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Predictors of Lost to Follow-Up (LTFU) among Paediatrics on Antiretroviral Therapy (ART) in Nigeria

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Predictors of Lost to Follow-Up (LTFU) among paediatrics on Antiretroviral Therapy (ART) in Nigeria.

A thesis submitted in partial fulfilment of the requirement for the degree of Master of Science in Public Health

by

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Signature:

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List of Abbreviations

ABC	Abacavir
AHR	Adjusted Hazard Ratio
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral drug
AZT	Zidovudine
BMI	Body Mass Index
CBO	Community-Based Organisation
CD4	Cluster of Differentiation 4
CHR	Crude Hazard Ratio
CI	Confidence Interval
DHIS2	District Health Information Software
DQA	Data Quality Assessment
EMR	Electronic Medical Record
FMoH	Federal Ministry of Health
FSW	Female Sex Worker
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
HIV	Human Immunodeficiency Virus
INH	Isoniazid
LGA	Local Government Area
LTFU	Lost to Follow-Up
M&E	Monitoring and Evaluation
MSM	Men who have Sex with Men
NACA	National Agency for the Control of AIDS
NAIIS	National HIV/AIDS Indicator and Impact Survey
NDR	National Data Repository
NGO	Non-Governmental Organisation
NMRS	Nigeria Medical Record System
NOMIS	National OVC Management Information System
NSF	National HIV/AIDS Strategic Framework
NSP	National HIV/AIDS Strategic Plan
OVC	Orphans and Vulnerable Children
PEPFAR	United States President's Emergency Plan for AIDS Relief
PLHIV	People Living with HIV
PMTCT	Prevention of Mother to Child Transmission
SDG	Sustainable Development Goals
SSA	Sub-Saharan Africa
STATA	Statistical Software for Data Science
TB	Tuberculosis
TDF	Tenofovir

UN	United Nations
UNAIDS	United Nations Joint Programme on HIV/AIDS
WHO	World Health Organisation

Glossary

ART	"ART is a life-long treatment that involves the use of a combination of three or more ARV drugs for treating HIV infection" (1).
Cox-proportional Logistic Regression	"This is a statistical method used to analyse the effect of several risk factors on time taken for an event to happen" (2).
Kaplan-Meier Analysis	This analysis calculates the time until the study participants present an event of interest (3).
LTFU in the ART program	LTFU occurs when children are without documented date of ARV refill, ARV regimen and ARV duration 28 days after an expected ARV refill appointment to the hospital and not documented as dead or transferred out in the NDR (4).
OVC	"These are children living with HIV, living with caregivers who are living with HIV, orphaned, at risk of becoming infected, or a combination of these factors" (5).

Abstract

Introduction:

Antiretroviral therapy (ART) aims to achieve undetectable viral load, improve patient health outcomes, and increase the survival of paediatrics living with HIV. However, despite the expansion of ART with a significant focus on paediatrics, lost to follow-up (LTFU) among this vulnerable population has become a considerable concern in public health, negatively impacting treatment outcomes. There is limited information about LTFU among paediatrics in Nigeria. This study estimates the incidence and predictors of LTFU among paediatrics on ART in Nigeria.

Methodology:

A longitudinal retrospective cohort study was conducted among 7,948 children in Nigeria who started ART in 2016. Kaplan-Meier cumulative hazard curve was used to estimate the incidence of LTFU, and hazard curves of categorical variables were compared using the log-rank test. Variables with a p-value of <0.05 in the multivariate Cox-proportional hazard model were considered statistically significant predictors of LTFU.

Results:

The overall incidence of LTFU was 40 per 100 child-years (95%CI: 39.77,41.27). Children aged 5–9 years (AHR: 0.9, 95%CI: 0.8,1.0), informally employed caregivers (AHR: 3.6, 95%CI: 1.5,8.7), children with advanced HIV disease (WHO stage III (AHR: 1.3, 95%CI: 1.1,1.5) and IV (AHR: 1.5, 95%CI: 1.1,2.2)), and CD4 count of ≥1,000 cells/mm^3 (AHR: 0.8, 95%CI: 0.6,1.0) were statistically significant predictors of LTFU.

Discussion:

Fifty-five per cent of children were LTFU from the ART program in Nigeria. Diverse socio-demographic and clinical factors influence LTFU among paediatrics. Hence, program interventions in Nigeria should focus on child-centred approaches.

Keywords: Lost to follow-up, Paediatric HIV, Incidence, Predictors, Nigeria

Word Count: 12,540

Introduction

For over seven years, I worked with various implementing partners on Human Immunodeficiency Virus (HIV) programming in Nigeria, including implementation for the paediatrics, general and key populations. Working in the strategic information department with one of the US president's emergency plan for AIDS relief (PEPFAR)-funded implementing partners in Nigeria, I conducted routine data analysis in the HIV program. I observed gaps during data analysis at various levels of the HIV care continuum, especially among paediatrics, and the high reported number of losses from the treatment program and unsuppressed viral load among this vulnerable sub-population. In addition, little research had been done among paediatrics in Nigeria on LTFU, which made me curious to know the reasons for the losses, and I decided to conduct this research. I took a bold step to learn various statistical analyses, including survival analysis using STATA.

This study aims to estimate the incidence and influencing factors of LTFU in the paediatric ART program in Nigeria. With this thesis, I hope to provide more insight into the issue of LTFU among paediatrics and provide recommendations to the national HIV/AIDS program, implementing partners, Federal Ministry of Health (FMoH) and the government of Nigeria on interventions to reduce LTFU of paediatrics on ART in Nigeria.

The structure of this thesis is as follows; chapter one gives background information about Nigeria, including the characteristics of paediatrics in the country, an analysis of the healthcare system and an overview of HIV globally and in Nigeria. Chapter two highlights the problem statement, justification, objectives, research questions and methodology. Chapter three presents the study results, and chapter four discusses the findings. Chapter five provides a conclusion of the study and recommendations.

CHAPTER ONE

1.1. Background Information of Nigeria

1.1.1. Geographic, Demographic, Ethnic and Socio-economic Features

Nigeria is in the western part of Africa with Niger, Gulf of Guinea, Chad and Cameroun, and Benin on the North, South, East, and West borders, respectively ***(see Figure 1)*** and is situated between latitude 4˚16' to 13˚N53' and longitude 2˚ to 15˚E (6,7). Nigeria has thirty-six states and the Federal Capital Territory; further divided into 774 local government areas (LGA) in six geo-political zones (North-East, North-West, North-Central, South-East, South-West, South-South) (6,7). The climate is tropical, with varying seasons at separate times of the year and between the northern and southern parts of the country (6,7). Rainfall is more in the south from March to November and in the North from mid-May to November when the dry season (harmattan) ends (6,7).

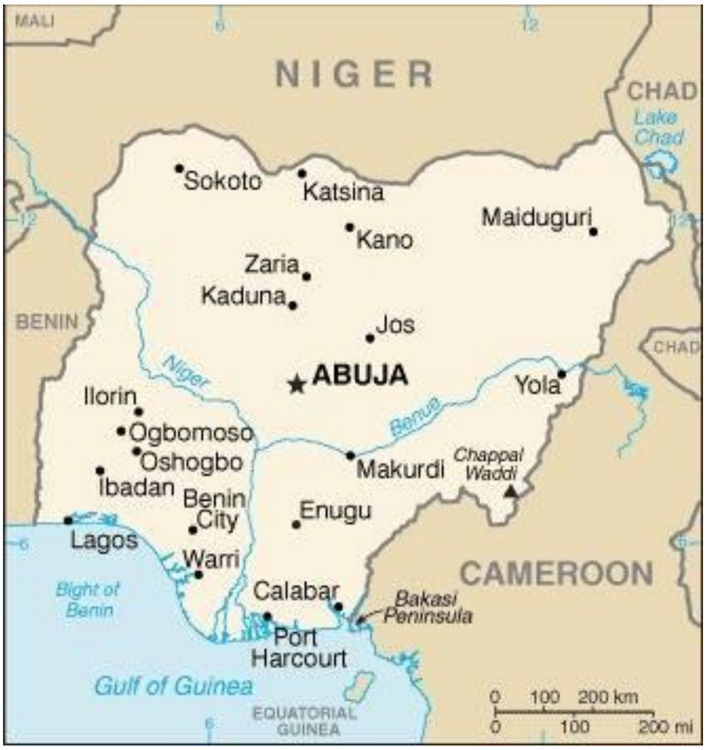


Figure 1: Map of Nigeria showing the respective borders (Source: The World Factbook, 2022) (8)

Nigeria is Africa's most populous country, with about 210 million people in 2021 living on approximately 923,768 square kilometres, and the population is estimated to increase in the coming years (9,10). Nigeria has a notably young population with a median age of 18.4 years, ranking as the 18th country with the lowest median age in Africa and the world (9,10). About 43.3% of Nigerians are below 15 years, 53.8% are between 15 and 64 years, while 2.7% are above 64 years of age ***(see Figure 2)***. The population comprises 50.6% males and 49.4% females (9,10).

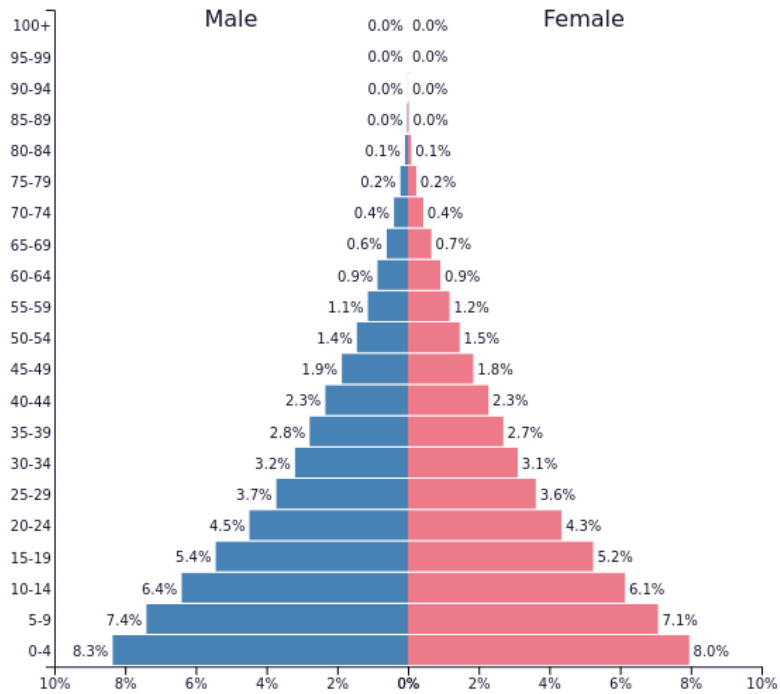


Figure 2: Population pyramid of Nigeria (Source: PopulationPyramid.net, 2021) (11)

About 50% of Nigerians live in urban areas with a 3.92% annual rate of urbanisation (8). The people of Nigeria are diverse, with over 250 ethnic groups and more than five hundred languages and English as the official language after the British colonisation (8,12). The three major ethnic groups are Hausa (29%), Igbo (18%) and Yoruba (21%), who dwell in the North, Southeast and Southwest, respectively (8,12).

Exports of crude oils are the primary source of foreign exchange earnings in Nigeria, accounting for about half of government revenues and a large share of the country's exports (80%) (13). The COVID-19 pandemic led Nigeria into the worst recession experienced in 20 years with a decrease in oil prices; however, in 2021, with the ease of lockdowns, the economy grew along with a recovery of oil prices (14).

The 2019 National Bureau of Statistics report stated that about 40% of Nigerians lived below the poverty line of $382 annually: 18% and 52.1% in the urban and rural areas, respectively (15). Nigeria has Africa's highest Gross Domestic Product (estimated at $1.05 trillion in 2021). However, the weak financing system, especially in healthcare, has led to a low life expectancy of 55 years and poor health outcomes (16,17).

The country has experienced security unrest in the North by the Boko haram terrorist group since 2011, an increased number of kidnappings and banditry in the North-West and turmoil in the South-East from nonconformist agitations (14). The unemployment rate in Nigeria has been steadily growing and was 33.3% in 2020, and the underemployment rate was 22.8% (18). Literacy level is higher among urban dwellers than their counterparts in rural areas (7,19). The education level of men is higher than that of women, with 17% of men and 11% of women having more than secondary education (19).

