - a measure which had been previously reported to predict virologic outcomes in the study site (Abah et al., 2014). To minimize the effect of differences in adherence due to different duration of ART exposure, percentage adherence at a specific time (24, 48, or 72 weeks) was used.

4.9 Reliability

In order to improve the reliability of the study, potential confounding variables were measured and adjusted for statistically for their impact on the relationship between exposure (ADRs) and outcome (virologic failure). Data extraction was done using a detailed data extraction form by an experienced data manager. Furthermore, extracted data was independently checked by the researcher for consistency. Finally, exploratory data analysis was conducted to determine if any data has been entered incorrectly (out of range values), to check for missing values and deciding how to deal with these values, as well as to check for outliers and test for normality.

4.10 Generalizability

The HSPH/APIN ART program at JUTH is one of the largest HIV treatment cohorts in Nigeria. Results from the study can be extrapolated to other ART settings using first-line ART in Nigeria as the clinic population cut across various tribes, socio-economic strata in the society which reflect the various ethnic nationalities in Nigeria. Extrapolation of the results to other settings should, however, be done with caution as differences may exist between individuals' in response to medicines, and quality of care across programmes which might impact on the study outcomes.

4.11 Ethics

The study protocol was submitted to the University of Western Cape (UWC) Research Ethics Committee and approval obtained (Appendix II). In addition, ethics approval for use of data was obtained from the Jos University Teaching Hospital ethical committee (Appendix III), and the use of secondary data was approved by Harvard School of Public Health (Appendix IV). A final approval for data extraction was obtained from the study facility (AIDS Prevention Initiative (APIN) JUTH HIV clinic) (Appendix V). As the study involved the use of retrospective data, there was no direct harm to patients. To ensure confidentially of patients' records, data extracted from the electronic medical record system was de-identified and stored in an encrypted format in a secure computer system accessible only to the researcher and supervisor. The results of the study could be of direct benefit to subsequent patients as data generated can be exploited in the rational selection of ARV regimens to achieve maximal and durable viral suppression as well as

foster retention of patients on treatment. The findings of the study will be disseminated through a published thesis and other scholarly publications which will be accessible to the public.

CHAPTER 5

RESULTS

5.1 Descriptive analysis

The flow diagram below (Figure 5.1) summarizes the distribution of study patients according to their initial antiretroviral treatment regimen. Between June 2004 and February 2012, 16,012 adults were commenced on ART at the study site. Of these, 3,897 (24.3%) were excluded from the analysis; 1,943 (12.1%) were treatment-experienced at enrolment and 1,954 (12.2%) had only one pharmacy pick-up. A total of 12,115 (87.9%) patients were included in the final analysis, of which the majority (98.5%) were on standard first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) based ART. Most of the patients (76.4%) received NVP based regimen at treatment initiation. The most commonly used ARV regimen for treatment initiation was with AZT-3TC-NVP (n=5,105, 42.1%) followed by TDF-3TC-NVP or TDF-FTC-NVP (n=2,527, 20.8%) and EFV-3TC-TDF (n=1,529, 12.9%) respectively.

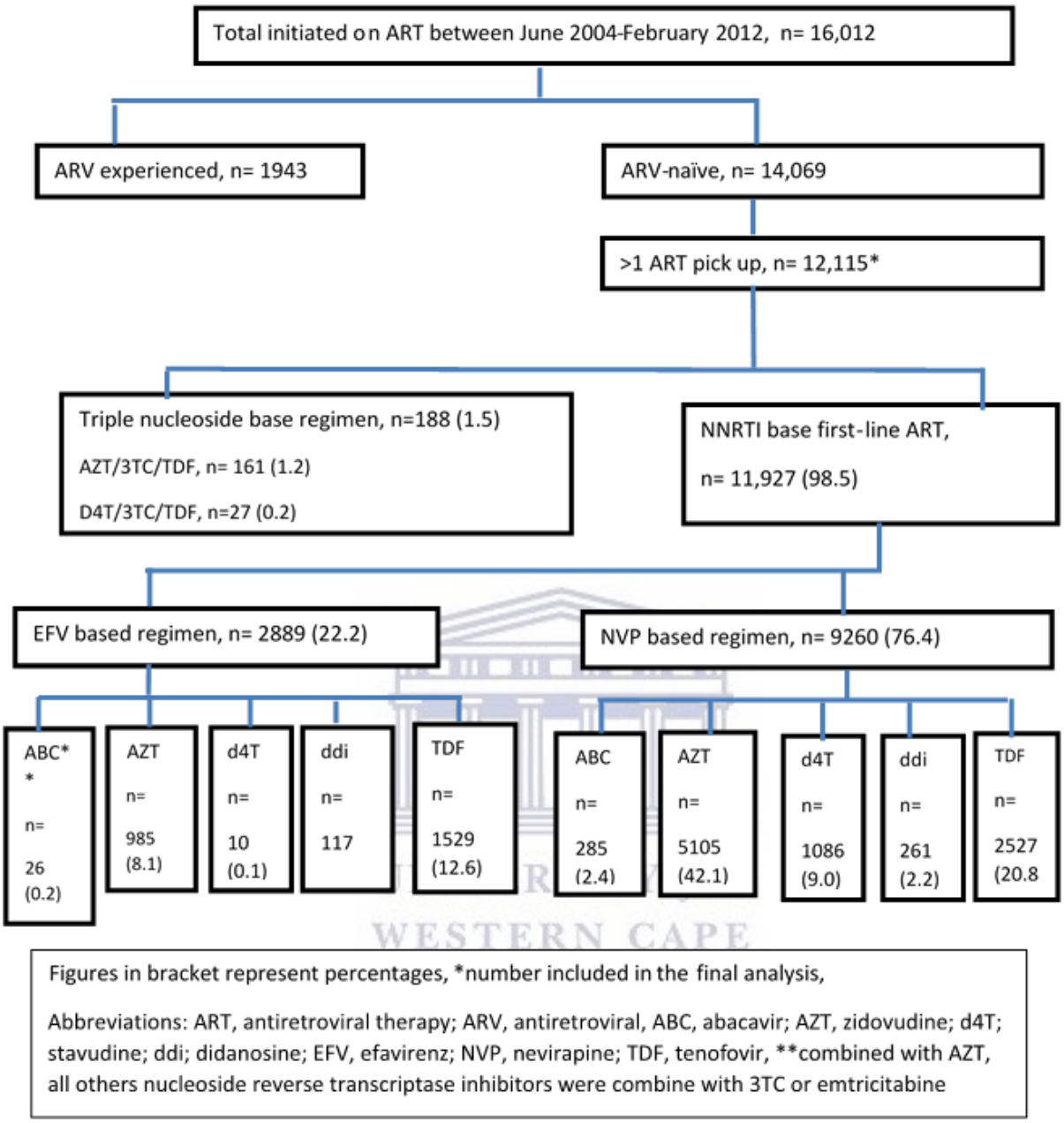


Figure 5.1: Flow diagram of patients and ART regimen received at treatment initiation

5.2 Characteristics of adults treated with first-line antiretroviral therapy at the study site, June 2004- February 2012

Table 5.1: Socio-demographic characteristics of –study participants (N=12,115)

Characteristics	Sub-group	Frequency	Percent
Sex	Females	8150	67.27
	Males	3965	32.72
Age, mean ± SD, years	All patients	35.77± 9.10	
	Female	33.71±8.48	
	Males	40.02±8.85	
Age range, years	15-24	711	5.86
	25-45	9445	77.96
	>45	1911	15.77
	Missing data	48	0.39
Marital Status	Divorced/Separated	995	8.21
	Married	6443	53.18
	Single	2375	19.60
	Widowed	1958	16.16
	Missing data	344	2.84
Highest Education	No formal education	1993	16.45
	Primary	2473	20.41
	Secondary	3651	30.14
	Tertiary	3654	30.16
	Missing data	344	2.84

IQR, interquartile range

Table 5.1 shows that majority of the study participants were females (67%) and young adults in

the age bracket of 25 to 45 years (78%). The mean age of females was significantly lower than that of male participants (34 versus 40 years; p <0.001). Just over half of the participants were married, while less than one-quarter (20%) were never married. Most participants were educated; with secondary and tertiary education reported as the highest educational attainment by one-third of the study participants, while less than 20% had no formal education. Clinical characteristics of participants prior to the commencement of ART are summarized in Table 5.2.

Table 5.2: Pre-treatment clinical characteristics of study participants (N=12,115)

Characteristics	Sub-group	Frequency (N)	Percent (%)
WHO disease stage	1	3964	32.72
	2	3567	29.44
	3	3085	25.46
	4	711	5.87
	Missing data	788	6.50
CD4 cell count, cell/mm^3	≤100	4240	35.00
	101 - 199	3921	32.36
	200 - 349	2888	23.84
	≥350	959	7.92
	Missing data	107	0.88
	Median (IQR)	142 (72 – 230)	
Viral load, copies/ml	≤10,000	3226	26.63
	10,001-100,000	4664	38.50
	>100,000	4164	34.37
	Missing data	61	0.50
	Median (IQR)	43, 680 (8,475 – 160,213)	
Hepatitis B status	Negative	8406	69.39
	Positive	2208	18.23
	Missing	1501	12.39
Tuberculosis infection	No	1388	11.46
	Yes	573	4.73
	Missing	10154	83.81

WHO, World Health Organisation, IQR; interquartile range

Overall, the median baseline CD4+ cell count was low and 35% of the participants had severe immunosuppression (CD4+ cell count ≤100 cells/mm^3) at baseline. Hepatitis B and HIV co-infection was less than 20%, while a high proportion of the participants (84%) did not have a

documented tuberculosis (TB) result. Of those with available TB data, only about 5% of were positive for TB.

5.3 Trend and pattern of patient enrolment on antiretroviral therapy June 2014 – February 2012

The trend in new patient enrolment on ART showed an increase in new patient enrolment from 180 patients in 2004 to 2180 patients in 2005 as shown in Figure 5.2. New patient enrolment peaked in 2006 and then dropped to under 1000 patients per year by 2010. In the figure, year 2012 enrolment was low as it only reflects two months of data.

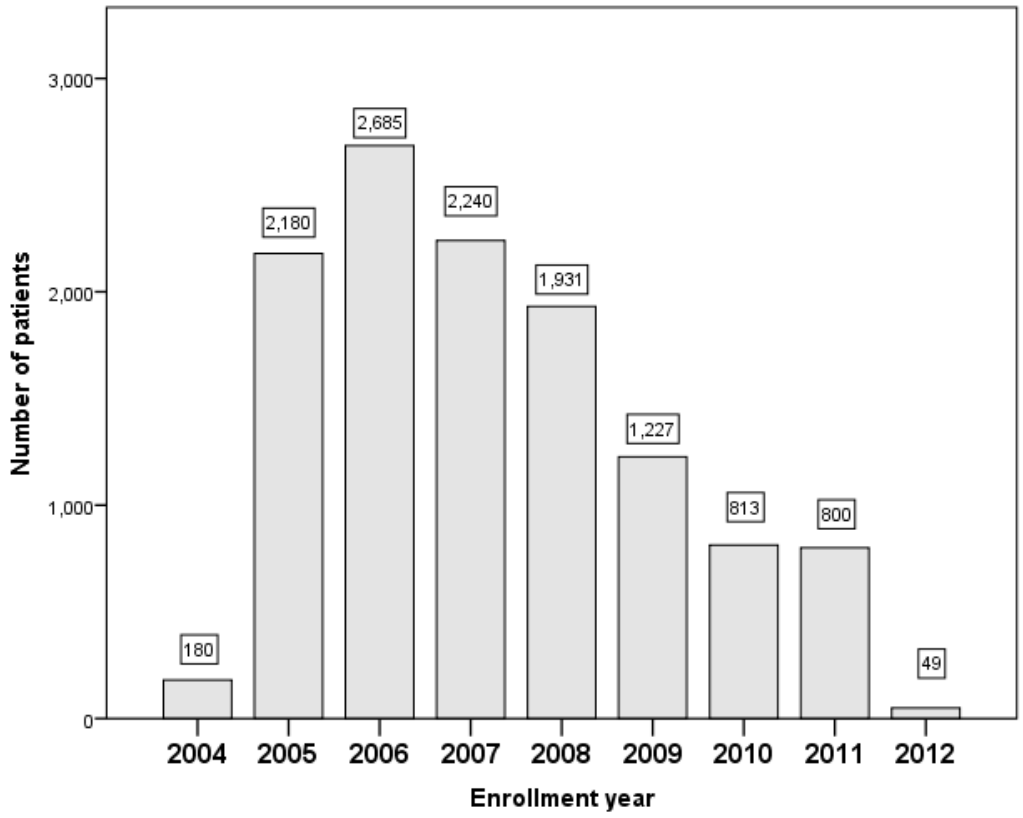


Figure 5.2: Trend in new patient enrolment on antiretroviral therapy

As shown in Figure 5.3, the combination of stavudine/lamivudine/nevirapine was the only antiretroviral (ARV) regimen used in 2004. However, from 2005 the number of ARV regimens increased to five and peaked at 12 regimens in 2006. By 2010 there were only three regimens. In line with WHO recommendations, the use of stavudine-based regimens decreased in 2006, and

was phased out completely in 2007. Between 2006 and 2008 zidovudine-based regimen was the dominant regimen used, while tenofovir (TDF)-based regimen was introduced in 2005 and its use peaked in 2008.