1.1.2. Paediatrics in Nigeria

In Nigeria, children aged 0–14 years are classified as paediatrics; this age group makes up almost half (43.3%) of the population (20). Those aged 0–4 years are 16.3%, 5–9 years are 14.5%, and 10 to 14 years are 12.5% of the total population (20). Boys in the paediatric age group (22.1%) are about 1% greater than girls in the same age group (21.2%) (20). In this study, paediatrics and children are used interchangeably. Primary education in public schools is free in Nigeria. However, only 67% of children are in primary schools, accounting for one-in-five out-of-school children globally, with girls disproportionately affected (20). The rate of out-of-school children is higher in northern Nigeria due to socio-economic, sociocultural beliefs, and security challenges, with only about 53% of children enrolled in primary school (21). Twenty-three million girls and women were child brides making it the highest number in Africa (20). In 2013, the United Nations children's fund reported an estimate of 11.5 million orphans and vulnerable children (OVC) in Nigeria due to all death causes and 19% (2.2 million) are due to acquired immunodeficiency syndrome (AIDS) (22).

1.1.3. Analysis of the Nigerian Health System and Disease Burden

Private and public sectors provide primary, secondary and tertiary healthcare services ***(see Figure 3)*** (23). Primary health care is the hinge upon which the Nigerian health system rests. The inferior quality of services at the primary and secondary healthcare levels has made people bypass these levels and seek care at the tertiary healthcare level, and some seek care overseas (23). The thriving private health sector, which accounts for about 30% of healthcare facilities, provides 60% of the healthcare services in Nigeria. This includes private-for-profit providers and not-for-profit services by faith-based and non-governmental organisations (NGOs) (23). Drug shops, complementary and alternative health practitioners, patent and proprietary medicine vendors and traditional medicine providers are also part of the health sector (23).

Socio-economic status and geographic location have led to health inequities evident in some of the country's poor health outcomes. Distance to the healthcare facility, cost of healthcare services and the attitude of healthcare workers are the significant barriers that prevent people from accessing healthcare services (7). In recent years, Nigeria has made remarkable achievements by eradicating guinea worm and controlling the Polio and Ebola Virus disease outbreaks (7). Progress has also been made in specific health indicators, such as infant and under-five mortality, but some other indicators are still lagging (7). As of 2018, infant mortality reduced from 75 to 67 deaths per 1,000 live births, under-five mortality from 157 to 132 per 1,000 live births but no observed change in neonatal mortality (39 per 1,000 live births) in the last decade (19).

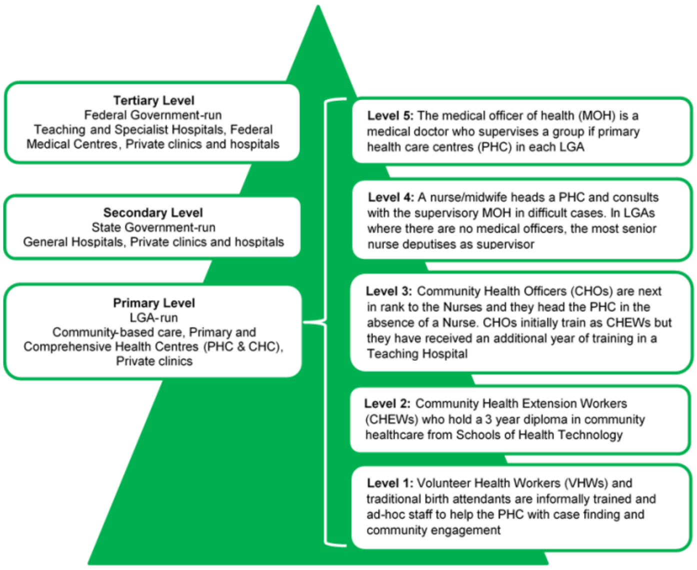


Figure 3: Structure of the Nigerian healthcare system (Source: Federal Government of Nigeria, 2018) (23)

Due to demographic and epidemiological transition, Nigeria has a high burden of communicable diseases and an increasing prevalence of non-communicable diseases (7). Human immunodeficiency virus (HIV), malaria, tuberculosis (TB), diarrhoea, measles and neglected tropical diseases, such as schistosomiasis, contribute to 66% of the total morbidity burden of the country (7). The avian influenza outbreak and Lassa fever have increased the disease burden (7). There is an increase in the morbidity and mortality rate of non-communicable diseases such as diabetes, chronic obstructive lung disease, cardiovascular disease, and cancer (7). The rise in violence and unrest have led to increased injuries, mental health disorders, disabilities, and other psychosocial problems (7). The leading causes of mortality among children are diarrhoea, malaria, vaccine-preventable diseases, pneumonia, and HIV (7). The incidence and mortality rate of HIV are declining; however, the absolute number of infected and affected persons is still a significant burden on the country's healthcare system and resources (7).

1.2. Overview of HIV

1.2.1. Burden of HIV

HIV is a global public health concern with no cure and a record of about 36.3 million AIDS-related deaths (24). In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) developed the 95-95-95 targets to ensure that 95% of people living with HIV know their status, 95% of those with HIV are on Antiretroviral Therapy (ART), and 95% of those on ART have viral suppression by 2030 (25). In addition, these targets were further emphasised in June 2021, during a political declaration on HIV/AIDS by the United Nations (UN) general assembly to end inequalities and AIDS by 2030 while making progress towards achieving the Sustainable Development Goal (SDG) on healthy lives and wellbeing (26). The declaration also included a commitment to stop vertical transmission of HIV and end AIDS among paediatrics by 2025 (26).

About 37.7 million people were living with HIV in 2020, with more than two-thirds of this population in Africa. In the same year, 1.5 million people were newly infected globally, with 680,000 HIV-related deaths (24,27). Globally, in 2020, only 54% of paediatrics living with HIV out of the estimated 1.72 million were on ART, with 84% of this population living in sub-Saharan Africa (SSA) (28). About 160,000 paediatrics were newly infected with HIV through vertical transmission from their mothers during pregnancy, delivery or while breastfeeding and 86,000 died from preventable AIDS-related causes globally in the same year (28). Treatment coverage among paediatrics (54%) was 20% less than the coverage among adults (74%), and only 40% had viral suppression in 2020 ***(see Figure 4)*** (29). Nigeria must intensify efforts to achieve the UNAIDS global 95-95-95 targets for the paediatric sub-population (24).

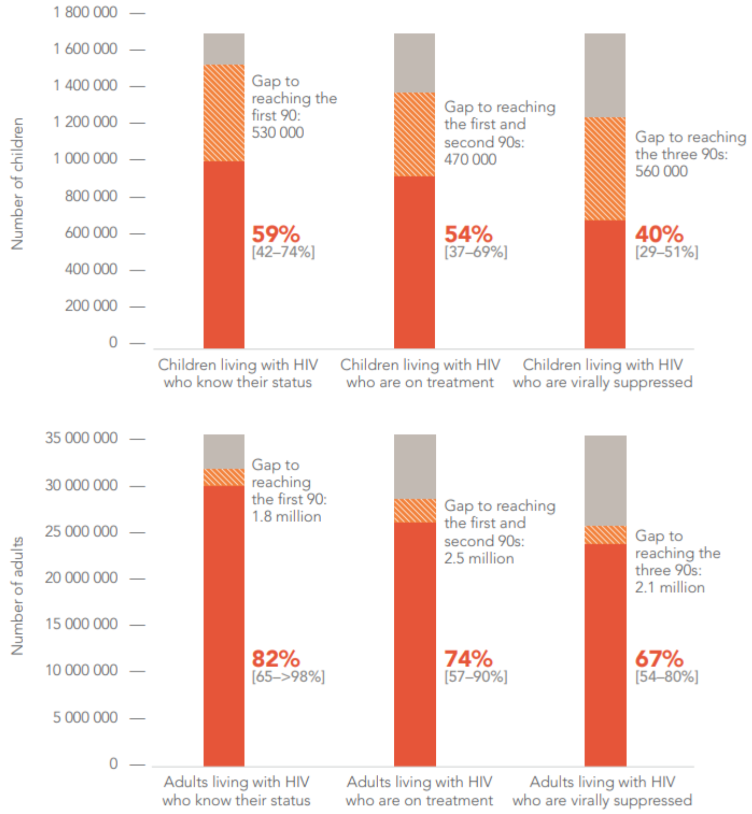


Figure 4: Global HIV testing and treatment coverage among paediatrics (0-14 years) and adults (15 years and older), 2020 (Source: UNAIDS special analysis, 2021) (29)

1.2.2. Transmission, Symptom and Diagnosis of HIV

HIV attacks the person's immune system and limits the ability to fight infections and cancers, thus leading to immunodeficiency (24). AIDS is the last stage of HIV infection, with diverse manifestations like cancers and conditions at varying progression rates depending on individuals and treatment (24). People Living with HIV (PLHIV) can live long and healthy lives with improved access to prevention, diagnosis, care, and treatment of HIV, making the disease a controllable chronic condition (24). HIV can be transmitted when an infected person transfers body fluids such as blood, semen, vaginal secretions, and breast milk (24). It can also be transmitted vertically during pregnancy and delivery from mother to child, with a risk of 15-45% without interventions (24,30). The chances of sexual transmission are reduced in infected persons on ART that have achieved virologic suppression (24).

The stages of infection have different manifestations. The first few months are usually the most infectious (24). The latency period of infection is shorter in children (30). A few weeks after infection, the first symptoms may be fever, headache, rash, sore throat, or no symptoms at all (24). Without ART, the immune system is further weakened, and other symptoms such as weight loss, fever, diarrhoea, and cough develop due to advanced diseases such as TB, Kaposi's sarcoma, bacterial infections, lymphomas and cryptococcal meningitis (24). In children, the predominant symptoms are respiratory infections, fever, weight loss, diarrhoea, lymphadenopathy, oral thrush, malnutrition, and septicaemia (31–33).

The rate of disease progression between children and adults differs. Children have a developing immune system and experience a faster disease progression and shorter duration for each phase of the disease (30). Out of the children infected with HIV perinatally, about 25% to 30% rapidly develop HIV/AIDS symptoms and die by one year of age. About 50% to 60% have early signs and die between the age of three to five years, and about 5% to 25% live beyond eight years of age (30).

The virus can be diagnosed through rapid diagnostic tests identifying antibodies in infected individuals above 18 months, with results on the same day (24). For children below the age of 18 months, HIV diagnosis is through nucleic tests (Polymerase Chain Reaction) (30). Confirmatory tests are done to get a complete HIV diagnosis using World Health Organisation (WHO)-certified tests and country-specific testing algorithms (24). Advancements in the HIV program have made it possible for people to conduct self-tests (24). Antiretroviral (ARV) medication administered to children is a triple-drug therapy (combination of three ARV medications) to reduce disease progression (34).

1.2.3. HIV Program in Nigeria

Nigeria accounted for about 5%, 6% and 7% of the global PLHIV, new infections and AIDS-related deaths, respectively, in 2020 (27,29). The National Agency for the Control of AIDS (NACA) manages the coordination of the country's overall HIV response while working with the Federal Ministry of Health (FMoH), which controls the response across the health sector and other relevant sectors ***(see Appendix 1 for the structure of the HIV response coordination)*** (35). The National HIV/AIDS Strategic Framework (NSF) and Plan (NSP) were developed as a national response to tackle the high burden of HIV by preventing new infections and to ensure the excellent health and wellbeing of people infected with and affected by HIV/AIDS (36). These documents set the country on course towards reducing the prevalence of HIV while increasing the uptake of testing, better access to ART, and improving the access of vulnerable children to treatment, care, and support. Nigeria adopted the test and treat initiative in 2016. Furthermore, the NSF was put in place to align the national response with the global strategy with a focus on the "Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030", the Sustainable Development Goals (SDGs), and the 90-90-90 target (37).

The thematic areas of focus for the NSF and NSP are:

i. Prevention of HIV among general and key populations
ii. HIV testing services
iii. Elimination of Mother to Child Transmission of HIV
iv. HIV treatment
v. Care, support, and adherence

HIV in Nigeria is a mixed epidemic, a general epidemic among the general population and concentrated epidemics among the key populations and other vulnerable groups with survey reports such as the National HIV Sero-prevalence Sentinel Survey among pregnant women attending antenatal care; the Integrated Behavioural and Biological Surveillance Survey for key populations; the National HIV/AIDS and Reproductive Health Survey among the general population; and National HIV/AIDS Indicator and Impact Survey (NAIIS) showing this trend (37). The disease's prevalence and trend vary across the country's different geographical regions ranging from 4.8% in Akwa Ibom and Benue states to 0.3% in Jigawa and Katsina States (38).

After the year two thousand, the rate of new infections was highest among children from vertical transmission due to limited options to avert mother-to-child transmission and the increased prevalence of HIV among women of reproductive age (39). However, the expansion of the Prevention of Mother to Child Transmission (PMTCT) program across the country has reduced the number of new infections among this group by 50% (39). Never married males and females are estimated to make the highest contribution to the number of new HIV infections among the adult population, followed by female sex workers (FSW) and men who have sex with men (MSM) (39). They all contribute 90% to the new infections. Key populations (FSW, MSM and people who inject drugs) are less than 2% of the overall population but represent about 11% of the new infections (39). Mother-to-child transmission accounts for 22% of all new infections in Nigeria, bearing an enormous burden in some states such as Ebonyi, where it accounts for more than 50% of all new infections (39). The paediatrics/adult ratio of new infections was about 0.31 (39). The prevalence of HIV among children aged 0–4 years and 5–9 years is 0.1%, and 0.2% for children aged 10–14 years (38). Adults between the age of 15–64 years have a prevalence of 1.4%, as shown in ***Figure 5*** (38).

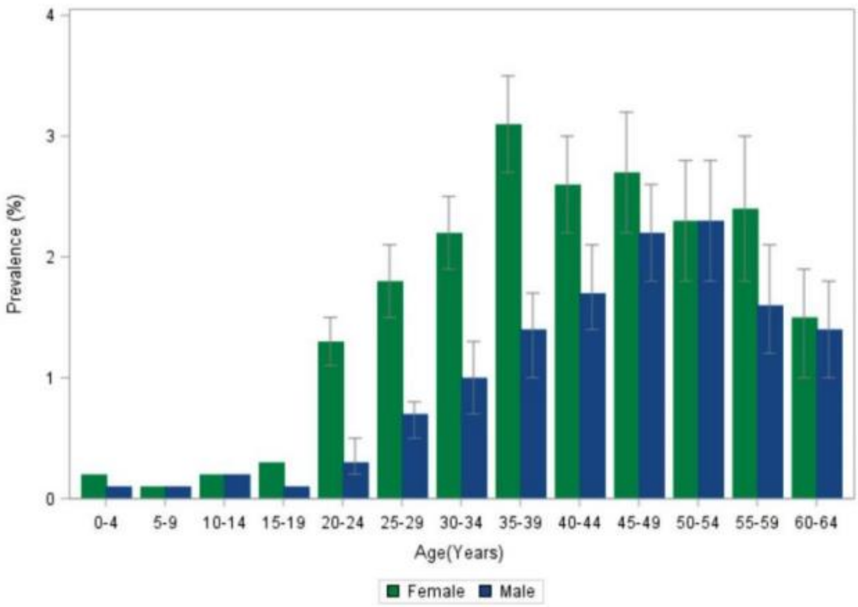


Figure 5: HIV Prevalence in Nigeria by age and sex (Source: Nigeria HIV/AIDS Indicator and Impact Survey, 2018) (38)

The paediatric population in Nigeria is far from achieving the UNAIDS target compared to the adult population (29). Forty-five per cent of paediatrics (0 to 14 years) living with HIV know their status, 45% of them are on ART, and 31% have viral suppression (29). Almost all new HIV infections among paediatrics are due to perinatal infections. As of 2020, only 44% of pregnant women living with HIV in Nigeria had access to ART, contributing to 24% of the global gap (29,40).

Nigeria's current economic situation has an impact on the HIV/AIDS response as poverty limits the ability of PLHIV to seek needed care, hinders optimal adherence to treatment and increases the vulnerability of people to HIV (37). The Boko Haram insurgency and the high number of armed clashes between Fulani herders and Indigenous communities could lead to an increase in HIV incidence in the country (37).

The HIV continuum of care measures patients' progress and highlights areas with gaps that limit patients' achievement of the HIV goal ***(see Figure 6)*** (41). The proportion of PLHIV reduces as the cascade progresses; however, this study will focus on identifying the factors that lead to the gap between receiving HIV care and retention in care, which prevents viral suppression (41).

Figure 6: HIV care continuum for patients (Source: HIV.gov, 2022) (41)

The booming global expansion of antiretroviral programs has changed the outcome of PLHIV in SSA and Nigeria, moving the disease from fatal to a long-standing illness with lifelong ART (42). ARV has helped transform the response to the AIDS epidemic in Nigeria, improve the overall health of the affected population, and reduce the spread of infection and HIV-related deaths (42). In Nigeria, expanding the provision of ART to the rising number of HIV-infected individuals is funded by a collaboration between the Government of Nigeria, the United States (US) President's Emergency Program for AIDS Relief (PEPFAR), the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM), and other donors (42).

PEPFAR, GFATM and the Federal Government of Nigeria support about two thousand healthcare facilities with HIV prevention, care, and treatment services. Two pieces of Electronic Medical Record (EMR) software, namely, the Nigeria Medical Record System (NMRS) and the Lafiya Management Information System, are used to collect the information of patients started on ART at the healthcare facility level. The District Health Information Software (DHIS2) collects aggregate data reported from the health facilities. The National Data Repository (NDR) and the National OVC Management Information System (NOMIS) are examples of databases managed by the FMoH that store patient information for the HIV and OVC programs respectively, in the country.

Following treatment recommendations for chronic illnesses is difficult for patients, with adherence to treatment at about 50% (43). An adherent patient actively responds to the uptake of the right drugs, correct dose, exact frequency, time, and scheduled clinic appointments as mutually agreed with the healthcare provider (44). Adherence (≥95%) to ARV determines the efficacy of ART (45). Patients' commitment to continue using ARVs after initiation is one of the most effective ways to make the disease manageable (45,46). In Nigeria, medication adherence is measured by self-report and pill count. One of the challenges in the management of HIV is when patients on ART stop accessing care due to the burden of returning to the healthcare facilities for clinic visits, follow-up tests, drug refills and counselling services, leading to poor adherence (45,46).

CHAPTER TWO

2.1. Problem Statement

HIV is one of the leading causes of mortality and morbidity in the paediatric age group in Nigeria, with about 130,000 paediatrics living with HIV and a prevalence of 0.1% (44,47). Although vertical transmission of HIV decreased in Nigeria by 15% in 2020, Nigeria contributes to 14% of the global burden of new HIV child infections, making it among the seven countries with half of the worldwide burden of new infections in the same year (40). There is a treatment gap in the HIV program in Nigeria, with paediatrics being only 3.5% of the total patients on antiretroviral therapy (ART) and contributing to about 30% of AIDS-related deaths in 2020 (47). Despite the progress in the scale-up of HIV prevention and treatment services, the 2018 Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS) mentioned that more than 50% of PLHIV have unsuppressed viral loads (38).

Global attempts to improve ART coverage and achieve the UNAIDS 95-95-95 targets have stalled by lost to follow-up (LTFU) (48). Using WHO's definition, LTFU occurs when PLHIV receiving ART become unaccounted for within 28 days from the last missed clinic appointment (4). LTFU leads to drug resistance, threatens the aim of viral suppression, worsens individual- and population-level treatment outcomes, and thus increases mortality (48). In 2011, WHO reported a 12-month post-ART start LTFU rate of 18.6% for Nigeria, which was above the WHO-recommended target of <15% (48). The LTFU rate among adults from studies in Nigeria ranged from 24% in 2015 in the Southeast (49) to 56% in 2019 in the Southwest (50). Among paediatrics, LTFU was 16% in 2015 in Massey Street Children Hospital, Lagos (51), 24% in 2020 in Dalhatu Araf Specialist Hospital, Lafia (52) and 41% in 2021 in the Southeast of Nigeria (53). The study on paediatrics by Onubogu et al. (53) monitored the LTFU trend over a time period of 6-, 12-, 24- and 36-months, with LTFU rates of 20.4%, 27.7%, 34.3% and 37.3%, respectively. These studies showed that the LTFU rate is high and differs across age groups and geographic locations.

The high rate of LTFU is one of the significant challenges of the ART program in Nigeria (54). ART aims to achieve undetectable viral load and support and restore the optimal health of PLHIV, while reducing the incidence of opportunistic infections; these can only be achieved by continuous adherence to ARVs (45,55). With the scale-up of ART in 2020, new HIV infections among paediatrics in Nigeria declined by 16% and AIDS-related deaths by 33% in the last decade (29). As paediatrics living with HIV grow into adolescence and adulthood, they deserve better health outcomes through a continuum of care, treatment, and social protection (29). Poor retention of children on ART and suboptimal paediatric regimen contribute partly to the poor health outcomes of paediatrics on ART which are worse than that of adults (29).

LTFU constitutes an obstacle to viral suppression because it is difficult to identify the main drivers of treatment interruption once patients are LTFU (56). PLHIV, especially paediatrics, encounter several barriers that could prevent them from treatment adherence and retention. To maintain adherence to ARVs, children rely on their parents or caregivers to access ART (55). Parents or caregivers not being HIV infected and non-disclosure of HIV status to paediatrics may increase the possibility of LTFU (57). Additionally, financial constraints may be a reason for LTFU. While ARVs are accessible at the healthcare facilities, the cost of added services, such as card fees, laboratory tests, treatment of other diseases and transportation costs, may be a burden for families, thus hindering caregivers from taking the paediatrics for follow-up clinic visits (53). Parents or caregivers forgetting to give drugs to the children, travelling, medication stock-out at home, ill health of the parent or caregiver and family issues are all reasons named by parents or caregivers for non-adherence of paediatrics to ART (55).

Non-adherence to ARVs can lead to the scarce resources being wasted, the onward transmission of HIV, and drug resistance. Acquired or developed resistance defeats the aim of ART, which is viral suppression (49,58). HIV disease may progress rapidly in children with a high rate of viral replication and a decrease in the cluster of differentiation 4 (CD4) cell count when treatment is interrupted or delayed (34). As LTFU increases poor outcomes at an earlier age, paediatrics need care for a more extended period, increasing the overall cost of treatment (59). With limited paediatric ARV formulations (55), LTFU increases the likelihood of drug resistance, especially to first-line drugs, which are cheaper, comparatively less toxic, and easier to administer than second-line regimens (34).

Therefore, the high rate of LTFU in Nigeria poses a severe challenge to patients, families, and program implementers, resulting in the inefficient use of scarce resources (60). Without treatment, half of the HIV-infected children would die before the age of two years. In the design of a chronic care program, adherence is vital to achieving the outcome of viral suppression.

2.2. Justification

LTFU is a challenge for healthcare providers because increased hospitalisation, outpatient department visits and rising cases of opportunistic infections lead to increased workload (55). Tracking children as they grow from infancy to childhood and adolescence is paramount, as LTFU raises the mortality rate of children (4). It is crucial to prevent and track paediatrics that are LTFU and find the reasons behind stopping the medications and the factors that predict LTFU. The rate of LTFU can be used to measure the effectiveness of the paediatric ART program in Nigeria and the efficiency of tracking.

Addressing the high rates of LTFU among paediatrics requires the implementation of child-centred policies to enable children to continue ART irrespective of the challenges around treatment adherence and retention (53). Healthcare providers and program implementers need to ensure that the impact of reducing LTFU rates among paediatrics and closing treatment gaps is understood. This study would help policy makers make informed decisions and implement tailored interventions to reduce the LTFU rate among the paediatric age group. Furthermore, it could give insight to NACA, and other ART program implementing partners on the ways to achieve the political declaration on HIV/AIDS made in 2021 for all children living with HIV, which is to achieve 75% and 85% viral suppression by 2023 and 2025, respectively, in line with the 95-95-95 targets (26).

This study will analyse a paediatric cohort that started ART in 2016. WHO recommends that cohort groups be based on the patient's ART start date and compared for patients for equal ART duration (61). Survival analysis has been used in several studies to understand disease patterns and time to an event or outcome; however, for HIV, it has been used to calculate the incidence of LTFU.

Additionally, Cox-proportional hazard models have been used to identify the factors that lead to and predict LTFU among patients on ART (49,53,62). Limited studies are available on the paediatric age group in Nigeria, and studies have not differentiated between the LTFU rates of adults and children on ART at the national level.

Furthermore, all studies have reported the LTFU rate only in selected healthcare facilities at distinct levels and in selected states. Still, none has been conducted for paediatrics across all the states in Nigeria, creating a gap in the estimation of LTFU among this age group in the national HIV program. This research aims to estimate the number of people in the paediatric age group that are LTFU, identify the determinants of LTFU among this age group in Nigeria and provide recommendations to the national HIV/AIDS programme. The findings from this study are expected to be compared with the outcomes of similar studies on the predictors of LTFU among paediatrics, and they can be used to address the factors that influence LTFU among paediatrics in Nigeria.

2.3. Objective

The general objective of this study is to estimate the incidence and identify the predictors of LTFU among paediatrics (0–14 years) on ART in Nigeria and recommend strategies to improve the management and retention on ART.