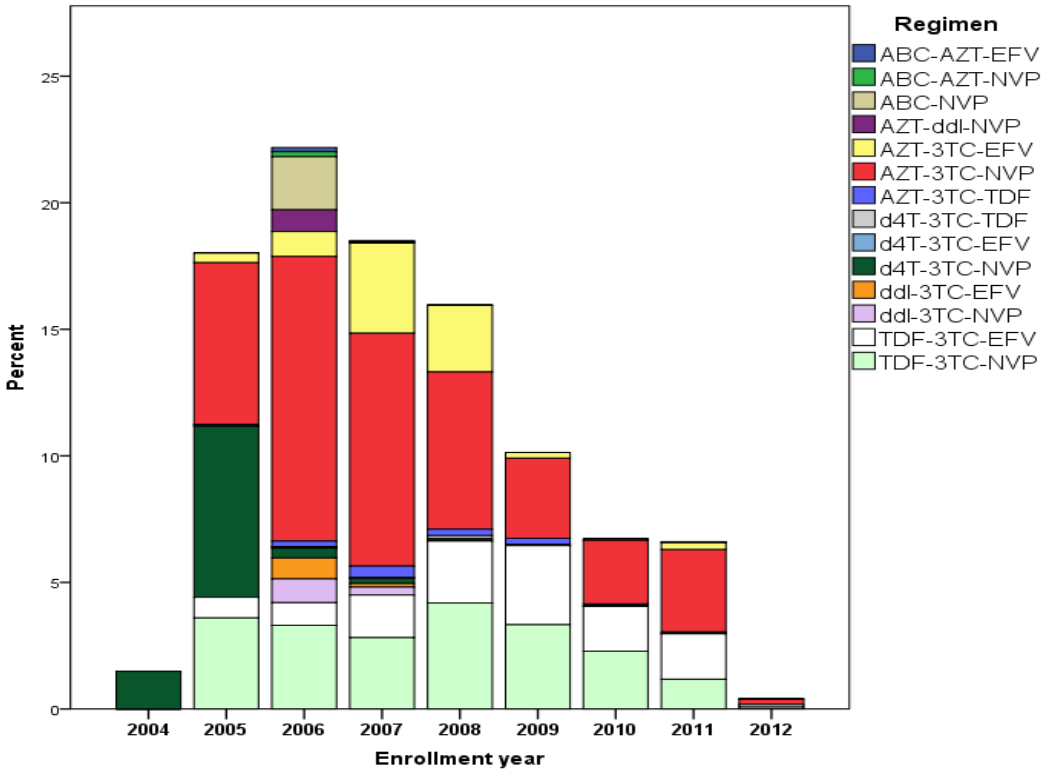


Figure 5.3: Distribution of initial antiretroviral regimen by year of enrolment

5.4 Incidence of adverse drug reactions in the study cohort

Table 5.2 shows that the incidence rate of any ADR was highest during the first year of ART (41/1000 py), after which it dropped sharply between the first and second year, and then increased to 21/1000 py between the second and third year. After the third year of ART, there was a consistent decline in the incidence rate of ADRs, with the lowest incidence rate of 5/1000 py recorded between the sixth and seventh year of treatment. However, the rate increased slightly to 8/1000 py between the seventh and eighth year after the drop observed. A comparison of the incidence rate between first and subsequent years of ART showed that the risk of ADRs almost tripled during the first year compared to the subsequent years (41 per 1000 py versus 14 per 1000 py, for ≤1 year and >1 of ART; crude incidence rate ratio, 2.87 (95% CI: 2.53-3.24))

Table 5.3: Incidence of adverse drug events in patients on first-line ART at Jos University Teaching Hospital HIV clinic June 2004 and February 2012

Period, years	Person-years (py)	Number of events	Incident rate per 1000 py (95% CI)	Crude incident rate ratio (95% CI)
0 - 1	10578	430	40.65 (36.98 - 44.68)	Reference
1 - 2	8868	91	10.26 (8.36 - 12.6)	3.96 (3.21 - 4.89)
2 - 3	7413	167	22.53 (19.36 - 26.22)	1.80 (1.51 - 2.45)
3 - 4	6147	116	18.87 (15.73 - 22.64)	2.15 (1.76 - 2.63)
4 - 5	4930	67	13.59 (10.7 - 17.27)	2.99 (2.34 - 3.82)
5 - 6	3582	28	7.82 (5.4 - 11.32)	5.20 (3.69 - 7.32)
6 - 7	2370	11	4.64 (2.57 - 8.38)	8.76 (5.33 - 14.37)
7 - 8	1033	8	7.75 (3.87 - 15.49)	5.25 (2.81 - 9.81)
> 8	112	0		
Total	45034	918	20.38 (19.11 - 21.75)	

CI, confidence interval

5.5 Prevalence and types of adverse drug reactions among adults on ART at Jos University Teaching Hospital (2004-2012)

A total of 918 out of the 12,115 (7.6%) patients experienced at least one ADR. The type of ADRs and the severity shown in Table 5.4 illustrates that compared to other ADRS, severe ADRs were more common (4.5%), followed by moderate (2.6%), and mild ADRs (0.8%), while life-threatening ADRs were rare (0.1%).

Table 5.4: Prevalence of specific adverse drug events in 12,115 patients on first-line ART at Jos University Teaching Hospital HIV clinic June 2004 to February 2012

Group/Specific adverse drug reactions	**Mild** N (%)	**Moderate** N (%)	**Severe** N (%)	**Life-threatening** N (%)	**All** N (%)
All events, n (%)	98 (0.81)	312 (2.58)	532 (4.47)	12 (0.10)	957 (7.90)
Metabolic symptoms	**33 (0.27)**	**148 (1.22)**	**144 (1.18)**	**1 (0.01)**	**326 (2.69)**
Lipodystrophy	29 (0.24)	144 (1.19)	141 (1.16)	1 (0.01)	315 (2.6)
Gynaecomostia	4 (0.033)	4 (0.03)	3 (0.025)		11 (0.09)
Systemic symptoms	**3 (0.03)**	**41 (0.34)**	**189 (1.56)**	**5 (0.04)**	**238 (1.97)**
Anaemia	3 (0.03)	34 (0.28)	185 (1.52)	5 (0.04)	227 (1.87)
Hypersensitivity reaction		5 (0.04)	3 (0.025)		8 (0.07)
Skin and appendages	**25 (0.21)**	**48 (0.39)**	**88 (0.72)**	**1 (0.01)**	**162 (1.34)**
Rash itching	16 (0.13)	37 (0.24)	36 (0.29)		82 (0.68)
Erythema multiforme /Exfoliative skin eruptions	1 (0.01)	7 (0.06)	33 (0.27)	1 (0.01)	42 (0.35)
Steven Johnson Syndrome		9 (0.07)	12 (0.10)		21 (0.17)
Exfoliative skin eruptions	1 (0.01)		2 (0.017)		3 (0.025)
Hyperpigmentation	6 (0.05)	2 (0.02)	5 (0.04)		13 (0.11)
Central nervous system	**3 (0.03)**	**23 (0.19)**	**46 (0.38)**	**5 (0.04)**	**77 (0.64)**
Nightmares	2 (0.02)	4 (0.03)	12 (0.10)	3 (0.03)	21 (0.17)
Insomnia		7 (0.06)	10 (0.08)	2 (0.02)	19 (0.16)
Anxiety/restlessness		3 (0.03)	11 (0.09)		14 (0.12)
Aggression/irrational talk	1 (0.02)	5 (0.04)	4 (0.03)		10 (0.08)
Somnolence		3 (0.03)	4 (0.03)		7 (0.06)
Dizziness			1 (0.01)		1 (0.01)
Seizures		1 (0.008)	2 (0.02)		3 (0.025)
Forgetfulness/confusion			3 (0.02)		3 (0.02)
Hallucination			2 (0.02)		2 (0.02)
Peripheral nervous system	**17 (0.14)**	**23 (0.19)**	**19 (0.16)**		**59 (0.49)**
Peripheral neuropathy	17 (0.14)	23 (0.19)	19 (0.16)		59 (0.49)
Gastro-intestinal	**11 (0.09)**	**14 (0.12)**	**25 (0.21)**		**50 (0.41)**
Nausea and vomiting	3 (0.03)	5 (0.041)	20 (0.17)		28 (0.23)
Diarrhoea	7 (0.06)	8 (0.07)	3 (0.03)		18 (0.15)
Abdominal pain	1 (0.01)	1 (0.01)	2 (0.02)		4 (0.03)
Others*	9 (0.07)	22 (0.18)	24 (0.20)		55 (0.45)

*****jaundice, body swelling, headache, conjunctivitis, oral sores, bone pain, dyspnea, muscle cramp

5.6 Factors associated with adverse drug reactions among adults on ART

Patients' characteristics that were significantly associated with adverse drug reactions in the bivariate analysis included: age, WHO disease stage at treatment initiation, Hepatitis B/ HIV co-infection, as well as NNRTI and NRTI regimen backbone as shown in Table 5.5. Comparatively, the prevalence of ADRs was lower in younger patients compared to older patients (prevalence of 5%, 7%, and 9% for age groups 15-24, 25-45, and > 45 years respectively; p =0.001), while those with more advanced disease (WHO disease stage 4) had lower ADRs compared with those at WHO stage 1 to 3. Patients not co-infected with hepatitis B had a significantly higher prevalence of ADRs compared to co-infected patients. When the prevalence of ADRs was compared according to ARV regimen category; for the NNRTIs, the prevalence of ADRs was significantly higher among patients on NVP-based ART compared to those on EFV, and triple nucleoside backbones. With respect to NRTI regimen backbone, the prevalence was highest in patients on d4T-based regimens, followed by ABC, and least in patients on TDF-based regimens.

Table 5.5: Bivariate analysis of association between patients and regimen characteristics with the occurrence of adverse drug reactions

Characteristics	Subgroup	Number without ADR (Row %)	Number with ADR (Row %)	P value*
Sex	Female	7540 (92.52)	610 (7.48)	0.580
	Male	3657 (92.23)	308 (7.77)	
Age, years	15-24	672 (94.51)	39 (5.49)	*0.001*
	25-45	8751 (92.65)	694 (7.35)	
	>45	1730 (90.53)	181 (9.47)	
WHO disease Class	1 or 2	6908 (91.70)	623 (8.31)	*0.006*
	3 or 4	3538 (93.20)	258 (6.82)	
CD4 cell count, cells/mm^3	≤100	3907 (92.15)	333 (7.85)	0.503
	101-200	3638 (92.78)	283 (7.22)	
	200-350	2665 (92.28)	223 (7.72)	
	>350	895 (93.33)	64 (6.67)	
HIV viral load	≤10,000	3006 (93.18)	220 (6.82)	0.093
	10,001-100,000	4315 (92.52)	349 (7.48)	
	>100,000	3824 (91.83)	340 (8.17)	
Tuberculosis positive	No	1101 (79.32)	287 (20.68)	0.696
	Yes	459 (80.10)	114 (19.9)	
Hepatitis B virus positive	No	7702 (91.63)	704 (8.37)	*<0.001*
	Yes	2082 (94.29)	126 (5.71)	
NNRTI regimen backbone	efavirenz	2520 (94.49)	147 (5.51)	*<0.001*
	nevirapine	8504 (91.84)	756 (8.16)	
NRTI regimen	abacavir	291 (93.57)	20 (6.43)	*<0.001*
	zidovudine	5972 (93.9)	388 (6.10)	
	stavudine	760 (67.68)	363 (32.32)	
	didanosine	251 (93.31)	18 (6.69)	
	tenofovir	3923 (96.82)	129 (3.18)	
ART enrolment year	2004-2006	4431 (0.88)	580 (0.12)	*<0.001*
	2007-2009	4995 (0.95)	265 (0.05)	
	2010-2012	1589 (0.97)	57 (0.03)	

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor, *chi-square comparison of proportion. Values in italics show significant association

Table 5.6: Multivariate logistic regression risk factor analysis for adverse drug reactions

Predictor variable		Odds ratio (OR)	95% CI of OR	P value
Sex	Females versus males	1.16	0.96 - 1.4	0.137
Age, years	Every 1-year increment	1.02	1.01 - 1.03	*<0.001*
WHO disease stage	1or 2 versus 3 or 4	1.05	0.88 - 1.24	0.546
HBV status	Negative	1.30	1.05 - 1.61	*0.015*
NNRT backbone	NVP versus EFV	0.78	0.6 - 1.02	0.069
NRTI backbone	abacavir	2.11	1.23 - 3.61	*0.007*
	zidovudine	2.22	1.74 - 2.84	*<0.001*
	stavudine	15.90	11.97 - 21.11	*<0.001*
	didanosine	2.13	1.25 - 3.63	*0.006*
	tenofovir	Reference		
Year of ART initiation	2004-2006	1.56	1.08 - 2.25	*0.018*
	2007-2009	1.26	0.87 - 1.82	0.220
	2010-2012	Reference		

CI, confidence interval; HBV, hepatitis B virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; EFV, efavirenz; Values in italics show significant association

The result of the multivariable analysis shown in Table 5.6 identified the following as independent predictors of ADRs: age, hepatitis B status, NRTI backbone, and year of ART enrolment. The likelihood of experiencing an ADR increased by 2% for every one-year increment in age. Hepatitis B co-infection was protective of ADRs; study subjects who were hepatitis B negative had 30% greater likelihood of an ADR compared to hepatitis B/HIV co-infected patients. Considering the NRTI backbone, compared those with a regimen containing tenofovir, the odds of an ADR was doubled in patients on abacavir-, stavudine-, and didanosine containing ARV regimen respectively. Additionally, the likelihood of an ADR was increased 16 times among those treated with stavudine-containing regimen compared to tenofovir.

Furthermore, there was 56% higher likelihood of experiencing an ADR among those initiated on ART in the period 2004 to 2006 compared to the those who commenced treatment between 2010 and 2012.

5.7 Prevalence of virologic failure among patients on ART at Jos University Teaching Hospital

Figure 5.4 depicts the prevalence of virologic failure at the different time points of ART. The proportion of patients with virologic failure (36% at 24 weeks) dropped slightly to 29% at 48 weeks and then increased to 34% at 72 weeks of ART.

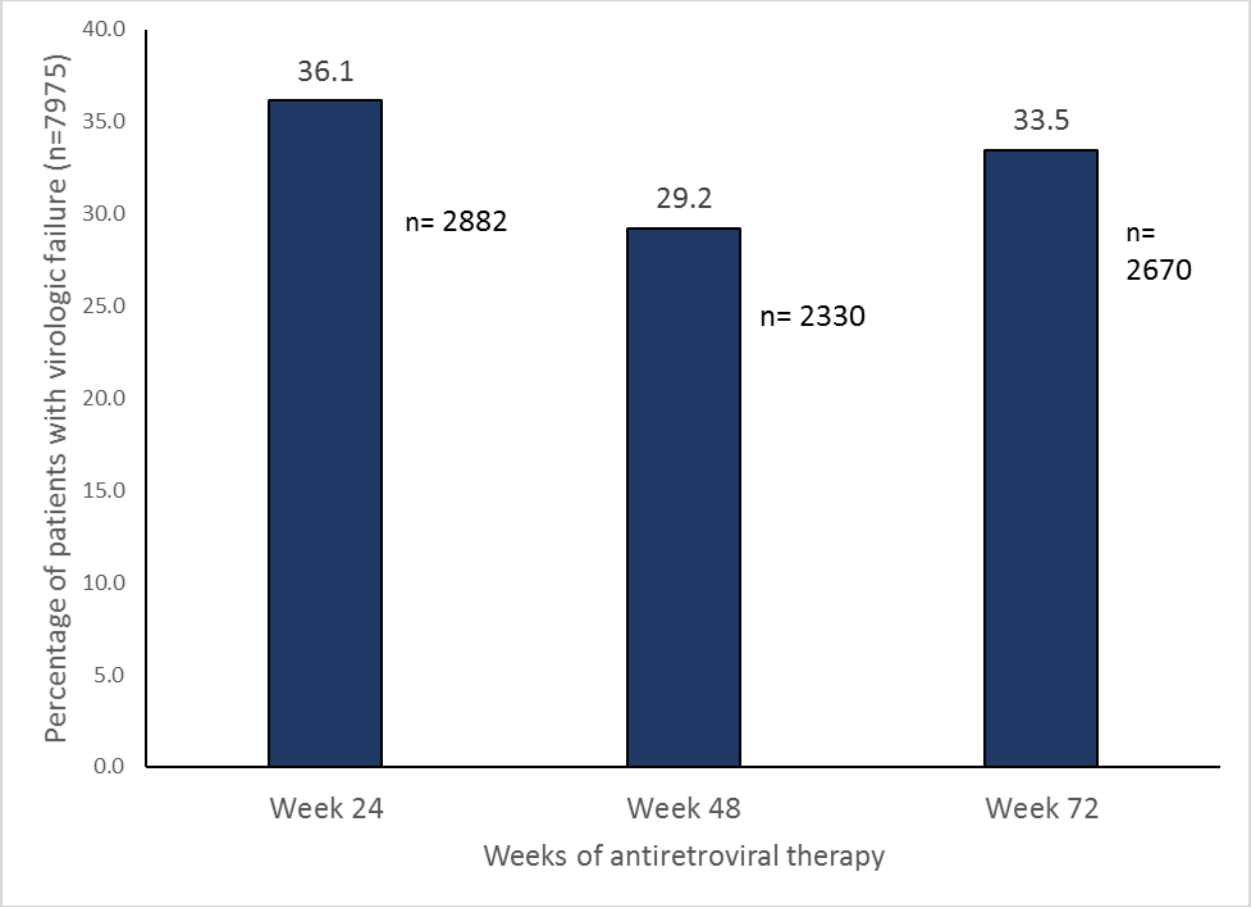


Figure 5.4: Percent prevalence of virologic failure at different time point among patients on first-line antiretroviral therapy at Jos University Teaching Hospital 2004 – 2012

5.8 Factors associated with virologic failure

Table 5.7: Association of participants demographic, clinical, and regimen characteristics with virologic failure

Characteristics	Sub-group	Number (%) of patients with early (24 weeks) virologic failure	P value	Number (%) of patients with late (72 weeks) virologic failure	P value
Sex	Female	2516 (31.02)	*0.001*	1768 (32.86)	0.093
	Male	1336 (33.89)		902 (34.76)	
Age, years	15-24	224 (31.64)	0.734	181 (39.61)	*0.008*
	25-45	3021 (32.14)		2071 (33.35)	
	>45	593 (31.24)		405 (31.71)	
WHO disease stage	1	975 (24.71)	*<0.001*	791 (29.88)	*<0.001*
	2	1119 (31.5)		826 (33.05)	
	3	1318 (42.89)		792 (38.06)	
	4	254 (35.93)		145 (34.04)	
CD4 cell count cells/mm3	≤100	1610 (37.97)	*<0.001*	1103 (38.91)	*<0.001*
	101-200	1300 (33.15)		824 (28.97)	
	201-350	767 (26.56)		587 (31.39)	
	>350	159 (16.58)		151 (38.42)	
HIV viral load copies/ml	≤10,000	814 (25.23)	*<0.001*	634 (31.31)	*0.001*
	10,001-100,000	1461 (31.33)		1015 (32.64)	
	>100,000	1577 (37.87)		1021 (35.95)	
Hepatitis B status	Negative	2780 (33.23)	0.098	1877 (32.94)	0.605
	Positive	691 (31.38)		469 (33.67)	
	Yes	243 (42.41)		138 (31.65)	
Tuberculosis	No	401 (28.95)	<0.001	319 (30.12)	0.561
Baseline regimen backbone	efavirenz	902 (34.1)	*0.001*	543 (33.5)	*<0.001*
	Triple NRTI	75 (39.9)		65 (52)	
	nevirapine	2875 (31.2)		2062 (33.1)	
Baseline NRTI	abacavir	124 (39.87)	*<0.001*	72 (30.9)	*<0.001*
	zidovudine	1879 (29.7)		1379 (31.7)	
	stavudine	317 (28.3)		244 (30.1)	
	didanosine	108 (40.2)		69 (36.3)	
	tenofovir	1424 (35.4)		906 (37.9)	
ART start year	2004-2006	1692 (33.6)	*<0.001*	1162 (30.3)	*<0.001*
	2007-2009	1811 (33.6)		1285 (34.9)	
	2010-2012	346 (21.5)		221 (47.9)	
Adherence†	<95%	715 (43.2)	*<0.001*	473 (45.7)	*<0.001*
	≥95%	3137 (30.2)		2197 (31.7)	

NRTI, nucleoside reverse transcriptase inhibitor; †average adherence at 24, and 72 weeks were included in the analysis of virologic outcome at 24, and 72 weeks respectively; the comparison was by chi-square analysis; Values in italics show significant association

Table 5.7 summarizes the association between baseline and time-updated patients' and regimen characteristics, and virologic failure. Early virologic failure was more prevalent in males than females (34% versus 31%; p = 0.001), while late virologic failure was more common in the younger patients (40%, 33%, and 32%, for age groups 15-24, 25-45, and >45 years respectively, p = 0.008). There was a trend toward higher early and late virological failure rates with more advanced WHO disease stage at treatment initiation. Additionally, study subjects who initiated treatment at higher viral load thresholds had significantly higher early and late virologic failure rates. The difference was more pronounced at 24 weeks of treatment; 25% compared to 38%, for those with baseline viral load of ≤10,000 compared >100,000 copies/ml respectively. For patients with available TB results at baseline, a significantly higher proportion of patients co-infected with tuberculosis had virologic failure at 24 weeks of therapy compared to non-co-infected subjects. This difference was not significant at 72 weeks of therapy. A significantly higher proportion of study patients who initiated treatment with an ARV regimen of triple NRTI had a virologic failure at 24, and 72 weeks of therapy compared to those who commenced treatment with EFV- or NVP-based regimen. Considering the NRTI backbone, virologic failure rate at 24 weeks was highest among patients who initiated treated with didanosine-based regimen, followed by abacavir, tenofovir, zidovudine, and stavudine respectively. However, at 72 weeks of therapy, patients who initiated ART with tenofovir-containing regimen had the highest virologic failure rate of 38%, followed by didanosine (36%), zidovudine (32%), abacavir (31%), and stavudine (30%) respectively. Early and late virologic failure was significantly more prevalent among those with average percentage adherence to on-time ARV refill schedules of <95% compared to those with ≥95% adherence.

5.9 Association between adverse drug reaction and virologic failure

Table 5.8 summarizes the result of comparison of the percentage of virologic failure between patients who experienced and those who did not experience an ADR.

Table 5.8: Comparison of virologic failure among study participants who experienced an ADR and those who did not experience an ADR

Type of ADR	Outcome	Number (%) of patients with early (24 weeks) virologic failure	*P* value	Number (%) of patients with late (72 weeks) virologic failure	*P* value
Any ADR	No	2647 (36.31)	0.297	2436 (33.42)	0.686
	Yes	235 (34.31)		234 (34.16)	
Grade 3 or 4 ADR	No	114 (29.08)	0.223	101 (32.69)	0.462
	Yes	171 (32.88)		134 (35.36)	
Anaemia	No	3765 (31.83)	*0.03*	2599 (33.22)	*<0.001*
	Yes	87 (38.84)		71 (46.71)	
CNS disorder	No	3739 (31.8)	0.326	2574 (33.10)	*0.048*
	Yes	38 (36.2)		31 (44.3)	
Lipodystrophy syndrome	No	3779 (32.18)	*<0.001*	2601 (33.76)	*<0.001*
	Yes	73 (23.47)		69 (25.46)	
Peripheral neuropathy	No	3835 (31.97)	0.725	2664 (33.61)	*<0.001*
	Yes	17 (29.82)		6 (12.5)	
Skin disorders	No	3814 (31.96)	0.851	2641 (33.44)	0.431
	Yes	38 (31.15)		29 (37.66)	

ART, antiretroviral therapy; CNS, central nervous system, numbers in parenthesis represent percentages. The comparison was by chi-square test. Values in italics show significant association

5.10 Assessment of predictors of virologic failure

A multivariate logistic regression model evaluated independent predictors of early (24 weeks) and late (72 weeks) virologic failure. Variables that were significantly associated with virologic failure to a p =0.05 in the bivariate analysis (Table 5.7 and Table 5.8) were included as covariates in the multivariable model to adjust for the effect of confounders on virologic failure. Sex and age were included in the model to account for any residual confounder based on the *apriori* knowledge of their association with ADRs (Cescon et al., 2013; Chen et al., 2017). The result of the multivariate risk factor analysis is presented in Table 5.9

Table 5.9: Multivariate risk factor analysis for virologic failure at 24 and 72 weeks of antiretroviral therapy

Characteristics	Early virologic failure		Late virologic failure	
	aOR (95% CI)	***P* value**	**aOR (95% CI)**	***P* value**
Males	1.07 (0.96 - 1.19)	0.253	1.18 (1.03 - 1.36)	*0.021*
Age, one-year increment	1 (0.99 - 1)	0.501	0.99 (0.99 - 1)	0.083
WHO disease stage (3 or 4 versus 1 or 2)	1.74 (1.59 - 1.9)	*<0.001*	1.11 (0.98 - 1.24)	0.091
CD4 cell count, cells/mm^3 (≤100 versus >100)	1.27 (1.16 – 1.38)	*<0.001*	1.37 (1.23 – 1.53)	*<0.001*
Viral load (>10,000 versus ≤10,000)	1.42 (1.28 - 1.56)	*<0.001*	1.09 (0.97 - 1.24)	0.164
NVP versus EFV	1.12 (0.99 - 1.28)	0.071	1.39 (1.17 - 1.65)	*<0.001*
ABC versus TDF	1.2 (0.93 - 1.54)	0.162	0.79 (0.57 - 1.11)	0.173
AZT versus TDF	0.78 (0.71 - 0.85)	*<0.001*	0.77 (0.68 - 0.87)	*<0.001*
D4t versus TDF	0.66 (0.55 - 0.79)	*<0.001*	0.88 (0.7 - 1.11)	0.281
ddi versus TDF	1.08 (0.83 - 1.41)	0.564	1.22 (0.87 - 1.71)	0.264
Year of ART initiation				
2007-2009 versus 2004-2006	0.91 (0.83 - 1.01)	0.073	1.25 (1.1 - 1.42)	*<0.001*
2010-2012 versus 2004-2006	0.52 (0.45 - 0.61)	*<0.001*	1.93 (1.51 - 2.46)	*<0.001*
Adherence (<95% versus ≥95%)*	1.82 (1.63 - 2.04)	*<0.001*	1.74 (1.47 - 2.06)	*<0.001*
Anaemia	1.34 (1 - 1.8)	*0.048*	1.76 (1.22 - 2.55)	*<0.001*
lipodystrophy	0.81 (0.6 - 1.1)	0.183	0.85 (0.61 - 1.18)	0.332
CNS disturbance	-		1.19 (0.68 – 2.05)	0.543
peripheral neuropathy	-		0.42 (0.18 - 1.02)	0.061

ART, antiretroviral therapy; aOR, adjusted odds ratio; CI, confidence interval; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; HBV, hepatitis B virus; CNS, central nervous system, *average adherence at 24, and 72 weeks were included in analysis of virologic outcome at 24, and 72 weeks respectively. Values in italics show significant association

.