2.3.1. Specific objectives

1. To estimate the incidence of LTFU among paediatrics on ART in Nigeria.
2. To identify the predictors (child and caregiver) of LTFU among paediatrics on ART in Nigeria.
3. To make recommendations for interventions to reduce LTFU of paediatrics on ART in Nigeria.

2.4. Research Questions

1. What is the incidence of LTFU among paediatrics on ART in Nigeria?
2. What factors predict LTFU among paediatrics on ART in Nigeria?

2.5. Hypothesis

Children and caregivers' socio-demographic and clinical factors predict LTFU among paediatrics on ART in Nigeria.

2.6. Methods and Conceptual Framework

2.6.1. Study Location

All healthcare facilities that provide ART services to children in Nigeria and report data on the National Data Repository (NDR) were included in the study.

2.6.2. Study Population

The study population included children aged 0 to 9 years enrolled on ART in 2016. This will allow all children followed up for five years to be less than 15 years old (paediatric HIV treatment age band in Nigeria).

2.6.3. Study Design

The study used a longitudinal retrospective cohort of routinely collected patient (children) level HIV treatment data at healthcare facilities uploaded to the NDR, including the patient (OVC enrolment status) and caregiver data from a Central OVC database in Nigeria.

2016 was selected as the year of interest because it marked certain milestones in the global HIV program and Nigeria. A new national guideline on HIV prevention, care and treatment was published in Nigeria with a recommendation to adopt the test and treat strategy initiated by WHO. The strategy involves starting ART for all persons (children, pregnant women, breastfeeding women, adults, and adolescents) identified as HIV positive irrespective of the clinical and immunological stages, and in Nigeria this is implemented in all healthcare facilities that provide HIV services across the 36 states and Federal Capital Territory (30).

2.6.4. Data Source

NDR is a database that stores patient-level data for HIV in Nigeria. Patient-level data is collected at the healthcare facilities on electronic medical record (EMR) systems, and de-identified data is uploaded to the FMoH NDR at least once per week after review by the implementing partners. The Central OVC database stores the Orphans and Vulnerable Children (OVC) data and that of their caregivers collected and reported by Community Based Organisations (CBOs).

2.6.5. Data Extraction

Routine longitudinal patient-level data collected at healthcare facilities and reported on NDR for patients enrolled on ART in the year 2016 with follow-up data for five years (2021) across all healthcare facilities in Nigeria that provide ART services; and OVC data collected by CBOs and reported on central OVC database for the same cohort of patients was used for this study. All children that met the inclusion criteria were included in the study. Data from the two databases (NDR for patient information and central OVC database for caregivers' information) were related using patients' ART unique identifier (the unique variable in both databases) to link respective caregivers' data to the children's ART data. Data was scrubbed of unique ART ID before it was released for this study. The study analyses the patient status (dependent variable) against other socio-demographic and clinical variables of the children and caregivers.

2.6.6. Conceptual Framework

Recognising that a range of factors influences LTFU, this study adapted the conceptual framework for determinants of LTFU among HIV-infected children in ART care from Sifr et al. ***(see Appendix 2)*** (63). The framework highlights the socio-demographic and clinical factors that influence LTFU among children. The author adapted the framework from similar literature (64–68) that conducted studies on PLHIV and a WHO guideline on patient monitoring for HIV care and ART (61); and found the selected factors to help analyse the determinants of LTFU among this group. The framework emphasizes the dynamic interactions between the socio-demographic and clinical factors that influence LTFU among children on ART. Hence, the framework was adapted to conceptualise the factors influencing LTFU among paediatrics on ART in Nigeria.

The framework corroborates the concept that LTFU among children on ART is not just about the individual but is an interaction among distinct factors, namely socio-demographic factors, including the caregiver's and the child's clinical factors.

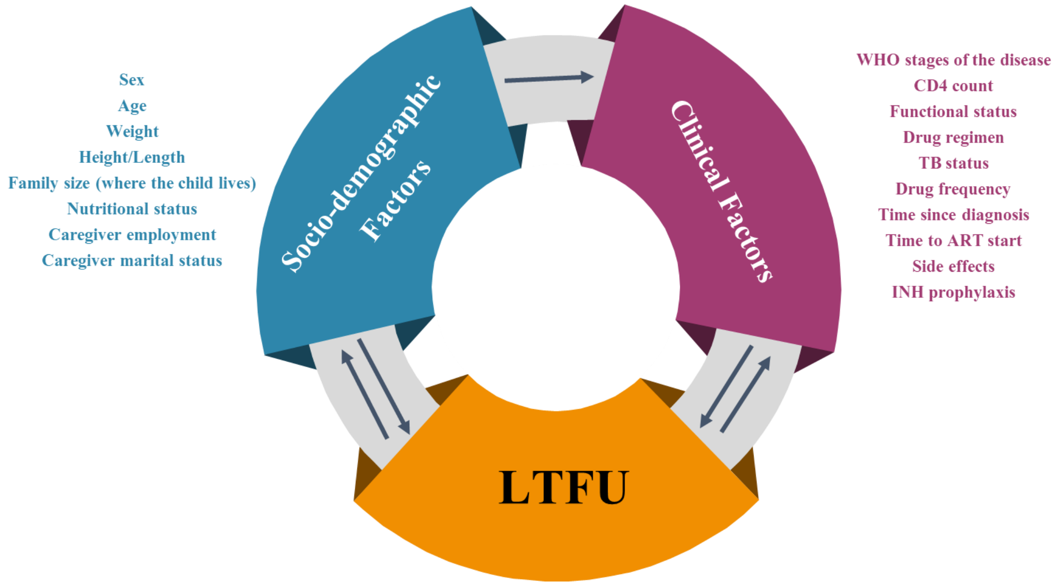


Figure 7: Conceptual framework for determinants of LTFU among HIV-infected children in ART care (Adapted from Sifr et al., 2021) (63)

As shown in Figure 7, the socio-demographic factors include the sex, age, weight, and height/length of the paediatric. It also includes family size (child's residence) and nutritional status. The caregiver's socio-demographic factors include employment and marital status. These factors link to the clinical factors, which include the WHO stages of the disease, CD4 count, drug regimen, and TB status. Both the socio-demographic and clinical factors have a link to LTFU. However, the clinical factors for this study were updated to include LTFU influencing factors identified in other studies as clinically relevant (53,69). The variables included are functional status, drug frequency, time since diagnosis, time to ART, side effects and INH prophylaxis. This adapted conceptual framework guided the selection of the independent variables in the databases. An independent variable is a variable that has an assumed effect on the dependent variable. A dependent variable is the outcome of interest, which changes from manipulating the independent variable (70).

2.6.7. Variables

Table 1 shows the operational definition of the variables used in this study, highlighting the independent and dependent variables from the two databases. The study's primary outcome (dependent variable) was the patient status with the interest variable as LTFU—defined as children without documented date of ARV refill, ARV regimen and ARV duration 28 days after an expected ARV refill appointment at the hospital and is not documented as dead or transferred out in the NDR

(4). The incidence of LTFU was at intervals of three months, six months and annually up to 5 years from the date of ART start for each patient. The follow-up period was selected based on the WHO recommendation for monitoring newly started ART patients (61). The time to LTFU was the interval between the ART start date and 28 days after the last missed appointment. Children LTFU was considered an event, while those who died (based on reported date or last visit date) while on treatment or were alive at the end of the study period (December 31, 2021) were considered censored. Patients that transferred out were not included in the censored patients because they were transferred to another healthcare facility within the country; hence, the patients might be captured in the database at another facility. The independent variables were socio-demographic and clinical variables. Socio-demographic variables were the child's age at the start of ART, sex, BMI (weight divided by the square of height) and OVC enrolment status, and caregiver's age, sex, marital status, education level, occupation, HIV status, ART enrolment status, and beneficiary type. Clinical variables were WHO clinical stage at the start of ART, CD4 count, drug regimen, and time of HIV diagnosis to the ART start date (time to ART start).

Table 1: Variables Derived from the databases and the respective inclusion status in the model and analysis.

Factors in the Conceptual Framework	Variable	Variable Description (analysis code)	Operational Definition in this Study	Type of Variable	Data Source	Included in the Analysis
Independent Variables						
	Children Variables					
Socio-demographic factors	Age at ART start (years)	0–4 (1) 5–9 (2) 10–14 (3)	Children aged 0 to 14 years	Categorical	NDR	Yes
	Current age (years)	0–4 (1) 5–9 (2) 10–14 (3) 15–19 (4)	Current calculated age of the children	Categorical	NDR	No
	Sex	Male (1) Female (2)	Reported sex of the patient	Categorical	NDR	Yes
	BMI (kg/m^2)	0–18.49 (1) 18.5–24.9 (2) 25–29.9 (3) $\geq$ 30 (4)	Calculated from weight and height at baseline (weight/height)	Categorical	NDR	Yes
	OVC enrolled	Yes (1) No (0)	Enrolment status in the OVC program	Categorical	Central OVC database	No
	Caregiver Variables					
	Age (years)	10–19 (1) 20–29 (2) 30–39 (3) 40–49 (4)	Adolescent caregivers (10 to 19 years), adult caregivers (20 to 59 years), and aged caregivers (60 years and above)	Categorical	Central OVC database	Yes

		50–59 (5) 60+ (6)				
	Sex	Male (1) Female (2)	Reported sex of the caregiver	Categorical	Central OVC database	Yes
	Marital status	Single (1) Married (2) Divorced (3) Separated (4) Widowed (5)	Reported marital status	Categorical	Central OVC database	Yes
	Education level	No education Primary Secondary Tertiary	Reported highest education level	Categorical	Central OVC database	Yes
	Occupation	Self-employed (1) Formally employed (2) Unemployed (3) Informally employed (4) Retired pensioner (5) Retired non-pensioner (6)	Reported occupation	Categorical	Central OVC database	Yes
	HIV status	Positive (1) Negative (0) Unknown (2)	Reported HIV status	Categorical	Central OVC database	Yes
	Enrolled on ART	Yes (1) No (0)	Reported enrolment status	Categorical	Central OVC database	No
	Beneficiary type	Caregiver (1) Household head (2) Household head and caregiver (3)	Status of caregiver in the house	Categorical	Central OVC database	Yes

	Children Variables					
Clinical Factors	*Baseline WHO stage	1 2 3 4	Reported based on WHO's clinical staging classification (71)	Categorical	NDR	Yes
	*Baseline CD4 count (cells/mm^3)	<200 (1) 200–499 (2) 500–999 (3) ≥1,000 (4)	Reported based on WHO's clinical staging classification (71)	Categorical	NDR	Yes
	Drug regimen	ABC-3TC-DTG (1) ABC-3TC-EFV (2) ABC-3TC-LPV/r (3) ABC-3TC-NVP (4) ABC-FTC-DTG (5) ABC-FTC-NVP (6) AZT-3TC-ABC (7) AZT-3TC-DTG (8) AZT-3TC-EFV (9) AZT-3TC-LPV/r (10) AZT-3TC-NVP (11) TDF-3TC-DTG (12) TDF-3TC-EFV (13) TDF-3TC-NVP (14) TDF-FTC-EFV (15) TDF-FTC-NVP (16) Implausible regimen	First-line regimen recommended for children at the start of ART by the FMoH (30)	Categorical	NDR	Yes

	Time to ART start	0–14 days $\geq$ 15 days	Calculated time difference from HIV diagnosis to ART start. The disaggregation was based on the test and treat guideline from WHO.	Categorical	NDR	Yes
	Time to LTFU	Time variable	Calculated interval between the ART start date and 28 days after the last missed appointment.	Continuous	NDR	Yes
Dependent Variable						
	Patient status	Event (LTFU) Censored (alive, dead)	LTFU: Children without documented date of ARV refill, ARV regimen and ARV duration 28 days after an expected ARV refill appointment to the hospital and not documented as dead or transferred out in the NDR.	Categorical	NDR	Yes

*Baseline: At the time of ART start

2.6.8. Data Management and Analysis

Figure 8 shows the data cleaning process. Data was received in Microsoft Excel. Data cleaning included removing duplicate patient records. Clinic visits with missing ARV drug refill duration, children with negative age values, dead children with missing date of death and children transferred to other facilities were removed from the data set. The clean dataset had deduplicated patient records, including ARV refill data and linked to the caregivers' information. Variables derived from the clean dataset include a) "OVC enrolled"—all children in the clean dataset that had caregivers' information in the central OVC database; b) "time to ART start"—the time from HIV diagnosis date to ART start date; c) "time to LTFU"—the interval between the ART start date and 28 days after the last missed appointment; d) BMI—weight divided by the square of height, expressed in kg/m².

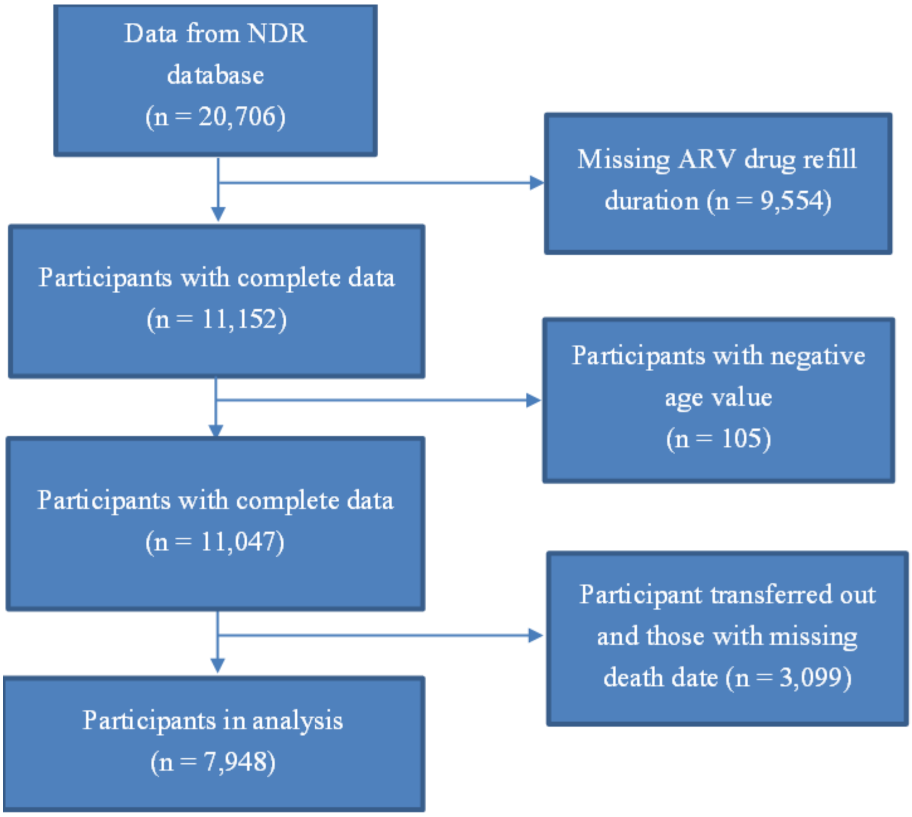


Figure 8: Data cleaning flow chart

Statistical analysis was done using statistical software for data science (STATA) version 17. Each child's outcome was grouped into LTFU (event) and censored (alive or dead). The univariate analysis (descriptive statistics) was used to calculate the frequencies and summary statistics to understand the data distribution for each variable and investigate the characteristics of the cohort.

Survival time (child-years LTFU) was calculated by assessing the time interval between the ART start date and the LTFU censoring date. Kaplan-Meier cumulative hazard curves were used to estimate the incidence of LTFU rates after ART start, and the categorical independent variables were compared using log-rank tests. In the bivariate analysis, the independent and dependent (LTFU) variables were entered into the Cox-proportional hazard regression model to assess the effect of the independent variables on LTFU. Significant ($\alpha \leq 0.20$) variables in the bivariate analysis were included in the multivariate Cox-proportional hazard regression model. Adjusted Hazard Ratio and Crude Hazard Ratio at a 95% confidence interval were calculated to identify a significant association between the independent and dependent variables. Variables with p-values <0.05 were considered statistically significant predictors. Groennesby and Borgan's test was used to assess the goodness of fit for the Cox-proportional hazard model.

2.6.9. Ethical Consideration

Data use approval was received, and a waiver of informed consent was received from the KIT Ethical Review Board ***(see Appendix 3)***. Patient confidentiality was ensured as the patients' personal information was not part of the datasets.

2.6.10. Limitations of Study Design

This study analysed secondary longitudinal data. The unavailability of socio-demographic (family size, nutritional status) and clinical variables (ARV side effects and INH prophylaxis) that influence LTFU in the databases restricted the potential of analysing this study with a comprehensive conceptual framework.

CHAPTER THREE

3.1. Results

A total of 7,948 children and 1,906 caregivers were included in the analysis.

3.1.1. Children and Caregiver Characteristics

3.1.1.1. Socio-demographic Characteristics of the Children

Table 2 shows the socio-demographic characteristics and the proportion of missing data. The mean age of the study participants at ART start was 3.8 years (SD: ±2.8 years); the majority, 4,817 (61%) of the children were 0–4 years, and 3,131 (39%) were 5–9 years. Also, about half, 4,036 (51%) of the participants were males. Furthermore, the mean BMI at the start of ART was 1.1 kg/m^2 (SD: ±5.8 kg). Less than a quarter, 1,456 (18%) of the participants had a BMI at ART start, out of which, 1417 (97%) had a BMI below the normal range (<18.5 kg/m^2), 19 (1.3%) had normal BMI range (18.5–24.9 kg/m^2), 6 (0.4%) of the participants were overweight (25–29.9 kg/m^2), and 14 (1%) were obese (≥30 kg/m^2). The majority, 6,492 (82%) participants, did not have a BMI because there was no record of weight and height at the start of ART. Slightly less than a quarter, 1,906 (24%) of the participants were enrolled in the OVC program at the time of this study ***(see Table 2)***.

3.1.1.2. Socio-demographic Characteristics of the Caregivers

The mean age of caregivers was 39 years (SD: ±9.7 years). Adolescent caregivers made up 0.3% (6), while adult caregivers (20–59 years) were 96% (1,823), and aged caregivers were 4% (77). Twenty-nine per cent (549) were male and 71% (1,357) were female. Regarding documented marital status, slightly above three-quarters, 1,327 (77%) of the caregivers were married, 18 (1%) divorced, 20 (1%) separated, 199 (12%) single, 164 (10%) widowed, and 178 (9%) had no documented marital status. In terms of education level, there was no recorded education level for the selected caregivers in the database. About 69% (598) of the caregivers with employment status were employed (self-, formally, and informally employed), 0.3% (3) were retired (pensioner and non-pensioner), 31% (271) reported being unemployed, and for more than half, 54% (1,034) there was no occupation recorded. Furthermore, 40% (710) were HIV positive, and all (100%) were on ART; more than half, 1,004 (57%), were HIV negative, 42 (2%) had unknown HIV status, and 150 (8%) had missing data. Based on the beneficiary status, 34% (657) were caregivers, 45% (860) were household heads, and 20% (389) were household heads and caregivers ***(see table 2)***.

Table 2: Socio-demographic characteristics of children and caregivers in the study

Variables	Frequency (n)	Percentage (%)
Children (n = 7,948)		
Age at ART start (years)		
0–4	4,817	60.6
5–9	3,131	39.4
Sex		
Male	4,036	50.8

Female	3,912	49.2
BMI (kg/m²)		
0–18.49	1,417	97.3
18.5–24.9	19	1.3
25–29.9	6	0.4
≥ 30	14	1.0
Missing data	6,492	81.7
OVC enrolled		
No	6,042	76.0
Yes	1,906	24.0
Caregiver (n = 1,906)		
Age (years)		
10–19	6	0.3
20–29	245	12.9
30–39	827	43.4
40–49	560	29.4
50–59	191	10.0
60+	77	4.0
Sex		
Male	549	28.8
Female	1,357	71.2
Marital status		
Single	199	11.5
Married	1,327	76.8
Divorced	18	1.0
Separated	20	1.2
Widowed	164	9.5
Missing data	178	9.3
Education level		
Missing	0	100.0
Occupation		
Self-employed	500	57.3
Formally employed	30	3.4
Unemployed	271	31.1
Informally employed	68	7.8
Retired pensioner	1	0.1
Retired non-pensioner	2	0.2
Missing data	1,034	54.3
HIV status		
Negative	1,004	57.2

Positive	710	40.4
Unknown	42	2.4
Missing data	150	7.9
Enrolled on ART		
No	0	0
Yes	710	100
Beneficiary type		
Caregiver	657	34.5
Household head	860	45.1
Household head and caregiver	389	20.4

3.1.1.3. Clinical Characteristics of the Children

More than three-quarters, 4,652 (85%) of the children had mild HIV disease (WHO stage I and II); 757 (14%) were at stage III, 75 (1%) at stage IV and 2,464 (31%) had no documented WHO clinical stage at ART start. For CD4 count, more than half, 1,727 (57%), had results between 0 and 199 cells/mm^3, 417 (14%) had results between 200 and 499 cells/mm^3, 525 (17%) had results between 500 and 999 cells/mm^3, 364 (12%) had results greater than 1,000 cells/mm^3, and 4,915 (62%) had no result at ART baseline.

Furthermore, 16 regimen combinations were prescribed to the study participants. Three hundred and eighty-nine (389) (8%) of the children received a prescription of a regimen containing abacavir (ABC); half of the participants, 3,981 (79%) were prescribed a regimen combination that contained zidovudine (AZT), and regimen containing tenofovir (TDF) were prescribed to 669 (13%) of the children. About 2,909 (37%) of the study participants did not have a regimen in the final analysis due to 887 implausible (11%) and 2,022 missing (25%) regimens. The study calculated that the mean time to ART start was 106 days (SD: ±364.1 days). Almost three-quarters, 5,871 (74%) of the children, started ART (time to ART start) within 14 days from HIV diagnosis, and 2,077 (26%) started after 14 days ***(see Table 3)***. Due to the high number of missing values in the BMI (62%) and CD4 count (82%), the single imputation method was employed using the mean of each variable to replace the blank entries (72).

Table 3: Clinical characteristics of children in the study

Variables (n = 7,948)	**Frequency (n)**	**Percentage (%)**
Baseline WHO stage		
I	3,713	67.7
II	939	17.1
III	757	13.8
IV	75	1.4
Missing data	2,464	31.0
CD4 count (cells/mm^3)		
<200	1,727	56.9

200–499	417	13.7
500–999	525	17.3
≥1,000	364	12.0
Missing data	4,915	61.8
Drug regimen at ART start		
ABC-3TC-DTG	39	0.8
ABC-3TC-EFV	57	1.1
ABC-3TC-LPV/r	61	1.2
ABC-3TC-NVP	229	4.5
ABC-FTC-DTG	1	0
ABC-FTC-NVP	2	0
AZT-3TC-ABC	12	0.2
AZT-3TC-DTG	8	0.2
AZT-3TC-EFV	355	7.0
AZT-3TC-LPV/r	34	0.7
AZT-3TC-NVP	3,572	70.9
TDF-3TC-DTG	76	1.5
TDF-3TC-EFV	484	9.6
TDF-3TC-NVP	81	1.6
TDF-FTC-EFV	20	0.4
TDF-FTC-NVP	8	0.2
Implausible regimen	887	11.2
Missing data	2,022	25.4
Time to ART start		
0–14 days	5,871	73.9
≥15 days	2,077	26.1

3.1.2. Incidence of LTFU

Child-year was used as the denominator to calculate the incidence of LTFU. The study participants (children) had follow-up periods from 3 months to five years. The study cohort had a total follow-up time of 9,879 child-years of observation. The overall incidence rate of LTFU among the children in the study cohort was 40 (95%CI: 38.8, 41.3) per 100 child-years of observation. Cumulative incidence showed that more than half, 4,387 (55% (95%CI: 54.1, 56.3%)) of the children on ART were LTFU by the end of the follow-up period. Cumulative LTFU rate of the children was 13% (95%CI: 12.0, 13.5%) at 3 months; 17% (95%CI: 16.2, 17.9%) at 6 months; 22% (95%CI: 20.9, 22.7%) at 12 months; and increased over time annually to 29% (95%CI: 28.3, 30.3%) at 2 years; 34% (95%CI: 33.3, 35.5%) at 3 years; 40% (95%CI: 39.1, 41.3%) at 4 years; and 55% (95%CI: 54.1, 56.3%) at the end of the follow-up period of five years. The overall mean survival time was two years (95%CI: 2, 2 years) ***(see Figure 9)***.