CHAPTER 6

DISCUSSION

6.1 Introduction

This chapter presents a detailed discussion of the results presented in Chapter 5. The discussion highlights key findings of the study with reference to the study objectives. In addition, findings of the study were compared with reports published in the literature. An initial brief discussion of the demographic and clinical data as well as regimen characteristics is presented. The rest of the chapter focuses on adverse drug reactions identified and recorded among patients on ART, identified risk factors for ADRs, and the prevalence and risk factors for virologic failure; with emphasis on the association between ADRs and virologic failure.

6.2 Participants characteristics

The study findings showed that more women (67%) than men were living with HIV; and as such more women were accessing antiretroviral viral therapy at the study site. This finding collaborates other Nigerian reports which suggest a feminization of the HIV epidemic (Awofala & Ogundele, 2015; National Agency for the Control of AIDS (NACA), 2015). Young adults in the productive age of 25 to 45 years (78%) were those mostly infected with HIV and accessing ART. This finding is consistent with a 2015 report reflecting this age group as the most at risk of HIV infection (National Agency for the Control of AIDS (NACA), 2015).

In terms of clinical characteristics, this study revealed that late presentation for treatment was common as more than one-third of the participants had severe immune-suppression at treatment initiation (CD4+ $\leq$100 cells/mm^3), which meets the European Consensus definition of late presentation (UK Collaborative HIV Cohort (UK CHIC) Steering Committee et al., 2010). Other Nigerian and African studies also reported late presentation for treatment as common among HIV infected patients (Agaba et al., 2014; Daniyam et al., 2011; Mojumdar, Vajpayee, Chauhan, & Mendiratta, 2010). Strategies for early detection and integration into care of HIV infected persons are needed in the studied setting as late presentation for treatment is a risk factor for early mortality in HIV infected patients (Dalhatu et al., 2016).

On the issue of regimens for ART, the number of different regimens rose sharply from five in

2005 to twelve in 2006, before they were streamlined to four in 2008. The sharp rise in the number of regimens used in managing HIV coincided with the period of increased external funding, mainly from three global health initiatives (GHIs) – the US President's Emergency Plan for AIDS Relief, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the World Bank Multi-Country HIV/AIDS Program (Chima & Homedes, 2015). However, using several regimen options in one programme to manage HIV infection was not sustainable in the studied setting as shown by the sharp decline in the number of available regimen option to four in 2008.

6.3 Incidence of adverse drug reactions

This study observed a lower incidence rate of ART-related ADRs (20.4 per 1000 py) compared to that reported in earlier African studies: Nigeria (46 per 1000 py) (Eluwa et al., 2012), Ethiopia (90 per 1000 py) (Gudina et al., 2017), and Uganda (45 per 1000 py) (Forna et al., 2007). The observed differences in the rate of ADRs between the cited studies and the findings of the current study could be attributed to several factors: the different pharmacovigilance practices in the different settings, the number of patients involved in the studies, the duration of follow-up, and individual participant differences in responding to the drugs. Furthermore, severe ADRs had the highest prevalence in the current study (Figure 4.5), suggesting a possibility of under-reporting or overlooking mild events– further studies are needed to verify this assumption.

Consistent with findings of previous studies (Abah, Akanbi, et al., 2015; Cespedes & Aberg, 2006; Eluwa et al., 2012; Gudina et al., 2017), this study identified the first year of ART as the period of greatest risk for ART-related ADRs [crude incident rate ratio, 2.87; 95% CI: 2.53-3.24)]. The findings of this study and that of similar studies highlight the importance of close monitoring of patients on ART during the first year of treatment to identify and promptly manage ADRs when they occur. This will help in mitigating negative consequences of ART-related ADRs on treatment success.

Type of adverse drug reactions

The most common ADRs reported in this study were fat distribution abnormalities (lipodystrophy; 2.6%), anaemia (1.9%), skin rash/itching (0.7%), and peripheral neuropathy (0.5%). The most prevalent ADRs reported by other Nigeria studies were those with early onsets

such as skin rash (Kenneth Anene Agu et al., 2014; Eluwa et al., 2012) and anaemia (Ogwuche et al., 2014; Reginald et al., 2012). The high rate of fat distribution abnormality reported in this study was not captured in earlier Nigerian studies probably due to their short follow up period. Although this study did not evaluate the risk factors for specific ADRs, the high prevalence of lipodystrophy could be attributed to the stavudine era which is documented in the literature (Baril et al., 2005; Joly et al., 2002; Schwenk et al., 2000). Anaemia, on the other hand, could be connected to the high use of zidovudine in the study setting. The association of zidovudine with anaemia has been documented in several Nigerian studies (Awodele et al., 2016; Ogwuche et al., 2014; Oreagba et al., 2014). Consistent to the findings of this study, data from a recent Nigerian study with up to five years follow up reported peripheral neuropathy as the most common ADR among adults on ART (Bassi et al., 2017). Peripheral neuropathy is a late-onset ADR with a reported prevalence in developed countries of about 10% to 21% in persons exposed to stavudine (Van-Oosterhout et al., 2005).

6.4 Factors associated with ADRs

Age: The prevalence of ADRs was lower in younger patients compared to older patients. After adjusting for other confounding variables, we found that the risk of ADRs increased for every 1-year age increment. Consistent with the study finding, increased risk of ART-related ADRs with advancing age had been reported in other African studies (Masenyetse, Manda, & Mwambi, 2015; Schwenk et al., 2000).

Disease stage: The prevalence of ADRs was found to be higher in patients who initiated ART at an early HIV disease stage (WHO clinical stage 1 or 2 compared to stage 3 or 4). Available evidence suggests that patients who initiate treatment at an early HIV disease are at higher risk of certain ADRs (Centers for Disease Control and Prevention (CDC), 2001). For instance, greater risk of NNRTI-related rash was reported in persons with earlier HIV disease after starting therapy (Ananworanich et al., 2005). Another possible explanation for the higher prevalence of ADRs in asymptomatic patients observed in this study is the fact the study focused on clinical ADRs, hence some clinical adverse drug events may overlap with symptoms of HIV/AIDS in symptomatic patients (WHO stage 3 or 4) and might be missed, potentially resulting in under-reporting of ADRs in symptomatic patients. However, HIV disease stage was not predictive of

ADRs in the multivariate analysis. This finding is consistent with findings of a multicentre randomized controlled study, which found that commencing treatment in early asymptomatic HIV infection was not associated with higher risk of adverse drug events (The INSIGHT START Study Group, 2015).

Association between regimen characteristics with ADRs

The association of the type of ARV regimen with the prevalence of ADRs was studied providing useful information for the management of antiretroviral therapy.

NNRTIs: The prevalence of ADRs was higher among patients on nevirapine-based ART compared to efavirenz-based ART (8.2% compared to 5.5%; p <0.001). This finding is in line with results of a systematic review which demonstrated a greater likelihood of ADRs among patients on nevirapine-based ART compared to efavirenz; specifically, with regards to severe hepatotoxicity, and severe hypersensitivity reactions (Shubber et al., 2013). However, the review found that compared to nevirapine, patients receiving efavirenz were more likely to experience severe central nervous system events (Shubber et al., 2013). After adjusting for other confounding risk factors in the current study, the risk of ADRs was not significantly different between the two drugs, which synchronizes a previous study report that suggested that the short- and long-term toxicity and withdrawal rates of the two drugs were comparable (Manfredi, Calza, & Chiodo, 2004).

NRTIs: When the NRTIs were compared, as expected, the use of stavudine (32.2%) and didanosine (6,9%) were associated with significant risk of ADRs compared to tenofovir (3.3%). However, these drugs (stavudine and didanosine) are no longer recommended for first-line therapy because of their greater potential for toxicity (World Health Organization (WHO), 2013), and their use has been discontinued at the study site. Comparatively, the odds of ADRs was doubled among patients exposed to AZT compared to TDF. This result is in line with findings in the literature (Gallant et al., 2006; Mudzviti et al., 2015).

Year of ART initiation: We found an almost double likelihood of ADRs among those who initiated treatment in the period 2004-2006 compared to those initiated on treatment between

2010-2012. Some peculiarities of these treatment periods which might have accounted for the observed differences in ADRs included the following: stavudine and didanosine are drugs associated with significant risk of ADRs - these were used mostly in the period 2004 – 2006, whereas, they were not used in the period 2010 – 2012, as their use had been discontinued based on treatment guidelines recommendation (Federal Ministry of Health (FMoH) Nigeria, 2010); and the availability of multiple regimen options between 2004 and 2006 compared to between 2010 and 2012. A higher number of regimen options have been reported to correlate with a high rate of regimen modifications (Abah, Darin, et al., 2015), which is associated with increased risk of adverse treatment effects (Korsnes, Goodwin, Murray, & Candrilli, 2016). Other possible reasons for the observed difference in the prevalence of ADRs related to the calendar years of ART initiation are not very apparent and deserve further investigation.

6.5 Prevalence of virologic failure

The virologic failure rates in the current study (36% at 6 months and 34% at 18 months) were higher than rates reported in Ugandan (20% at 12 months) (Kityo et al., 2014), and South Africa (10% at 16 months) (Fox et al., 2012; Sanne et al., 2009). However, the virologic failure rate observed in this study was close to estimates of virologic failure rates reported in a systematic review and meta-analysis of African studies which put the proportion of patients with undetectable viral load at above 64% (35% failure rate) for all time points (Hammond & Harry, 2008). Another more recent review and meta-analysis of studies from low and middle income countries put the number patients with viral suppression after 6 and 48 months on ART at 74.7% (95% CI, 72.2–77.2) and 61.8% (95% CI, 44.0–79.7) respectively, which does not differ significantly from the result of the current study. This study highlights the need to adopt more practical and effective strategies to achieve a higher virologic success rate of 90% in line with the United Nations 90-90-90 target (UNAIDS, 2017).

6.6 Factors associated with virologic failure

Factors predictive of virologic failure in the current study include the following:

***Male gender*:** The results showed that late virologic failure was higher in males compared to females (adjusted odds ratio; 1.18 95% CI:1.03 - 1.36). In contrast to the findings of this study, higher virologic failure rates have been reported in females compared to males in other studies;

in a Chinese study the adjusted relative risk of virologic failure was 1.02, 95% CI: 1.01 to 1.03 for females compared to males and (Chen et al., 2017), while a Canadian study reported that women were significantly less likely to achieve virologic suppression compared to men (adjusted hazard rate; 0.82, 95% CI=0.72–0.93, p=0.002) (Cescon et al., 2013). The inconsistencies in gender-related HIV treatment outcomes may be setting specific, and underlying factors in each setting need further investigations.

Disease stage: Consistent with results of previous studies (Egger et al., 2002; Law et al., 2015; McMahon et al., 2013; Meloni et al., 2016; Scarsi et al., 2015) initiation of ART at more advanced HIV disease stage such as WHO disease stage 3 or 4 compared to stage 1 or 2 (OR, 1.74; 95% CI: 1.59 - 1.9) or severe immunosuppression (pre-treatment $CD4^+$ cell count of ≤100 compared to >100 cells/mm^3) (OR, 1.27; 95% CI: 1.16 – 1.38) increased the likelihood of early virologic failure. The implication of this evidence is that late presentation for treatment, which was a prominent finding in this study, could be a contributory factor to the poor virologic success rate observed in this study. Strategies that support early detection of HIV infection and engagement into care are needed in the studied setting to improve treatment outcomes in patients on ART.

***NNRTI*:** This study found a higher likelihood of late virologic failure in patients on nevirapine-based ART compared to efavirenz (OR, 1.39; 95% CI: 1.17 - 1.65). In agreement with findings of the current study, the lower hazard of treatment failure among patients on efavirenz-compared to nevirapine-based regimens (hazard ratio, 0.66; 95% CI: 0.49-0.88]) had been reported in an Ethiopian study (Kedir, Gemeda, & Suleman, 2015). However, evidence regarding the superiority of efavirenz compared to nevirapine with regards to virologic suppression rate from systematic reviews and meta-analysis are mixed. One systematic review and meta-analysis that included 10 trials with 2438 participants suggested that there may be little or no difference between efavirenz and nevirapine in virological success rate (Mbuagbaw, Irlam, Spaulding, Rutherford, & Siegfried, 2010), whereas, another review which included 38 studies, comprising 114,391 patients, reported that patients on efavirenz-based ART were more likely to achieve virologic success than those on nevirapine-based ART, though the difference was marginally significant, (Pillay, Ford, Shubber, & Ferrand, 2013). From the practice point of view, stable

patients on either of the drugs (nevirapine or efavirenz) should not be switched except if there are compelling reasons.

***NRTI*:** In contrast to evidence from previous studies (Amoroso et al., 2012; Gallant et al., 2006), this study found that the likelihood of early (OR, 0.78; 95% CI: 0.71 - 0.85) and late virologic failure (OR, 0.77; 95% CI: 0.68 - 0.87) were lower in patients on zidovudine-based ART compared to tenofovir-based ART. The superiority of zidovudine compared to tenofovir with regards to viral suppression was reported earlier by a retrospective cohort multicentre Nigerian study (Scarsi et al., 2015).

***Year of ART initiation*:** In support of a previous multicentre observational cohort study in Nigeria (Meloni et al., 2016), we found a significant association between year of ART initiation and the risk of virologic failure, with early calendar years of ART initiation being predictive of early virologic failure, but protective of late virologic failure. The reason for variability in the virologic outcomes between the different cohort of patients merits further investigation as it may provide clues on strategies that can be used to improve virologic success rates in the studied setting.