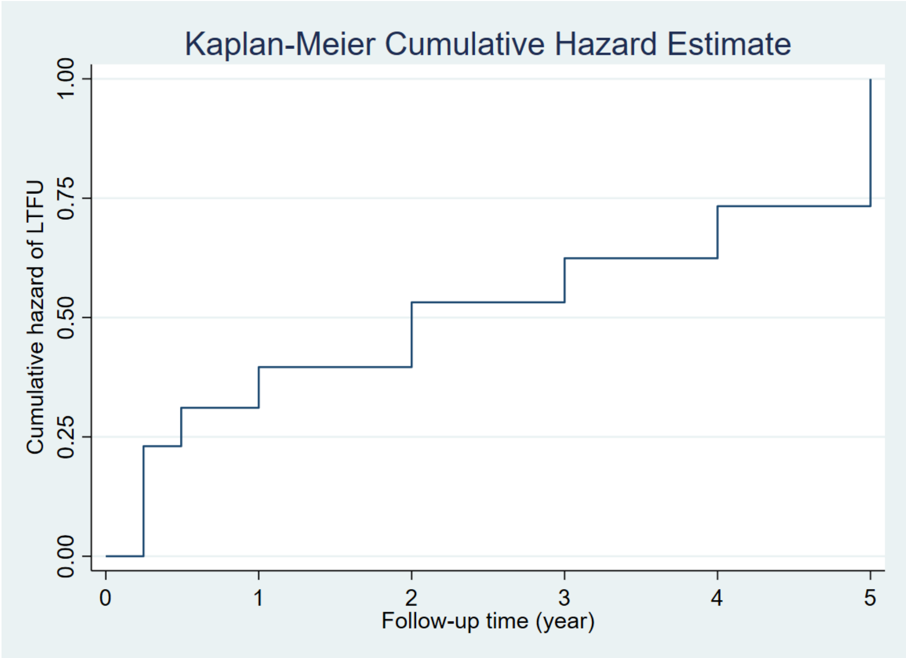


Figure 9: Overall Kaplan-Meier survival curve of LTFU among children on ART in Nigeria

Table 4 shows the distribution of LTFU and censored children in the study population. This includes the updated values for BMI and CD4 count from the imputation process. Children LTFU were 4,388 (55%), while children censored children were 3,560 (45%); children (3,265 (92%) alive and 295 (8%) deaths). At the end of the follow-up period, 2,893 (66%) children LTFU were 0–4 years old, and 1,495 (34%) were 5–9 years old. For the censored (alive or dead) patients, 54% and 46% were aged 0–4 years and 5–9 years, respectively. Male children were about half, 2,245 (51%) of the children that became LTFU; there was equal distribution between the male (50%) and female (50%) censored patients. Within males and females, 2,245 (56%) and 2,143 (55%) were LTFU. About 99% and 100% of the patients that were LTFU and censored, respectively, had a BMI of <18.5 kg/m2, 0.2% of those with BMI between 18.5 and 24.9 kg/m2 were LTFU, and 0.3% were either alive or dead, while, 0.1% (LTFU) and 0.1% (censored) had a BMI of 25–29.9 kg/m2, and 0.3% obese children were LTFU and 0.03 were censored.

Children enrolled in the OVC program had a 25% (476/1906) LTFU rate. Out of the 476 that were LTFU, 1 (0.2%) had an adolescent caregiver, 452 (95%) had adult caregivers (20–59 years), and 23 (5%) had elderly caregivers (60+ years). LTFU children with male caregivers were 172 (32%) lower than those with female caregivers (68%). Of the 433 children that were LTFU with a documented caregiver's marital status, 13%, 75%, 1%, 1%, and 11% lived with single, married, divorced, separated, and widowed caregivers, respectively. None of the children that were LTFU had a caregiver that was retired. Sixty-six per cent of the children with employed caregivers were LTFU, and 54% were self-employed. Based on the HIV status of the caregivers, the proportion of LTFU and censored patients were equally distributed across the documented status. Also, 25% of the children had caregivers with documented HIV status. Seventy-five (75%) per cent of the children with documented patients/caregiver's beneficiary type were censored. Caregivers, household heads, and household and caregivers had a 36%, 43%, and 21% proportion of LTFU, respectively.

Children with early disease stage (WHO stage I and II) were 82% of those that became LTFU, and the remaining 18% had advanced HIV disease (WHO stage III and IV) classification at the start of ART. About two-thirds (63%) of the children that started ART at WHO stage IV were LTFU at the end of the follow-up period, followed by those at stage III (62%), then those at stage II (55%) and stage I (48%). For the children with a documented regimen, 52% (2,609) were LTFU and 48% (2,430) were censored. Of the 389 (8%) children on a regimen containing abacavir (ABC), 156 (40%) were LTFU, and 233 (60%) were either alive or died during the follow-up period. Out of the children that were prescribed a regimen with zidovudine (AZT), 3,981 (79%); half, 2,128 (53%) were LTFU, and 1,853 (47%) were censored. 327 (49%) were LTFU, and 342 (51%) were censored out of the 669 (13%) patients that were started on a regimen containing tenofovir (TDF).

3.1.3. Predictors of LTFU among paediatrics on ART in Nigeria

Table 4 presents the results of the bivariate and multivariate Cox proportional hazard regression analysis. In the bivariate Cox-proportional regression analysis, eleven (11) variables, namely, age of children between 5–9 years at baseline, WHO stage III and IV, CD4 counts of 200–499 cells/mm^3 and ≥1,000 cells/mm^3, ABC-FTC-NVP and TDF-3TC-EFV regimen, and 15 days or more time to ART start, married caregivers, divorced caregivers, informally employed caregivers, had a p-value less than 0.20, out of which eight (8) were significant. The eleven variables were selected for the multivariate Cox-proportional hazard model. The choice of the p-value (0.2) was based on suggested optimal p-values at the bivariate level for inclusion in the multivariate analysis (73).

In the multivariate Cox-proportional hazard regression analysis, one (1) variable (informally employed caregivers) was a statistically significant (<0.05) predictor of LTFU when both child and caregiver variables were combined. The multivariate Cox-proportional hazard regression analysis that included only the child variables that were less than 0.2 in the bivariate Cox-proportional hazard regression analysis was computed; the age of children between 5–9 years at baseline, WHO stage III and IV, and ≥1,000 cells/mm^3 CD4 count were statistically significant. Five variables were statistically significant predictors of LTFU, children aged 5–9 years at baseline, WHO stage III and IV, ≥1,000 cells/mm^3 CD4 count, and children with informally employed caregivers ***(see Table 4)***.

3.1.3.1. Socio-demographic Factors

Children 5–9 years old was statistically associated with LTFU at 0.9 (AHR: 0.9; 95%CI: 0.81,1.0; α : 0.02) times higher than the children between the age of 0–4 years. The cumulative hazard rate of LTFU among children on ART and log-rank over their age is shown graphically in ***Figure 10***. In the bivariate and multivariate Cox-proportional hazard analysis, sex and BMI were not significantly associated with LTFU among paediatrics.

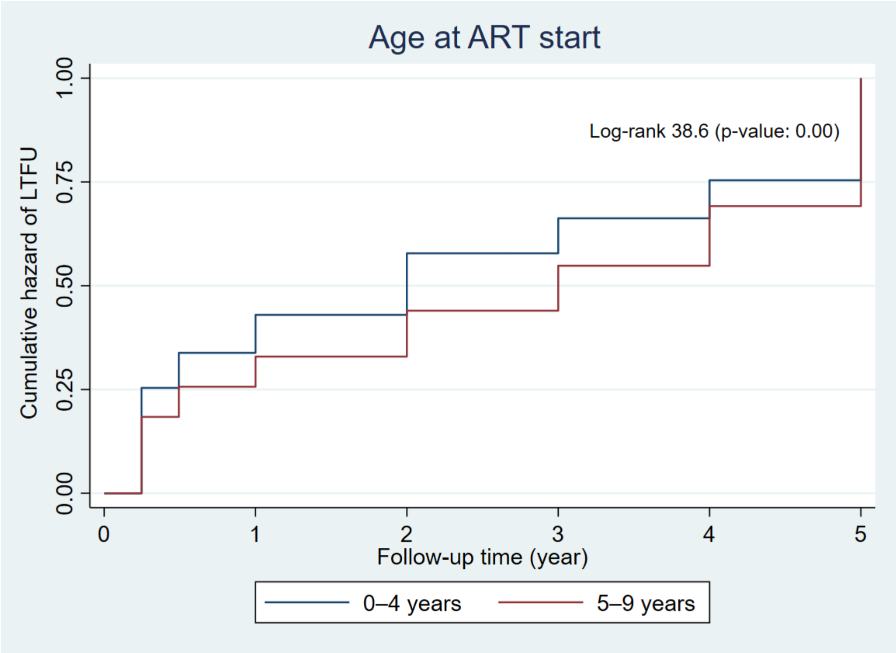


Figure 10: The hazard rate of LTFU among children on ART and log-rank over their age (2016 to 2021)

Children living with female caregivers had a 1.1 (CHR: 1.1; 95%CI: 0.9,1.4; α: 0.34) times higher risk of being LTFU than paediatrics with male caregivers. However, the sex of the caregiver was not a significant predictor of LTFU at the bivariate and multivariate levels.

For the marital status, not all the caregivers' marital status was statistically significant; however, divorced and married caregivers were significant in the bivariate analysis. In the multivariate analysis, the children with divorced caregivers had a 6.0 (AHR: 6.0; 95%CI: 0.7,53.8; α : 0.11) times increase in hazard to be LTFU, followed by those with married caregivers who had a 1.5 (AHR: 1.5; 95%CI: 0.67,3.27; α : 0.33) higher hazard compared to children with single caregivers. However, in the Cox-proportional multivariate analysis, none of the marital statuses was a statistically significant predictor of LTFU among children in Nigeria.

Caregivers in informal employment were statistically significant at both the bivariate and multivariate levels. The hazard of LTFU among children enrolled in the OVC program with self-employed caregivers was 96% (AHR: 3.6; 95%CI: 1.5,8.7; α : 0.00), lower than children living with caregivers who were informally employed. Caregivers that were unemployed and formally employed were not statistically associated with LTFU among children. The cumulative hazard rate of LTFU among children on ART and log-rank over their caregiver's occupation is shown graphically in ***Figure 11***. The HIV status of the caregivers was not a statistically significant predictor of LTFU in the bivariate and multivariate analysis. The HIV enrolment status of the caregiver was dropped from the analysis due to collinearity, which occurs when STATA removes a variable because of a linear relationship with another variable. Furthermore, the beneficiary type of the caregiver, either caregiver, household head or household head and caregiver, was not significant in the bivariate and multivariate analysis.

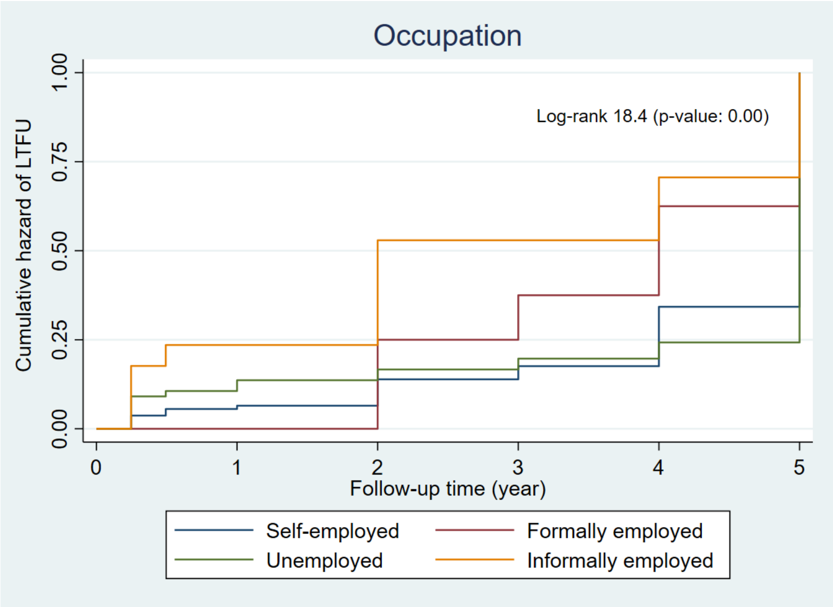


Figure 11: The hazard rate of LTFU among children on ART and log-rank over their caregiver's occupation (2016 to 2021)

Table 4: Cox-proportional regression analysis of predictors of LTFU among children in Nigeria

Variables	Status		CHR (95%CI)	AHR (95%CI)	p-value
	LTFU (n = 4,388) (%)	Censored (n = 3,560 (%)			
Children					
Age at ART start (years)					
0–4	2,893 (65.9)	1,924 (54.0)	1		
5–9	1,495 (34.1)	1,636 (46.0)	0.85 (0.80,0.91)*¤	0.90 (0.81,0.99)*	0.035*
Sex					
Male	2,245 (51.2)	1,791 (50.3)	1		
Female	2,143 (48.8)	1,769 (49.7)	0.98 (0.92,1.04)		
BMI (kg/m^2)					
0–18.49	4,365 (99.5)	3,544 (99.6)	1		
18.5–24.9	8 (0.2)	11 (0.3)	0.99 (0.50,1.99)		
25–29.9	2 (0.1)	4 (0.1)	1.46 (0.37,5.86)		
≥ 30	13 (0.3)	1 (0.0)	1.17 (0.65,2.11)		
Caregiver					
Age (years)					
10–19	1 (0.2)	5 (0.4)	1		
20–29	47 (9.9)	198 (13.9)	1.30 (0.18,9.48)		
30–39	212 (44.5)	615 (43.0)	1.41 (0.20,10.08)		
40–49	140 (29.4)	420 (29.4)	1.33 (0.19,9.53)		
50–59	53 (11.1)	138 (9.7)	1.63 (0.22,11.83)		
60+	23 (4.8)	54 (3.8)	1.31 (0.17,9.85)		
Sex					