***Adherence to drug refill schedules*:** Adherence to on-time ARV refill schedules was associated with higher virologic failure rates; proportion of patients with early and late virologic failure of 43% versus 30%, and 46% versus 32%, respectively for <95% versus ≥95% adherence respectively (Table 5.7). After controlling for other confounding variable, patients who were not consistent with their drug pick up schedule were more likely to have virologic failure (OR, 1.82; 95% CI:1.63 - 2.04 for early virologic failure and OR, 1.74; 95% CI:1.47 - 2.06 for late virologic failure). The relationship between sub-optimal adherence to drug refill schedules and increased risk of virologic failure has been documented in several published reports (Abah et al., 2014; Bisson et al., 2008; El-Khatib et al., 2011).

***Adverse drug reactions**:* When specific ADRs were considered in the current study, we found that ART-related anaemia increased the odds of late virologic failure (OR, 1.76; 95% CI:1.22 - 2.55). Studies comparing the impact of ART-related anaemia are scarce, but a recent study found

that ADRs were significantly associated with poor immunological and virological outcomes in HIV/AIDS patients (Syed et al., 2016). Additionally, in support of the current study finding better survival has been reported among HIV patients on ART with the absence of ADRs (Khan, Khan, Sulaiman, & Soo, 2015). The relationship between ADRs and virologic suppression may be explained by the fact that ADRs are a risk factor for poor adherence (Bezabhe et al., 2015), which is on the causal pathway to virologic failure. This fact is supported by the study by Bezabhe et al. (2015), who reported that patients who experienced a severe ADR were less likely (OR 0.4, 95 % CI 0.2–0.9) to be ≥90 % adherent to ART.

6.7 Strengths and limitations of the study

6.7.1 Strengths of the study

Strengths of the descriptive design

Findings presented in this study reflect real-life HIV management practices and patients' experiences with regards to ADRs and viral suppression rates in a resource-limited setting.

Strength of the retrospective cohort design

The retrospective cohort study design enabled the researcher to examine longitudinal data spanning a period of 8 years, making it possible to describe the incidence rate and profile of ADRs in the studied population. This enabled the researcher to describe the incidence rate of ADRs at the different time points of ART and identified a higher incidence of ADRs during the first year of therapy compared to subsequent years.

Another strength of the study was the large sample size utilized and long duration of follow-up. The availability of electronic medical records made it possible to examine records of all patients that met the inclusion criteria (over 12,000 patients were included). As a result, it was possible to describe some rare ADRs and to determine the incidence rate of ADRs in the studied population. Additionally, the long period of follow up (over 45,000 person-years of observation) enabled the researcher to describe late onset ADRs that were not commonly reported in other studies in similar settings. Furthermore, the availability of viral load data enabled the researcher to examine the risk of virologic failure in those who experienced an ADR and those who did not. Evidence

examining this association is scarce. The large sample size and length of follow up provided statistical strength to reinforce our findings.

6.7.2 Limitations of the study

Retrospective cohort study design

Instances of missing data for specific variables were encountered because of the retrospective use of data. In addition, data were not collected on certain desirable variables such as non-ARV medications, which are important in assessing the risk of ADRs. Consequently, we were not able to control for all factors related to ADRs and virologic failure, and there might be residual confounding that must be considered in the interpretation of the study results. Furthermore, because of the retrospective data use, it was not possible to perform a qualitative causality assessment of the clinical adverse events.

There also exists the possibility of selective or under-reporting of ADRs by patients and caregivers. The study observed that the prevalence of severe ADRs was higher than other grades of ADRs. The tendency to overlook mild reaction by patients is high and might have potentially underestimated the true prevalence of ADRs in the studied population. In addition, since the study focused on clinical ADRs, some adverse drug events which overlap with symptoms of HIV/AIDS may have been missed. Furthermore, the researcher observed a trend toward documenting the first ADRs reported by patients. The report of subsequent ADRs was very sparse and could not be addressed due to the retrospective nature of the study.

Analytic study design

The retrospective nature of the study made it difficult to confirm the temporal sequence of ADRs and virologic failure. While ADRs could occur at any time point in the course of therapy and may be transient or chronic, virologic failure was assessed at fixed intervals. When a temporal sequence of exposure and outcome cannot be confirmed analytically, it is difficult to estimate the risk of the outcome based on the exposure (Bonita et al., 2006).

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusions

Antiretroviral therapy related ADRs were common in the studied population with an incident rate of 20 per 1000 py, mostly severe in grade, and occurred more frequently in the first year of therapy. The observed ADRs rate was lower than rates reported in other resource-poor settings. Virologic failure rate at 24, and 72 weeks was high (above 30%) but comparable to those reported in similar settings.

The most prevalent ADRs were fat distribution abnormalities such as lipodystrophy (2.7%), anaemia (1.9%), skin rash (0.7%) and peripheral neuropathy (0.5%). Other rare but serious ADRs such as Stevenson's Johnsons Syndrome (0.2%) and seizures (0.02%) were also observed in the study setting.

A number of risk factors associated with ADRs were identified. ADRs were independently predicted by older age; 2% greater likelihood of ADR for every year increment, and the use of abacavir or stavudine or didanosine ARV regimen compared to TDF containing regimen. In addition, there was a 56% greater likelihood of ADRs in the 2004 to 2006 patient cohort compared to the 2010 to 2012 cohort partly attributed to the higher use of stavudine and didanosine in 2004 to 2006.

A higher than expected rate of virologic failure ≥30% was observed at 24, 48, and 72 weeks of ART, however, the rates were comparable to rates reported in other resource-limited settings.
Marginal differences were observed in the predictors of early (24 weeks) and late (72 weeks) virologic failure. Early virologic was not associated with gender, but late virologic failure was independently predicted by male gender with a 19% greater likelihood in males. The likelihood of late virologic failure was 29% higher among patients initiated on nevirapine-based ART compared to efavirenz. Zidovudine and stavudine-based ARV regimen were protective of both early and late virologic failure compared to tenofovir-based regimens. Pre-treatment clinical characteristics that independently predicted early virologic failure included WHO disease stage

2, stage 3 and 4, $CD4^+$ cell count <200 cells/mm^3, and HIV RNA levels >10,000 copies/mL. Late virologic failure was predicted by WHO disease stage 2 and 3, $CD4^+$ cell count ≤100 cells/mm^3, and HIV RNA >100,000 copies/mL. Other predictors of virologic failure included earlier calendar year of ART initiation (2004 to 2009) which was predictive of early virologic failure, but protective of late virologic failure, and poor adherence to drug refill schedules (<95%) which was associated with higher likelihood of both early and late virologic failure.

Of all the ADRs observed in the study, only anaemia was significantly associated with virologic failure; with a 74% increase in the likelihood of late virologic failure, after adjusting for age, sex, baseline disease stage and $CD4^+$ cell count, antiretroviral regimen, and year of ART initiation.

7.2 Recommendations

Policy and practice: The comparatively low rates of ADRs reported in the studied population suggests that ARV medication were generally well tolerated among adults, but it also throws an important challenge of possible under-reporting of ART-related ADRs. A careful, intensive, aggressive and close follow-up of patients, throughout the duration of ART, is recommended to track both early and late onset ADRs and to manage them promptly. In addition, causality assessments using the appropriate algorithm should be performed and documented for all identified ADRs.

Although the use of more toxic ARV drugs such as stavudine and didanosine has been discontinued, the association of anaemia with late virologic failure is disconcerting and brings to the fore the need for close monitoring of haemoglobin levels in patients on ART for early identification and management of anaemia.

There is also an urgent need to adopt more pragmatic and intensive strategies to drive up the proportion of patients with virologic success, which is currently <70%, to the United Nations optimal target of 90%. In addition, patients who have failed first-line ART should be urgently identified and switched to effective second-line therapies. Maintaining patients on failing regimens increases the risk of accumulation of resistant mutations and limits future treatment options (Rawizza et al., 2013).

Future Research:

To accurately quantify the magnitude of and risk factors for ADRs in the patient population, a longitudinal, prospective observational design is recommended, as this will enable a time to event analysis of risk factors. Further studies are also recommended to accurately describe the profile of early and late onset ART-related ADRs in the patient population.

The reason why the 2004 to 2009 patients' cohort had better late virologic outcomes compared to the 2010 to 2012 cohort should be further investigated, as this might give insight into effective strategies to improve virologic outcomes in the study setting.

Three important research questions, which may be pursued in the future, arose from the present study. The questions are:

1. What is the effect of early and late onset ART-related ADRs on patients' adherence to ART?
2. What is the effect of early and late onset ART-related ADRs on patients' health-related quality of life?
3. What are effective strategies required to achieve both early and late viral suppression rate of 90% among patients on ART in the study setting?

REFERENCES

Abah, I. O., Akanbi, M., Abah, M. E., Finangwai, A. I., Dady, C. W., Falang, K. D., … Kanki, P. J. (2015). Incidence and predictors of adverse drug events in an African cohort of HIV-infected adults treated with efavirenz. *Germs*, *5*(3), 83–91. https://doi.org/10.11599/germs.2015.1075

Abah, I. O., Darin, M. K., Ebonyi, A. O., Ugoagwu, P., Ojeh, V. B., Naima, N., … Kanki, P. J. (2015). Patterns and Predictors of First-Line Antiretroviral Therapy Modification in HIV-1-Infected Adults in a Large Urban Outpatient Cohort in Nigeria. *Journal of the International Association of Providers of AIDS Care (JIAPAC)*. https://doi.org/10.1177/2325957414565508

Abah, I. O., Ojeh, V. B., Musa, J., Ugoagwu, P., Agaba, P. A., Agbaji, O., & Okonkwo, P. (2014). Clinical utility of pharmacy-based adherence measurement in predicting virologic outcomes in an adult HIV-infected cohort in Jos, North Central Nigeria. *Journal of the International Association of Providers of AIDS Care (JIAPAC)*, 2325957414539197. https://doi.org/10.1177/2325957414539197

Adeyemi, A., Olaogun, O., & Adesola, O. (2008). Challenges to adherence among HIV-positive patients on antiretroviral therapy in Lagos, Nigeria. *Journal of the International AIDS Society*, *11*(Suppl 1), P172. https://doi.org/10.1186/1758-2652-11-S1-P172

Agaba, P. A., Meloni, S. T., Sule, H. M., Agbaji, O. O., Ekeh, P. N., Job, G. C., … Kanki, P. J. (2014). Patients who present late to HIV care and associated risk factors in Nigeria. *HIV Medicine*, *15*(7), 396–405. https://doi.org/10.1111/hiv.12125

Agbaji, O. O., Abah, I. O., Falang, K. D., Ebonyi, A. O., Musa, J., Ugoagwu, P., … Kanki, J. (2015). Treatment Discontinuation in Adult HIV-Infected Patients on First-Line Antiretroviral Therapy in Nigeria. *Current HIV Research*, *13*(6), 184–192.

Agu, K. A., Isah, M. A., Oqua, D., Habeeb, M. A., Agada, P. O., Samuel, I., … Wutoh, A. K. (2013). Incidence of adverse drug reactions in patietnt on antiretroviral therapy: A study of pharmaceutical care in HIV interventions in Nigeria. *West African Journal of Pharmacy*, *24*(1), 30–42.

Agu, K. A., Oqua, D., Adeyanju, Z., Isah, M. A., Adesina, A., Ohiaeri, S. I., … Wutoh, A. K. (2014). The Incidence and Types of Medication Errors in Patients Receiving Antiretroviral Therapy in Resource-Constrained Settings. *PLoS ONE*, *9*(1), e87338. https://doi.org/10.1371/journal.pone.0087338

AIDSinfo. (2015). AIDSinfo Glossary of HIV/AIDS-Related Terms. [Online] https://aidsinfo.nih.gov/contentfiles/GlossaryHIVrelatedTerms_English.pdf [Accessed on August 1, 2017 15h45]

Amoroso, A., Etienne-Mesubi, M., Edozien, A., Ojoo, S., Sheneberger, R., Obiefune, M., … Redfield, R. R. (2012). Treatment Outcomes of Recommended First-Line Antiretroviral Regimens in Resource-Limited Clinics. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *60*(3), 314–320. https://doi.org/10.1097/QAI.0b013e31824e5256

Ananworanich, J., Moor, Z., Siangphoe, U., Chan, J., Cardiello, P., Duncombe, C., … Cooper, D. A. (2005). Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs. *AIDS (London, England)*, *19*(2), 185–92.

Arts, E. J., & Hazuda, D. J. (2012). HIV-1 Antiretroviral Drug Therapy. *Cold Spring Harbor Perspectives in Medicine*, *2*(4), a007161–a007161. https://doi.org/10.1101/cshperspect.a007161

Awodele, O., Ibrahim, A., & Orhii, P. (2016). Patterns of adverse drug reaction signals in NAFDAC Pharmacovigilance activities from September to November, 2014. *International Journal of Risk & Safety in Medicine*, *28*(1), 13–23. https://doi.org/10.3233/JRS-160669

Awofala, A. A., & Ogundele, O. E. (2015). HIV epidemiology in Nigeria. *Saudi Journal of Biological Sciences*. https://doi.org/10.1016/j.sjbs.2016.03.006

Balogun, S. H., & Adeleye, O. A. (2014). Patient reporting practices of suspected adverse drug reactions to antiretroviral drugs in a tertiary health facility in Nigeria. *The Nigerian Postgraduate Medical Journal*, *21*(4), 331–7.

Bangsberg, D. R., Hecht, F. M., Charlebois, E. D., Zolopa, A. R., Holodniy, M., Sheiner, L., … Moss, A. (2000). Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *Aids*, *14*(4), 357–366. [Online] http://journals.lww.com/aidsonline/Abstract/2000/03100/Adherence_to_protease_inhibitors,_HIV_1_viral.8.aspx [Accessed October 5, 2017 20h30]

Baril, J.-G., Junod, P., Leblanc, R., Dion, H., Therrien, R., Laplante, F., … Weiss, K. (2005). HIV-associated lipodystrophy syndrome: A review of clinical aspects. *The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses et de La Microbiologie Médicale*, *16*(4), 233–43.

Bärnighausen, T., Chaiyachati, K., Chimbindi, N., Peoples, A., Haberer, J., & Newell, M.-L. (2011). Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *The Lancet. Infectious Diseases*, *11*(12), 942–51. https://doi.org/10.1016/S1473-3099(11)70181-5

Barré-Sinoussi, F., Chermann, J. C., Rey, F., Nugeyre, M. T., Chamaret, S., Gruest, J., … Montagnier, L. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science (New York, N.Y.)*, *220*(4599), 868–71.

Barrett, J. S., Joshi, A. S., Chai, M., Ludden, T. M., Fiske, W. D., & Pieniaszek, H. J. (2002). Population pharmacokinetic meta-analysis with efavirenz. *International Journal of Clinical Pharmacology and Therapeutics*, *40*(11), 507–19.

Bartlett, J. A., Chen, S.-S., & Quinn, J. B. (2007). Comparative efficacy of nucleoside/nucleotide reverse transcriptase inhibitors in combination with efavirenz: results of a systematic overview. *HIV Clinical Trials*, *8*(4), 221–6. https://doi.org/10.1310/hct0804-221

Bassi, P., Gashau, W., Olaf, K., Dodoo, A., Okonkwo, P., & Kanki, P. (2017). Prevalence of adverse drug reactions among hiv/aids patients on haart in university of maiduguri teaching hospital (umth), nigeria: a four-year retrospective study. *BMJ Global Health*, *2*(Suppl 2), A39.2-A39. https://doi.org/10.1136/bmjgh-2016-000260.103

Bezabhe, W. M., Bereznicki, L. R., Chalmers, L., Gee, P., Kassie, D. M., Bimirew, M. A., & Peterson, G. M. (2015). Adverse Drug Reactions and Clinical Outcomes in Patients Initiated on Antiretroviral Therapy: A Prospective Cohort Study From Ethiopia. *Drug Safety*, *38*(7), 629–639. https://doi.org/10.1007/s40264-015-0295-7

Bisson, G. P., Gross, R., Bellamy, S., Chittams, J., Hislop, M., Regensberg, L., … Nachega, J. B. (2008). Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLoS Medicine*, *5*(5), 0777–0788. https://doi.org/10.1371/journal.pmed.0050109

Bonita, R., Beaglehole, R., & Kjellström, T. (2006). *Basic epidemiology* (2nd ed.). India: World Health Organization. https://doi.org/10.1016/S0015-0282(01)03155-7

Bonnet, F., Balestre, E., Bernardin, E., Pellegrin, J. L., Neau, D., & Dabis, F. (2005). Risk factors for hyperlactataemia in HIV-infected patients, Aquitaine cohort, 1999-2003. *Antiviral Chemistry and Chemotherapy*, *16*(1), 63–67.

Calmy, A., Hirschel, B., Cooper, D. A., & Carr, A. (2009). A new era of antiretroviral drug toxicity. *Antiviral Therapy*, *14*(2), 165–179.

Centers for Disease Control (CDC). (1981). Kaposi's sarcoma and Pneumocystis pneumonia

among homosexual men--New York City and California. *MMWR. Morbidity and Mortality Weekly Report*, *30*(25), 305–8.

Centers for Disease Control and Prevention (CDC). (2001). Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures--worldwide, 1997-2000. *Morbidity and Mortality Weekly Report (MMWR)*, *49*(51–52), 1153–6.

Cescon, A., Patterson, S., Chan, K., Palmer, A. K., Margolese, S., Burchell, A. N., … Yip, B. (2013). Gender differences in clinical outcomes among HIV-positive individuals on antiretroviral therapy in Canada: A multisite cohort study. *PLoS ONE*, *8*(12), 6–13. https://doi.org/10.1371/journal.pone.0083649

Cespedes, M. S., & Aberg, J. a. (2006). Neuropsychiatric complications of antiretroviral therapy. *Drug Safety*, *29*(10), 865–874. https://doi.org/10.2165/00002018-200629100-00004

Chen, M., Dou, Z., Wang, L., Wu, Y., Zhao, D., Gan, X., … Zhang, F. (2017). Gender Differences in Outcomes of Antiretroviral Treatment Among HIV-Infected Patients in China. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *76*(3), 281–288. https://doi.org/10.1097/QAI.0000000000001500

Chima, C. C., & Homedes, N. (2015). Impact of global health governance on country health systems: the case of HIV initiatives in Nigeria. *Journal of Global Health*, *5*(1), 10407. https://doi.org/10.7189/jogh.05.010407

Coulter, D. (2013). *A practical handbook on the pharmacovigilance of antiretroviral medicines*. Geneva: World Health Organization. [Online] http://apps.who.int/medicinedocs/documents/s16882e/s16882e.pdf [Accessed September 17, 2017 24h20]

Dalhatu, I., Onotu, D., Odafe, S., Abiri, O., Debem, H., Agolory, S., … Ellerbrock, T. V. (2016). Outcomes of Nigeria's HIV/AIDS treatment program for patients initiated on antiretroviral

treatment between 2004-2012. *PLoS ONE*, *11*(11), 1–25. https://doi.org/10.1371/journal.pone.0165528

Daniyam, C., Iroezindu, M., Shehu, N., Essien, M., Sati, A., & Agaba, E. (2011). Characteristics of HIV/AIDS Patients Presenting Late at a Teaching Hospital in Nigeria. *Journal of Medicine in the Tropics*, *13*(2), 68–71. https://doi.org/10.4314/jmt.v13i2.70699

Deeks, S., Lewin, S., & Havlir, D. (2013). The End of AIDS: HIV Infection as a Chronic Disease. *Lancet*, *382*(9903), 1525–1533. https://doi.org/10.1016/S0140-6736(13)61809-7.

Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Lancet*, *356*(9237), 1255–9. https://doi.org/10.1016/S0140-6736(00)02799-9

Egger, M., May, M., Chêne, G., Phillips, A. N., Ledergerber, B., Dabis, F., … Sterne, J. A. C. (2002). Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: A collaborative analysis of prospective studies. *Lancet*, *360*(9327), 119–129. https://doi.org/10.1016/S0140-6736(02)09411-4

El-Khatib, Z., Katzenstein, D., Marrone, G., Laher, F., Mohapi, L., Petzold, M., … Ekström, A. M. (2011). Adherence to drug-refill is a useful early warning indicator of virologic and immunologic failure among HIV patients on first-line art in South Africa. *PLoS ONE*, *6*(3). https://doi.org/10.1371/journal.pone.0017518

Eluwa, G. I., Badru, T., & Akpoigbe, K. J. (2012). Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. *BMC Clinical Pharmacology*, *12*(1), 7. https://doi.org/10.1186/1472-6904-12-7

Falang, K., Abah, I., Amos, F., Paul, I., Oche, A., Idoko, J., & Kanki, P. (2008). Reasons for first switches at the Jos university teaching hospital APIN centre ARV clinic. *XVII International AIDS Conference. 3-8 August 2008, Mexico City, Mexico*. XVII International AIDS Conference. 3-8 August 2008, Mexico City, Mexico.

Federal Ministry of Health (FMoH) [Nigeria]. (2010). *A Road Map for Impact on Malaria in Nigeria*. *A 5-year Strategic Plan: 2006-2010*.

Federal Ministry of Health (FMoH) Nigeria. (2007). National Guidelines for HIV and AIDS Treatment and Care in Adolescents and Adults. [Online] http://www.who.int/hiv/amds/Nigeria_adult_2007.pdf [Accessed August 15, 2015 18h20]

Federal Ministry of Health (FMoH) Nigeria. (2010). National Guidelines for HIV and AIDS Treatment and Care in Adolescents and Adults. [Online] http://www.who.int/hiv/pub/guidelines/nigeria_art.pdf [Accessed August 15, 2015 21h5]

Federal Ministry of Health (Nigeria). (2013). National HIV & AIDS and Reproductive Health Survey 2012 (NARHS Plus). *Fmoh*, (November), 527.

Federal Ministry of Health Abuja, N. (2016). (2016). *National guidelines for HIV prevention treatment and care ,National AIDS and STI's control programme.*

Forna, F., Liechty, C. A., Solberg, P., Asiimwe, F., Were, W., Mermin, J., … Weidle, P. J. (2007). Clinical Toxicity of Highly Active Antiretroviral Therapy in a Home-Based AIDS Care Program in Rural Uganda. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *44*(4), 456–462. https://doi.org/10.1097/QAI.0b013e318033ffa1

Fox, M. P., Cutsem, G. Van, Giddy, J., Maskew, M., Keiser, O., Prozesky, H., … Boulle, A. (2012). Rates and Predictors of Failure of First-line Antiretroviral Therapy and Switch to Second-line ART in South Africa. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *60*(4), 428–437. https://doi.org/10.1097/QAI.0b013e3182557785

Gallant, J. E., DeJesus, E., Arribas, J. R., Pozniak, A. L., Gazzard, B., Campo, R. E., … Cheng, A. K. (2006). Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *The New England Journal of Medicine*, *354*(3), 251–260. https://doi.org/10.1056/NEJMoa051871

Gilks, C. F., Crowley, S., Ekpini, R., Gove, S., Perriens, J., Souteyrand, Y., … De Cock, K. (2006). The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet (London, England)*, *368*(9534), 505–10. https://doi.org/10.1016/S0140-6736(06)69158-7

Granich, R., Gupta, S., Hersh, B., Williams, B., Montaner, J., Young, B., & Zuniga, J. M. (2015). Trends in AIDS Deaths, New Infections and ART Coverage in the Top 30 Countries with the Highest AIDS Mortality Burden; 1990–2013. *PLOS ONE*, *10*(7), e0131353. https://doi.org/10.1371/journal.pone.0131353

Gudina, E. K., Teklu, A. M., Berhan, A., Gebreegziabhier, A., Seyoum, T., Nega, A., … Assefa, Y. (2017). Magnitude of Antiretroviral Drug toxicity in adult HIV patients in Ethiopia: A cohort study at seven teaching hospitals. *Ethiopian Journal of Health Sciences*, *27*(1), 39. https://doi.org/10.4314/ejhs.v27i1.5S

Haas, D. W., Ribaudo, H. J., Kim, R. B., Tierney, C., Wilkinson, G. R., Gulick, R. M., … Acosta, E. P. (2004). Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS*, *18*(18), 2391–2400.

Hammond, R., & Harry, T. C. (2008). Efficacy of Antiretroviral Therapy in Africa: Effect on Immunological and Virological Outcome Measures – A Meta-Analysis . *International Journal of STD & AIDS*, *19*(5), 291–296. https://doi.org/10.1258/ijsa.2007.007248

Hawkins, T. (2010). Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Research*, *85*(1), 201–9. https://doi.org/10.1016/j.antiviral.2009.10.016

HUCE/PACE, & NAFDAC. (2009). *GHAIN Project, Pharmacovigilance for Antiretroviral Drugs Training for Health Care Professionals Participant's Manual*. (R. C. King, D. A. N. Oqua, & K. A. Agu, Eds.). Howard University Continuing Education PACE Center. https://doi.org/10.1177/0091270007308034

Inzaule, S., Otieno, J., Kalyango, J., Nafisa, L., Kabugo, C., Nalusiba, J., … Karamagi, C. (2014). Incidence and predictors of first line antiretroviral regimen modification in western Kenya. *PloS One*, *9*(4), e93106. https://doi.org/10.1371/journal.pone.0093106

Johnson, L. F., Mossong, J., Dorrington, R. E., Schomaker, M., Hoffmann, C. J., Keiser, O., … Boulle, A. (2013). Life Expectancies of South African Adults Starting Antiretroviral Treatment: Collaborative Analysis of Cohort Studies. *PLoS Medicine*, *10*(4). https://doi.org/10.1371/journal.pmed.1001418

Joly, V., Flandre, P., Meiffredy, V., Leturque, N., Harel, M., Aboulker, J.-P., & Yeni, P. (2002). Increased risk of lipoatrophy under stavudine in HIV-1-infected patients. *AIDS*, *16*(18), 2447–2454. https://doi.org/10.1097/00002030-200212060-00010

Kedir, M. S., Gemeda, D. H., & Suleman, S. (2015). Treatment Outcomes of Nevirapine-Versus Efavirenz-Based Highly Active Antiretroviral Therapy Regimens Among Antiretroviral-Naive Adult Patients in Ethiopia: A Cohort Study. *Therapeutic Innovation & Regulatory Science*, *49*(3), 443–449. https://doi.org/10.1177/2168479014565472

Keiser, O., Fellay, J., Opravil, M., Hirsch, H. H., Hirschel, B., Bernasconi, E., … Yerly, S. (2007). Adverse events to antiretrovirals in the Swiss HIV Cohort Study: Effect on mortality and treatment modification. *Antiviral Therapy*, *12*(8), 1157–1164.

Khan, K., Khan, A. H., Sulaiman, S. A. S., & Soo, C. T. (2015). P17.34 Survival trend and impact of adverse drug reactions during haart on survival function in hiv/aids patients. *Sexually Transmitted Infections*, *91*(Suppl 2), A236.1-A236. https://doi.org/10.1136/sextrans-2015-052270.612

Kingston-Riechers, J. (2011). The Economic Cost of HIV/AIDS in Canada. *Canadian AIDS Society*, *25*(8), 1–19. https://doi.org/10.1097/00126334-200206010-00006

Kityo, C., Gibb, D. M., Gilks, C. F., Goodall, R. L., Mambule, I., Kaleebu, P., … Dunn, D. T.