Male	152 (31.9)	397 (27.8)	1		
Female	324 (68.0)	1,033 (72.2)	1.11 (0.90,1.37)		
Marital status					
Single	54 (12.5)	145 (11.2)	1		
Married	326 (75.3)	1,001 (77.3)	1.24 (0.90,1.72)¤	1.48 (0.67,3.27)	0.334
Divorced	3 (0.7)	15 (1.2)	5.58 (1.34,23.24)*¤	5.96 (0.66,53.75)	0.112
Separated	3 (0.7)	17 (1.3)	1.24 (0.39,4.02)	1.39 (0.26,7.51)	0.700
Widowed	47 (10.9)	117 (9.0)	1.27 (0.83,1.95)	1.57 (0.57,4.36)	0.383
Occupation					
Self-employed	127 (54.0)	373 (58.6)	1		
Formally employed	9 (3.8)	21 (3.3)	1.45 (0.70,2.97)	1.18 (0.32,4.38)	0.805
Unemployed	80 (34.0)	191 (30.0)	0.92 (0.68,1.25)	0.78 (0.45,1.36)	0.385
Informally employed	19 (8.1)	49 (7.7)	1.83 (1.10,3.06)*¤	3.61 (1.50,8.66)*	0.004*
Retired pensioner	0 (0)	1 (0.2)			
Retired non-pensioner	0 (0)	2 (0.3)			
HIV status					
Positive	178 (40.4)	532 (40.5)	1		
Negative	253 (57.4)	751 (57.1)	0.97 (0.79,1.19)		
Unknown	10 (2.3)	32 (2.4)	0.97 (0.49,1.90)		
Beneficiary type					
Caregiver	171 (35.9)	486 (34.0)	1		
Household head	203 (42.7)	657 (45.9)	0.88 (0.71,1.10)		
Household head and caregiver	102 (21.4)	287 (20.1)	0.90 (0.69,1.18)		
Baseline WHO stage					
I	1,785 (63.2)	1,928 (72.5)	1		

II	520 (18.4)	419 (15.8)	1.08 (0.97,1.20)	1.12 (0.99,1.27)	0.067
III	471 (16.7)	286 (10.8)	1.18 (1.06,1.31)*¤	1.29 (1.13,1.47)*	0.000*
IV	47 (1.7)	28 (1.1)	1.81 (1.33,2.45)*¤	1.52 (1.06,2.17)*	0.024*
CD4 count (cells/mm^3)					
<200	869 (19.8)	858 (24.1)	1		
200–499	196 (4.5)	221 (6.2)	0.79 (0.67,0.94)*¤	0.81 (0.64,1.01)	0.067
500–999	3,137 (71.5)	2,303 (64.7)	0.97 (0.89,1.05)	0.94 (0.84,1.05)	0.258
≥1,000	186 (4.2)	178 (5.0)	0.74 (0.63,0.88)*¤	0.77 (0.63,0.95)*	0.013*
Drug regimen at ART start					
ABC-3TC-DTG	17 (0.7)	22 (0.9)	1		
ABC-3TC-EFV	23 (0.9)	34 (1.4)	0.97 (0.51,1.85)	0.94 (0.41,2.13)	0.880
ABC-3TC-LPV/r	20 (0.8)	41 (1.7)	0.91 (0.45,1.82)	1.11 (0.49,2.51)	0.811
ABC-3TC-NVP	93 (3.6)	136 (5.6)	0.93 (0.54,1.59)	0.76 (0.40,1.46)	0.409
ABC-FTC-DTG	1 (0.0)	0 (0)	2.79 (0.37,21.06)		
ABC-FTC-NVP	2 (0.1)	0 (0)	3.18 (0.73,13.85)¤	2.69 (0.60,12.07)	0.196
AZT-3TC-ABC	8 (0.3)	4 (0.2)	0.79 (0.32,1.91)	0.66 (0.15,2.96)	0.587
AZT-3TC-DTG	4 (0.2)	4 (0.2)	2.02 (0.59,6.95)		
AZT-3TC-EFV	168 (6.4)	187 (7.7)	1.20 (0.72,2.01)	1.16 (0.64,2.12)	0.620
AZT-3TC-LPV/r	23 (0.9)	11 (0.5)	1.08(0.57,2.08)	0.86 (0.41,1.78)	0.679
AZT-3TC-NVP	1,923 (73.7)	1,649 (67.9)	1.20 (0.73,1.97)	1.12 (0.63,1.98)	0.702
TDF-3TC-DTG	23 (0.9)	53 (2.2)	0.73 (0.38,1.43)	0.71 (0.33,1.50)	0.369
TDF-3TC-EFV	265 (10.2)	219 (9.0)	1.51 (0.91,2.51)¤	1.51 (0.84,2.72)	0.170
TDF-3TC-NVP	22 (0.8)	59 (2.4)	0.84 (0.43,1.64)	0.75 (0.34,1.66)	0.484
TDF-FTC-EFV	11 (0.4)	9 (0.4)	1.38 (0.64,2.97)	1.52 (0.57,4.05)	0.407
TDF-FTC-NVP	6 (0.2)	2 (0.1)	1.36 (0.53,3.47)	0.86 (0.24,3.05)	0.815
Time to ART start					

0–14 days	3,374 (76.9)	2,497 (70.1)	1		
≥15 days	1,014 (23.1)	1,063 (29.9)	0.82 (0.76,0.89)*¤	0.90 (0.79,1.00)	0.052

¤=p<0.2 (Variables included in the multivariate model); *=p<0.05 (Statistically significant variables); CI: Confidence Interval; CHR=Crude hazard ratio; AHR=Adjusted hazard ratio

3.1.3.1. Clinical Factors

The clinical factors included in the analysis were WHO stage, CD4 count, drug regimen at baseline, and time to ART start.

Irrespective of OVC enrolment status, the likelihood of LTFU based on the WHO clinical stage was higher with advanced disease at the bivariate level. Children with WHO stage IV at ART start were twice (CHR: 1.8; 95%CI: 1.3,2.5; α : 0.00) as likely to become LTFU, followed by those with WHO stage III (CHR: 1.2; 95%CI: 1.1,1.3; α : 0.00) than children with WHO stage II (CHR: 1.1; 95%CI: 1.0,1.2; α : 0.16) and least likely compared to WHO stage I. However, in the multivariate analysis, only WHO stage III and IV were statistically significant predictors of LTFU, with stage IV being twice (AHR: 1.5; 95%CI: 1.1,2.2; α : 0.02) and stage III once (AHR: 1.3; 95%CI: 1.1,1.5; α : 0.00) the hazard of being LTFU compared to children with WHO stage I. The LTFU rate among children on ART and log-rank over the WHO stage is presented in ***Figure 12***.

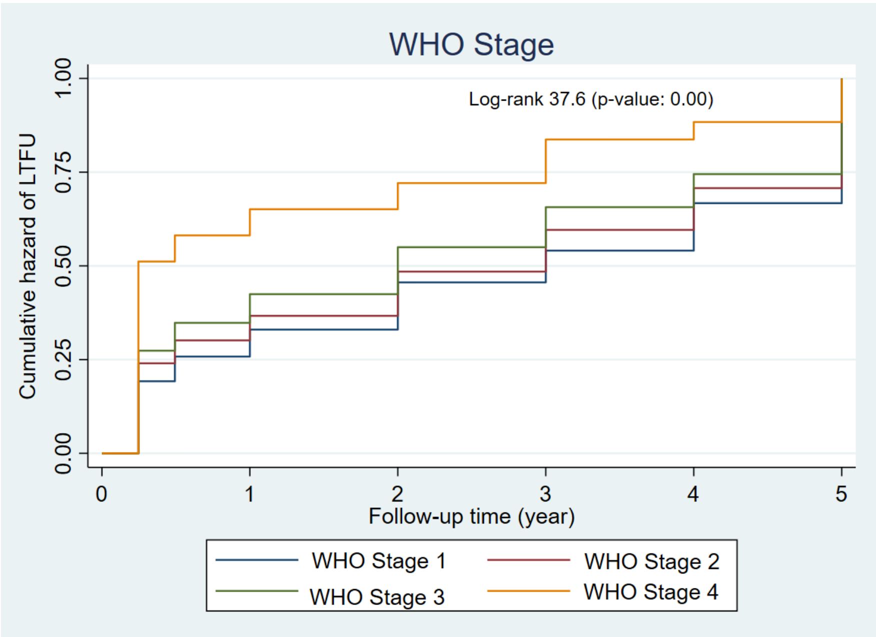


Figure 12: The hazard rate of LTFU among children on ART and log-rank over the WHO stage (2016 to 2021)

CD4 counts of 200–499 cells/mm3 and ≥1,000 cells/mm^3 at the start of ART were significantly associated with LTFU among children in the bivariate analysis. Children with a CD4 count of <200 cells/mm^3 were at a 21% (CHR: 0.8; 95%CI: 0.67,0.94; α : 0.01) lower risk of being LTFU than those with 200–499 cells/mm^3 CD4 count and 3% (CHR: 1.0; 95%CI: 0.9,1.1; α : 0.41) lower risk compared to those with 500–999 cells/mm^3. Furthermore, children who had CD4 count ≥1,000 cells/mm^3 were 26% (CHR: 0.74; 95%CI: 0.63,0.88; α : 0.00) more at risk of LTFU compared to those with CD4 counts of <200 cells/mm^3. Children with ≥1,000 cells/mm^3 (AHR: 0.77; 95%CI: 0.6,0.9; α : 0.01) CD4 count remained significant in the multivariate analysis. ***Figure 13*** shows the LTFU rate among children on ART and log-rank over their CD4 count. The goodness of fit assessment for the Cox-proportional regression model was performed using Groennesby and Borgan test, and the model was fit (0.47, p-value: 0.49).

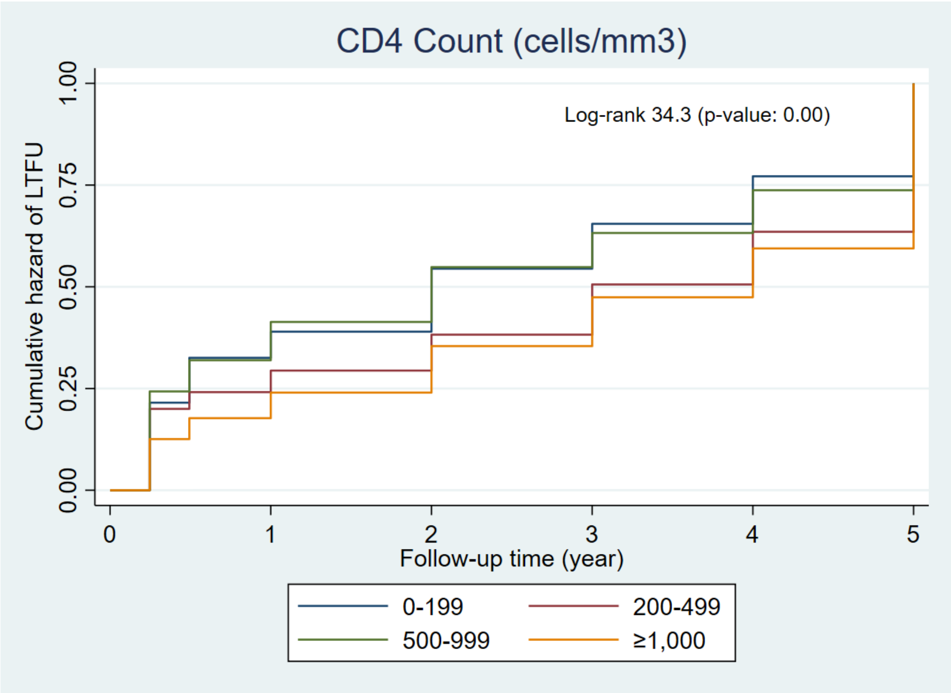


Figure 13: The hazard rate of LTFU among children on ART and log-rank over the CD4 count (2016 to 2021)

Furthermore, out of the 17 regimen disaggregation included in the model, two were statistically significant at the bivariate level and none at the multivariate level. In the bivariate analysis, children on the AZT-FTC-NVP regimen had the highest hazard of LTFU being three (CHR: 3.2; 95%CI: 0.7,13.9; α : 0.12) times more likely to be LTFU than those on ABC-3TC-DTG regimen. At the same time, children on TDF-3TC-EFV followed with one and a half (CHR: 1.5; 95%CI: 0.9,2.5; α : 0.11) times the higher hazard of LTFU than children who started on ABC-3TC-DTG.