(2014). High level of viral suppression and low switch rate to second-line antiretroviral therapy among HIV-infected adult patients followed over five years: Retrospective analysis of the DART trial. *PLoS ONE*, *9*(3). https://doi.org/10.1371/journal.pone.0090772

Korsnes, J. S., Goodwin, B. B., Murray, M., & Candrilli, S. D. (2016). Antiretroviral Treatment Switching and Its Association With Economic Outcomes and Adverse Treatment Effects Among Commercially Insured and Medicaid-Enrolled Patients With HIV in the United States. *Annals of Pharmacotherapy*, *50*(12), 989–1000. https://doi.org/10.1177/1060028016659888

Lartey, M., Essel, A., Asante-Quarshie, A., Kenu, E., Ganu, V., & Neequaye, A. (2014). Dverse drug reactions to antiretroviral therapy during the early art period at a tertiary hospital in Ghana. *Pan African Medical Journal*, *18*, 1–6. https://doi.org/10.11604/pamj.2014.18.25.3886

Law, M. G., Achhra, A., Deeks, S. G., Gazzard, B., Migueles, S. A., Novak, R. M., … International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START Study Group. (2015). Clinical and demographic factors associated with low viral load in early untreated HIV infection in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. *HIV Medicine*, *16 Suppl 1*, 37–45. https://doi.org/10.1111/hiv.12232

Leutscher, P. D. C., Stecher, C., Storgaard, M., & Larsen, C. S. (2013). Discontinuation of efavirenz therapy in HIV patients due to neuropsychiatric adverse effects. *Scandinavian Journal of Infectious Diseases*, *45*(8), 645–651. https://doi.org/10.3109/00365548.2013.773067

Lucas, G. M., Chaisson, R. E., Moore, R. D., B, D., MA, C., NS, H., & al, et. (1999). Highly Active Antiretroviral Therapy in a Large Urban Clinic: Risk Factors for Virologic Failure and Adverse Drug Reactions. *Annals of Internal Medicine*, *131*(2), 81. https://doi.org/10.7326/0003-4819-131-2-199907200-00002

Manfredi, R., Calza, L., & Chiodo, F. (2004). Efavirenz Versus Nevirapine in Current Clinical Practice : *J Acquir Immune Defic Syndr*, *35*(5), 492–502. https://doi.org/10.1310/N4VT-3E9U-4BKN-CRPW

Masenyetse, L. J., Manda, S. O., & Mwambi, H. G. (2015). An assessment of adverse drug reactions among HIV positive patients receiving antiretroviral treatment in South Africa. *AIDS Research and Therapy*, *12*, 6. https://doi.org/10.1186/s12981-015-0044-0

Max, B., & Sherer, R. (2000). Management of the adverse effects of antiretroviral therapy and medication adherence. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *30 Suppl 2*(Supplement_2), S96-116. https://doi.org/10.1086/313859

Mbuagbaw, L. C., Irlam, J. H., Spaulding, A., Rutherford, G. W., & Siegfried, N. (2010). Efavirenz or nevirapine in three-drug combination therapy with two nucleoside-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals. *Cochrane Database of Systematic Reviews*, (12), CD004246. https://doi.org/10.1002/14651858.CD004246.pub3

McMahon, J. H., Elliott, J. H., Bertagnolio, S., Kubiak, R., & Jordan, M. R. (2013). Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: A systematic review. *Bulletin of the World Health Organization*, *91*(5), 377–385. https://doi.org/10.2471/BLT.12.112946

Meloni, S. T., Chang, C. A., Eisen, G., Jolayemi, T., Banigbe, B., Okonkwo, P. I., & Kanki, P. J. (2016). Long-Term Outcomes on Antiretroviral Therapy in a Large Scale-Up Program in Nigeria. *Plos One*, *11*(10), e0164030. https://doi.org/10.1371/journal.pone.0164030

Mojumdar, K., Vajpayee, M., Chauhan, N. K., & Mendiratta, S. (2010). Late presenters to HIV care and treatment, identification of associated risk factors in HIV-1 infected Indian population. *BMC Public Health*, *10*(1), 416. https://doi.org/10.1186/1471-2458-10-416

Monjok, E., Smesny, A., Okokon, I. B., Mgbere, O., & Essien, E. J. (2010). Adherence to antiretroviral therapy in Nigeria: an overview of research studies and implications for policy and practice. *HIV/AIDS (Auckland, N.Z.)*, *2*, 69–76.

Montaner, J. S. G., Reiss, P., Cooper, D., Vella, S., Harris, M., Conway, B., … JSG, M. (1998). A Randomized, Double-blind Trial Comparing Combinations of Nevirapine, Didanosine, and Zidovudine for HIV-Infected Patients. *Jama*, *279*(12), 930. https://doi.org/10.1001/jama.279.12.930

Moreno, S., López aldeguer, J., Arribas, J. R., Domingo, P., Iribarren, J. A., Ribera, E., … Pulido, F. (2010). The future of antiretroviral therapy: Challenges and needs. *Journal of Antimicrobial Chemotherapy*, *65*(5), 827–835. https://doi.org/10.1093/jac/dkq061

Mouton, J. P., Mehta, U., Parrish, A. G., Wilson, D. P. K., Stewart, A., Njuguna, C. W., … Cohen, K. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: A cross-sectional survey. *British Journal of Clinical Pharmacology*. https://doi.org/10.1111/bcp.12567

Mudzviti, T., Mudzongo, N. T., Gavi, S., Chimbetete, C., Maponga, C. C., & Morse, G. D. (2015). A Time to Event Analysis of Adverse Drug Reactions Due to Tenofovir, Zidovudine and Stavudine in a Cohort of Patients Receiving Antiretroviral Treatment at an Outpatient Clinic in Zimbabwe. *Pharmacology & Pharmacy*, *6*(3), 201–206. https://doi.org/10.4236/pp.2015.63021

Murphy, R. A., Sunpath, H., Kuritzkes, D. R., Venter, F., & Gandhi, R. T. (2007). Antiretroviral Therapy–Associated Toxicities in the Resource-Poor World: The Challenge of a Limited Formulary. *The Journal of Infectious Diseases*, *196*(s3), S449–S456. https://doi.org/10.1086/521112

National Agency for the Control of AIDS (NACA). (2015). Global AIDS Response Country

Progress Report - Nigeria GARPR 2015. [Online] https://doi.org/10.1016/S0140-6736(73)92790-6 [Accessed September 20, 2017 16h25]

National Population Commission (NPC) Nigeria. (2006). Population Distribution by Sex, State, LGAs and Senatorial District: 2006 Census Priority Tables (Vol 3). [Online] http://www.population.gov.ng/index.php/publications/140-population-distribution-by-sex-state-lgas-and-senatorial-district-2006-census-priority-tables-vol-3 [Accessed August 18, 2015 23h15]

Nemaura, T., Dhoro, M., Nhachi, C., Kadzirange, G., Chonzi, P., & Masimirembwa, C. (2012). Evaluation of the prevalence, progression and severity of common adverse reactions (Lipodystrophy, CNS, peripheral neuropathy, and hypersensitivity reactions) associated with Anti-Retroviral Therapy (ART) and anti-tuberculosis treatment in outpatients in . *Journal of AIDS and Clinical Research*, *4*(4). https://doi.org/10.4172/2155-6113.1000203

Ogwuche, L. O., Ojeh, V. B., London, I. A., Naima, N., Dady, C., Finangwai, A. I., … Agbaji, O. A. (2014). Adverse Drug Reaction Reports in an Antiretroviral Treatment Centre in Jos, North Central Nigeria. *British Journal of Pharmaceutical Research*, *4*(6), 714.

Oreagba, I. A., Usman, S. O., Olayemi, S. O., Oshikoya, K. A., Opanuga, O., Lesi, O. A., … Akanmu, A. S. (2014). Pharmacoepidemiology of antiretroviral drugs in a teaching hospital in lagos , nigeria. *Ghana Medical Journal*, *48*(4).

Ostrop, N. J., Hallett, K. A., & Gill, M. J. (2000). Long-term patient adherence to antiretroviral therapy. *Annals of Pharmacotherapy*, *34*(6), 703–709.

Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., … Singh, N. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine*, *133*(1), 21–30.

Pfister, M., Labbé, L., Hammer, S. M., Mellors, J., Bennett, K. K., Rosenkranz, S., & Sheiner, L. B. (2003). Population pharmacokinetics and pharmacodynamics of efavirenz, nelfinavir,

and indinavir: Adult AIDS Clinical Trial Group Study 398. *Antimicrobial Agents and Chemotherapy*, *47*(1), 130–7.

Pillay, P., Ford, N., Shubber, Z., & Ferrand, R. A. (2013). Outcomes for Efavirenz versus Nevirapine-Containing Regimens for Treatment of HIV-1 Infection: A Systematic Review and Meta-Analysis. *PLoS ONE*, *8*(7). https://doi.org/10.1371/journal.pone.0068995

Rajesh, R., Vidyasagar, S., Muralidhar, D., & Guddattu, V. (2012). Evaluation of direct cost of adverse drug reactions to highly active antiretroviral therapy in Indian human immunodeficiency virus positive patients. *Clincical Research in HIV AIDS and Prevention*, *1*(1), 12–22. https://doi.org/10.14302/issn.2324

Rawizza, H. E., Chaplin, B., Meloni, S. T., Darin, K. M., Olaitan, O., Scarsi, K. K., … Ambroise, A. (2013). Accumulation of Protease Mutations among Patients Failing Second-Line Antiretroviral Therapy and Response to Salvage Therapy in Nigeria. *PLoS ONE*, *8*(9), e73582. https://doi.org/10.1371/journal.pone.0073582

Reginald, O. O., Haruna, M. M., Sani, G. B., Eric, T. A., Adebola, O. T., Mathew, I., … Ibrahim, A. A. (2012). Adverse reactions associated with antiretroviral regimens in adult patients of a university teaching hospital HIV program in Zaria, Northern Nigeria: An observational cohort study. *Journal of Antivirals and Antiretrovirals*, *4*(1), 006–013. https://doi.org/10.4172/jaa.1000039

Rosen, S., Fox, M. P., & Gill, C. J. (2007). Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review. *PLoS Medicine*, *4*(10), 1691–1701. https://doi.org/10.1371/journal.pmed.0040298

Sanne, I. M., Westreich, D., Macphail, A. P., Rubel, D., Majuba, P., & Van Rie, A. (2009). Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study. *Journal of the International AIDS Society*, *12*, 38. https://doi.org/10.1186/1758-2652-12-38

Sarfo, F. S., Zhang, Y., Egan, D., Tetteh, L. a., Phillips, R., Bedu-Addo, G., … Chadwick, D. R. (2014). Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of ghanaian HIV-infected patients. *Journal of Antimicrobial Chemotherapy*, *69*(2), 491–499. https://doi.org/10.1093/jac/dkt372

Scarsi, K. K., Eisen, G., Darin, K. M., Meloni, S. T., Rawizza, H. E., Tchetgen Tchetgen, E. J., … Kanki, P. J. (2015). Superior Effectiveness of Zidovudine Compared with Tenofovir When Combined with Nevirapine-based Antiretroviral Therapy in a Large Nigerian Cohort. *Clinical Infectious Diseases*, *62*(4), 512–518. https://doi.org/10.1093/cid/civ928

Schwenk, A., Breuer, J. P., Kremer, G., Römer, K., Bethe, U., Franzen, C., … Salzberger, B. (2000). Risk factors for the HIV-associated lipodystrophy syndrome in a cross-sectional single-centre study. *European Journal of Medical Research*, *5*(10), 443–8.

Shet, A., Antony, J., Arumugam, K., Kumar Dodderi, S., Rodrigues, R., & DeCosta, A. (2014). Influence of adverse drug reactions on treatment success: Prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India. *PLoS ONE*, *9*(3). https://doi.org/10.1371/journal.pone.0091028

Shubber, Z., Calmy, A., Andrieux-Meyer, I., Vitoria, M., Renaud-Théry, F., Shaffer, N., … Ford, N. (2013). Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS (London, England)*, *27*(9), 1403–12. https://doi.org/10.1097/QAD.0b013e32835f1db0

Sivadasan, A., Abraham, O. C., Rupali, P., Pulimood, S. a., Rajan, J., Rajkumar, S., … Mathai, D. (2009). High rates of regimen change due to drug toxicity among a cohort of South Indian adults with HIV infection initiated on generic, first-line antiretroviral treatment. *Journal of Association of Physicians of India*, *57*(5), 384–388.

Spire, B., Carrieri, P., Garzot, M.-A., L'henaff, M., & Obadia, Y. (2004). Factors associated with

efavirenz discontinuation in a large community-based sample of patients. *AIDS Care*, *16*(5), 558–64. https://doi.org/10.1080/09540120410001716342

Strengthening Pharmaceutical Systems Program. (2011). Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Science, 1–143. [Online] http://apps.who.int/medicinedocs/documents/s19152en/s19152en.pdf [Accessed June 18, 2016 20h10]

Subbaraman, R., Chaguturu, S. K., Mayer, K. H., Flanigan, T. P., & Kumarasamy, N. (2007). Adverse effects of highly active antiretroviral therapy in developing countries. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *45*(8), 1093–1101. https://doi.org/10.1086/521150

Syed, I. A., Sulaiman, S. A. S., Hassali, M. A., & Lee, C. K. C. (2015). Adverse drug reactions and quality of life in HIV/AIDS patients: Advocacy on valuation and role of pharmacovigilance in developing countries. *HIV & AIDS Review*, *14*(1), 28–30. https://doi.org/10.1016/j.hivar.2014.07.004

Syed, I. A., Sulaiman, S. A. S., Hassali, M. A., Syed, S. H., Shan, L. H., & Lee, C. K. C. (2016). Factors associated with poor CD4 and viral load outcomes in patients with HIV/AIDS. *Journal of Medical Virology*, *88*(5), 790–797. https://doi.org/10.1002/jmv.24389

Tadesse, W. T., Mekonnen, A. B., Tesfaye, W. H., & Tadesse, Y. T. (2014). Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study. *BMC Pharmacology & Toxicology*, *15*(1). https://doi.org/10.1186/2050-6511-15-32

Taiwo, B. O., Idoko, J. A., Welty, L. J., Otoh, I., Job, G., Iyaji, P. G., … Murphy, R. L. (2010). Assessing the viorologic and adherence benefits of patient-selected HIV treatment partners

in a resource-limited setting. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *54*(1), 85–92.

Teklay, G. (2013). Adverse Effects and Regimen Switch among Patients on Antiretroviral Treatment in a Resource Limited Setting in Ethiopia. *Journal of Pharmacovigilance*, *1*(4), 1–5. https://doi.org/10.4172/2329-6887.1000115

The INSIGHT START Study Group. (2015). Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *New England Journal of Medicine*, *373*(9), 795–807. https://doi.org/10.1056/NEJMoa1506816

Torres, T. S., Cardoso, S. W., Velasque, L. S., Veloso, V. G., & Grinsztejn, B. (2014). Incidence rate of modifying or discontinuing first combined antiretroviral therapy regimen due to toxicity during the first year of treatment stratified by age. *Brazilian Journal of Infectious Diseases*, *18*(1), 34–41. https://doi.org/10.1016/j.bjid.2013.04.005

U.S. Department of Health and Human Services. U.S. Food and Drug Administration (FDA). (2014). FDA Adverse Event Reporting System (FAERS), 211414. [Online] Retrieved from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ [Accessed on November 15, 2016 20h30]

UK Collaborative HIV Cohort (UK CHIC) Steering Committee, Sabin, C. A., Schwenk, A., Johnson, M. A., Gazzard, B., Fisher, M., … Phillips, A. N. (2010). Late diagnosis in the HAART era: proposed common definitions and associations with mortality. *AIDS (London, England)*, *24*(5), 723–7. https://doi.org/10.1097/QAD.0b013e328333fa0f

UNAIDS. (2010). *Combination HIV Prevention: tailoring and coordinating biomedical, behavioural and structural strategies to reduce new HIV infections. A UNAIDS Discussion Paper*. [Online] http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/JC2007_Combination_Prevention_paper_en.pdf. [Accessed on August 16, 2016 19h30]

UNAIDS. (2014). THE GAP REPORT. https://doi.org/ISBN 978-92-9253-062-4

UNAIDS. (2016). Global Aids Update. [Online] http://www.who.int/hiv/pub/arv/global-AIDS-update-2016_en.pdf?ua=1 [Accessed on September 9, 2016 10h15]

UNAIDS. (2017). *Ending AIDS: Progress towards the 90–90–90 targets*. [Online] http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf [Accessed on June 16, 2016 21h35]

United Nations. (2016). *Political Declaration on HIV and AIDS: On the Fast Track to Accelerating the Fight against HIV and to Ending the AIDS Epidemic by 2030* (Vol. A/RES/70/2). [Online] http://www.unaids.org/sites/default/files/media_asset/2016-political-declaration-HIV-AIDS_en.pdf [Accessed on May 15, 2016 22h05]

Uzochukwu, B. S. C., Onwujekwe, O. E., Onoka, A. C., Okoli, C., Uguru, N. P., & Chukwuogo, O. I. (2009). Determinants of non-adherence to subsidized anti-retroviral treatment in southeast Nigeria. *Health Policy and Planning*, *24*(3), 189–96. https://doi.org/10.1093/heapol/czp006

Van-Griensven, J., Zachariah, R., Rasschaert, F., Mugabo, J., Atté, E. F., & Reid, T. (2010). Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *104*(2), 148–153. https://doi.org/10.1016/j.trstmh.2009.07.009

Van-Oosterhout, J. J., Bodasing, N., Kumwenda, J. J., Nyirenda, C., Mallewa, J., Cleary, P. R., … Zijlstra, E. E. (2005). Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. *Tropical Medicine and International Health*, *10*(5), 464–470. https://doi.org/10.1111/j.1365-3156.2005.01409.x

Wester, C. W., Okezie, O. A., Thomas, A. M., Bussmann, H., Moyo, S., Muzenda, T., … Marlink, R. G. (2007). Higher-Than-Expected Rates of Lactic Acidosis Among Highly Active Antiretroviral Therapy-Treated Women in Botswana. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *46*(3), 318–322. https://doi.org/10.1097/QAI.0b013e3181568e3f

World Health Organization (WHO). (2006). The Safety of Medicines in Public health programmes: Pharmacovigilance an essential tool. *WHO Library Cataloguing-in-Publication Data*, 61. [Online] http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf [Accessed on June 20, 2016 12h45]

World Health Organization (WHO). (2010). *AntiretrovirAl therApy for hiv infection in Adults And Adolescents: Recommendations for a public health approach* (Vol. 4911). [Online] http://www.who.int/hiv/pub/arv/adult2010/en/index.html [Accessed on March 19, 2017 09h15]

World Health Organization (WHO). (2012). SAFETY MONITORING of MEDICINAL PRODUCTS. *WHO Publications*. [Online] http://www.who.int/medicines/areas/quality_safety/safety_efficacy/ConsumerReporting.pdf?ua=1 [Accessed on March 14, 2017 20h16]

World Health Organization (WHO). (2013). WHO | Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. [Online] http://www.who.int/hiv/pub/guidelines/arv2013/download/en/ [Accessed on August 18, 2015 15h20]

World Health Organization (WHO). (2016a). *Consolidated Guideline on the use of antiretroviral drugs for treating and preventing HIV infection* (2nd ed.). Geneva: World Health Organization. [Online] http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1

[Accessed on October 15, 2016 14h45]

World Health Organization (WHO). (2016b). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach* (2nd ed.). France: World Health Organization. [Online] http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf [Accessed on October 20, 2017 08h35]

APPENDICES

APPENDIX 1: Data Extraction Form

Part A: Socio-demographics

1. Unique identifier:

2. Sex-

Male	
Female	

3. Marital status-

Single	
Married	
Separated	
Divorced	
Widow/Widower	

4. Highest education

No formal education	
Primary	
Secondary	
Tertiary	

5. Occupation-

Unemployed	
Informal employment	
Formal employment	

Part B: HIV risk characteristics

6. Mode of HIV transmission

Specify	

Part C: Clinical characteristics

7. WHO clinical disease stage at base line

1	2	3	4

8. TB co-infection at base line

Yes	No

9. Hepatitis B virus co-infection at baseline

Yes	No

–

10. Hepatitis C virus co-infection at baseline	Yes	No
11. CD4 cell count (cells/mm3)-	Baseline.	
	6 month	
	12 month	
	24 Month	
	36 month	
	48 month	
12. HIV RNA levels (Viral load) copies/ml-	Baseline	
	6 month	
	12 month	
	24 Month	
	36 month	
	48 month	

Part D: Adverse drug reactions (ADR)

13. Experience an ADR-	Yes	No		
14. Date of first ADR (If yes to 13 above)- Date				
15. Severity of ADR (WHO grade)-	1	2	3	4
16. Type of first ADR (clinical description based on ICD-10)				
17. Other ADRs with dates				
18. Total number of ADRs				

Part E: Medication characteristics

19. Date commenced ART: Date	
20. First Antiretroviral regimen- names and codes	
21. Other non-antiretroviral drugs	

Part F: Medication adherence characteristics

22. Medication refill adherence at months	6	12	24	36	48

APPENDIX II: University of Western Cape (UWC) Research Ethics Committee approval letter

UNIVERSITY of the WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

Private Bag X17, Bellville 7535
South Africa
T: +27 21 959 2988/2948
F: +27 21 959 3170
E: research-ethics@uwc.ac.za
www.uwc.ac.za

19 January 2017

Dr OI Abah
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM/17/1/13

Project Title: Adverse drug reactions to antiretroviral drugs: effect on virologic failure in a Nigerian cohort of HIV infected adults on first line antiretroviral therapy.

Approval Period: 15 December 2016 – 15 December 2017

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval. Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER -130416-050

APPENDIX III: Jos University Teaching Hospital letter of ethical clearance

JOS UNIVERSITY TEACHING HOSPITAL
JOS, NIGERIA

Phone: 073-456226-9
E-mail: juth@infoweb.abs.net

Cables & Telegram: JUTH
P.M.B. 2076
JOS

JUTH/DCS/ADM/127/XIX/6684

Ref: .....

25th January, 2017.

Date: .....

Abah Okoh Isaac,
Department of Pharmaceutical Services,
Faculty of Medical Science,
University of Jos,
Jos-Nigeria.

RE: ETHICAL CLEARANCE/APPROVAL

I am directed to refer to your application dated 25th January, 2017 on the research proposal titled:

"Adverse drug reactions to antiretroviral drugs: Effect on Virologic Failure in a Nigerian Cohort of HIV-infected Adult on first-line Antiretroviral therapy"

Following recommendation from the Institutional Health Research Ethics Committee, I am to inform you that Management has given approval for you to proceed on your research topic as indicated.

You are however required to obtain a separate approval for use of patients and facilities from the department(s) you intend to use for your research.

The Principal Investigator is required to send a progress report to the Ethical Committee at the expiration of three (3) months after ethical clearance to enable the Committee carry out its oversight function.

Submission of final research work should be made to the Institutional Health Research Ethical Committee through the Secretary, Administration Department, please.

On behalf of the Management of this Hospital, I wish you a successful research outing.

Comfort A. Onoja
For: Chairman, *MAC*

RESEARCH AND CONTINUING EDUCATION
25 JAN 2017

APPENDIX IV: Harvard T. H. Chan approval letter for use of secondary data

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Harvard T.H. Chan School of Public Health
Immunology & Infectious Diseases
651 Huntington Avenue, FXB Room 405
Boston, MA 02115

Notification of Approval for Secondary Use of Data

30 January 2017

Abah Okoh Isaac
Assistant Director of Pharmaceutical Services
Jos University Teaching Hospital, AIDS Prevention Initiative in Nigeria
Jos, Plateau State, NIGERIA
isaacabah@gmail.com

Dear Mr. Isaac Abah:

Thank you very much for completing the Secondary Use of Data Form for the use of the Harvard PEPFAR Database and Repository Bank. Dr. Phyllis Kanki and I have reviewed your application and approve your use of data and/or samples for the following study:

Adverse drug reactions to antiretroviral drugs: effect on virologic failure in a Nigerian cohort of HIV-infected adults on first-line antiretroviral therapy

Please note, this is an approval for secondary use of data, not for human research. You must obtain all necessary IRB approvals or waivers as required by your study institution(s) before commencing human research. Should your study undergo any changes in protocol or require additional data and/or samples from the Harvard PEPFAR Database and Repository Bank that are not already indicated in your completed form, please be sure to contact Dr. Kanki (pkanki@hsph.harvard.edu) or myself (cachang@hsph.harvard.edu) before effecting these changes.

For any publications that result from this research, please be sure to:

1. Indicate the use of informed consent. Your publication should include a statement that affirms that all study participants in the Harvard/APIN PEPFAR program provided informed consent for use of their data and/or samples for research.
2. Acknowledge the source of funding for support of the patients and their care. You may use the following statement as an example:
   This work was funded in part by the US Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and the Centers for Disease Control and Prevention (CDC) through a cooperative agreement with APIN (PS 001058). The contents are solely the responsibility of the authors and do not represent the official views of the funding institutions.

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

If you have any questions, please contact me. Once again, thank you very much for your application and best of luck as you begin your research.

Sincerely,

Charlotte Chang
Harvard PEPFAR IRB Coordinator

cc: Phyllis Kanki, DVM SD

APPENDIX V: APIN Centre Jos University Teaching Hospital approval for use of secondary data

APIN CENTRE
Jos University Teaching Hospital

2nd February, 2017

Aboh Okoh Isaac
Pharmacy Department,
Jos University Teaching Hospital,
Jos.

RE: APPLICATION FOR USE OF SECONDARY DATA

I am directed to refer to your application dated 25th January, 2017 requesting permission to use data in JUTH-APIN for your study on *"Adverse Drug Reactions to Antiretroviral Drugs: Effects on Virologic Failure in a Nigerian Cohort of HIV-infected Adults on First-line Antiretroviral Therapy"* for which you have obtained ethical clearance and approval from the JUTH Health Research Ethics Committee.

JUTH-APIN Management has given approval for you to access secondary data of patients in the Adult ARV clinic covering the period June 2004 – February 2012 in line with your specified data extraction areas.

Prior to the commencement of the work, you are to meet the Research Coordinator for guidance on researches. The Data Manager will grant you the access to the data requested.

Upon your obtaining approval from Harvard T. H. Chan for secondary use of Data, you are advised to acknowledge the funding support of the patients in any publication resulting from the study using this data.

On behalf of the Management, I wish you a fruitful research.

ALECHENU EMMANUEL O.
for Principal Investigator

Office of the Principal Investigator
DESPATCHED
JUTH APIN, JOS
Date 02/02/17
Sign

Cc:
Research Coordinator, JUTH-APIN
Data Manager, JUTH-APIN

2 Murtala Mohd Way, Jos Plateau State, Nigeria. E-mail: juthapin@yahoo.com
Box 10255, Unijos P. O. Tel: 097830955