CHAPTER FOUR

4.1. Discussion

4.1.1. Incidence of LTFU among Paediatrics on ART in Nigeria

Antiretroviral therapy aims to achieve undetectable viral load, improve patient health outcomes, and increase the survival of PLHIV (54). Recently, LTFU among paediatrics on ART has become a significant challenge in public health, negatively impacting treatment outcomes and impeding the success of ART (29). Therefore, this longitudinal retrospective cohort study of paediatrics on ART estimates the incidence and predictors of LTFU in a national ART program in Nigeria.

The findings from this study revealed a high LTFU rate among paediatrics on ART in Nigeria. The incidence rate of LTFU in this study at the end of the follow-up period was 40 (95%CI: 38.8, 41.3) per 100 child-years (higher than the WHO's target of <15%). Furthermore, at the end of the follow-up period, about 55% (95%CI: 54.1, 56.3%) of paediatrics were LTFU from ART. The cumulative incidence of LTFU from ART for the paediatrics in the study cohort steadily increased with the longer duration of ART: 13% (95%CI: 12.0, 13.5%) at 3 months; 17% (95%CI: 16.2, 17.9%) at 6 months; 22% (95%CI: 20.9, 22.7%) at 12 months; 29% (95%CI: 28.3, 30.3%) at 2 years; 34% (95%CI: 33.3, 35.5%) at 3 years; and 40% (95%CI: 39.1, 41.3%) at 4 years.

The cumulative incidence of LTFU in this study corroborates with a study conducted in Nigeria that found the LTFU rate among paediatrics to be 56% (74). A potential elucidation for the high rate of LTFU among paediatrics may be due to the decentralisation of ART services from tertiary healthcare centres to secondary and primary healthcare centres in the country (74). It is plausible that with the expansion and decentralisation of ART services, caregivers moved their children to healthcare centres close to their residence without documenting the transfer. However, due to stigmatisation, caregivers may prefer to access services in a healthcare facility far from their homes (53). Though ARVs are free, accessing healthcare services in Nigeria comes with added charges, some of which include card fees, specific laboratory tests, treatment of other diseases and transportation to the healthcare facility, thus adding to the financial burden of the caregivers (53). Purchase of these added services may lead to catastrophic expenditure among people in Nigeria, with the dwindling state of the economy, and currently, more than 40% of the population lives below the poverty line of $382 annually (15). Also, the insecurity challenges in Nigeria due to the Boko haram insurgency, banditry and kidnappings have made people move to new locations, thus contributing to the increasing rate of LTFU among paediatrics.

Another explanation for the high rate of LTFU may be due to the inadequate quality of data collection and reporting systems at the healthcare facility, which is a familiar issue with health information systems in low- and middle-income countries with less focus on service quality (75,76). With the scale-up of ART in Nigeria, there was a need for EMR to manage chronic diseases like HIV (77). However, there may have been data loss when certain healthcare facilities moved from paper-based to electronic monitoring systems. There may be no documentation of follow-up visits in the EMR at healthcare facilities. Also, there are chances of human error during data entry by the data entry officers.

Additionally, paediatrics depend on their caregivers for ART dispensation. Caregivers may experience medication refusal from the paediatrics when they become toddlers and start pre-school (78). The paediatrics in school begin to understand the notion of illness and treatment but, in most cases, are unaware of their illness. As expected, the children would want to conform with their peers and may be curious about why they are on daily medications (79). Furthermore, other reasons could be that the caregivers travel, forget to give the drugs to the children, encounter medication stock-out at home, or fall ill (55).

On the other hand, the result for this study is higher than studies done in South Africa that reported a LTFU incidence rate of 10.8 per 100 child-years of observation (80), and in Ethiopia, 6.2 per 100 child-years of observation (81). The potential elucidation for the differences might be due to the variations in the measurement of LTFU. This study measured LTFU as no clinical contact for 28 days or more after the last clinic visit of the child; however, the studies in South Africa and Ethiopia used a more extended window period by calculating LTFU as no clinical contact 90 days or more after the last clinic visit. A study in Ethiopia had a similar measurement of LTFU (30 days); however, the incidence rate was 6.3 per 100 child-years of observation (82). A probable reason for this variation might be the differences in the sample size, study design and setting and follow-up period. This study analysed data of paediatrics enrolled in all the ART healthcare facilities in Nigeria with a follow-up period of 5 years, but the Ethiopian study was institution-based and followed up the paediatrics for ten (10) years.

4.1.2. Predictors of LTFU among Paediatrics on ART in Nigeria

The second objective of this study was to identify the children and caregiver factors that predict LTFU among paediatrics on ART in Nigeria. Children with divorced caregivers, those that started ART greater than 14 days from HIV diagnosis and had 200–499 cells/mm^3 CD4 count were statistically significant at the bivariate level. In addition to the above-mentioned, children with married caregivers and those on ABC-FTC-NVP and TDF-3TC-EFV regimen had a p-value below 0.2 in the bivariate but were not statistically significant (p-value <0.05). Five variables were significant in the multivariate model when adjusted for the child's age, WHO stage, CD4 count, and caregiver's employment status.

Children aged 5–9 years, those starting ART with a WHO stage III, IV, and CD4 count of ≥1,000 cells/mm^3, and having an informally employed caregiver were the statistically significant predictors of LTFU from the multivariate Cox-proportional hazard model.

4.1.2.1. Socio-demographic Factors

This study showed the child's age to be a predictor of LTFU. Children aged 5–9 years had a higher risk of LTFU than paediatrics aged 0–4 years. Studies show that children who start ART at an older age have more suppressed immune systems and other measures of poor health, like malnutrition and anaemia (64). Also, a possible reason for the higher risk of LTFU among paediatrics 5–9 years than those 0–4 years could be the success of the PMTCT program in Nigeria that has established a mother-baby pair between a HIV-positive mother and her baby. Another potential reason for the higher risk of LTFU among this age group may be stigma and discrimination. In Nigeria, children begin school on average at five years; mothers may not want to administer drugs to their children in public, nor would they want to pass the responsibility of drug administration to the schoolteachers for fear of HIV status disclosure. Chandiwana et al. (80) supported this explanation through a quantitative study in South Africa, stating that the younger paediatrics receive more attention and care from their caregivers than the older ones leading to better drug adherence and attendance of clinic visits (p.4). Also, attending clinic visits may be difficult for the caregivers when the children start school (80). Despite the government of Nigeria passing an anti-discrimination law against PLHIV in 2014 and setting up a stigma reduction strategy (83–85), many PLHIV are not aware of the laws, and neither are the laws duly enforced.

The sex and BMI of the paediatrics were not significant predictors of LTFU in this study. A study conducted in Nigeria had consistent findings of sex not being a significant predictor of LTFU among paediatrics on ART (49). On the contrary, the sex of the paediatrics was a predictor of LTFU in some studies. Male children had a higher risk of LTFU than female children in Northeast Ethiopia (82) and Kenya (86). The study in Northeast Ethiopia attributed the finding to the characteristics of the patients, where more than half of the male participants started ART at an advanced HIV disease stage (82). On the contrary, in this study, most patients started ART at WHO stage I.

For the paediatrics enrolled in the OVC program, age, sex, and marital status of the caregiver were not significant predictors of LTFU in this study. A study in Nigeria also proved that the caregiver's age was not a predictor of LTFU (55). However, evidence from rural Kenya and South Africa which are also SSA countries show that paediatrics living with female caregivers have a higher risk of LTFU than their peers that live with male caregivers (86,87). A probable reason for this given by the authors was that most of the HIV infections among paediatrics are perinatal, and the mothers who are HIV positive may be too sick to attend clinic visits, deny the positive HIV status, or feel guilty. Also, it could be due to misclassifying the caregiver's status as female (86,87). These findings are similar to the Nigerian context; hence it is challenging to explain why caregiver's sex is not significant. A qualitative study would be needed in Nigeria to establish the reasons for these differences.

Paediatrics with caregivers who were informally employed had four times the higher hazard of LTFU than their counterparts with self-employed caregivers. In Nigeria, the high unemployment rate (33%) has made people engage in informal employment. The informal sector forms about 68% of the workforce and is not covered by any form of health insurance by the government, leading to health inequity (16). This may discourage them from seeking care at the healthcare facilities and resolve to alternative means, such as pharmacies, drug shops, or traditional healers, or not seeking care at all (16). In addition, families may face financial constraints in paying for services, including transport fares to the healthcare facilities and prioritising other purchases like food due to the economic constraints in Nigeria. Informally employed persons have unscheduled work hours, may engage in multiple jobs and may not want to sacrifice time to attend clinic visits. The long waiting time and unpleasant attitude of healthcare workers in certain healthcare facilities may also discourage them from seeking care. The caregivers may have little to no knowledge of the benefit of ART, thus paying less attention to clinic appointments (81).

The HIV status of the caregivers was not a statistically significant predictor of LTFU in this study. Nonetheless, evidence in Nigeria shows that children living with parents that are living with HIV are more likely to be adherent to ART (57). With children's dependency on their caregivers for care and access to treatment, it is possible that having seropositive parents that need similar care may enhance their access to ART (57).

4.1.2.2. Clinical Factors

This study found advanced HIV disease (WHO stage III and IV) statistically significant predictor of LTFU. Children with WHO stage III and IV were about twice more likely to be LTFU than those with earlier WHO stages. Studies have shown a correlation between WHO stage III and IV and LTFU and proposed that paediatrics with advanced HIV disease (WHO stage III and IV) at the start of ART are more likely to become LTFU than those with WHO stage I and II. This is clear in studies conducted in Ethiopia (81,82,88), Botswana (89), West Africa (90), and across multiple countries (Kenya, Mozambique, Rwanda, and Tanzania) (91). A probable explanation might be that paediatrics that have an advanced disease stage (WHO stage III and IV) at the start of ART have a high mortality rate and are more likely to have opportunistic infections that result in morbidity and undocumented deaths (82,92). In the advanced stage, children have rapid disease progression, which is already a challenge for paediatrics living with HIV and may develop side effects of the ARV (30,93). The caregivers may see the drugs as harmful and stop the child’s medication when they notice side effects. This outcome was also reported in a qualitative study on pregnant women on ART in Malawi, and the authors further explained how the side effects experienced by the mothers significantly influence the use of ARV (94). The side effects vary, but children on a regimen containing NVP may experience slight rashes, and those on a regimen containing AZT may experience anaemia (95).

On the other hand, studies in a hospital in rural Kenya (86) and South Africa (80) reported that patients with advanced HIV disease were less likely to be LTFU than their counterparts with lower WHO stages (I and II). The authors argued that caregivers might believe that paediatrics with mild disease (WHO stage I and II) are not sick and do not need to adhere to clinic appointments (86). Furthermore, asymptomatic paediatrics (WHO stage I and II) may be perceived to have lower exposure to opportunistic infections and better health; thus, they may not receive comprehensive HIV services at the healthcare facility.

Only 38% of the study participants had a baseline CD4 count; however, the missing 62% were updated with the imputation method using the mean of 875 cells/mm^3. Having CD4 counts of $\geq$1,000 cells/mm^3 at the start of ART significantly increased the hazard of LTFU among paediatrics. Patients with high CD4 counts may appear healthier than their counterparts with lower CD4 counts. This high rate of LTFU may also be due to the test and treat strategy, with the majority (74%) of patients in this study starting ART within 14 days of HIV diagnosis. The caregivers of children with a high CD4 count may assume that their children are healthy and do not need follow-up visits to the healthcare facilities, thus resulting in LTFU. Also, before the test and treat strategy, HIV-positive paediatrics were started on ART based on clinical and immunological evaluations (30). Then, it is possible that caregivers who noticed the clinical improvement of their children that were previously sick after starting ART would probably be encouraged to continue their children on treatment (94). However, lower CD4 counts were mentioned as a predictor of LTFU in other studies (82).

This study did not identify drug regimen as a predictor of LTFU. In the context of Nigeria, it could be because the caregivers are not necessarily aware of the different regimen classification given to their children. While Hibstie et al. (62) stated that children who start on nevirapine (NVP) or efavirenz-based (EFV) regimen in Ethiopia were at a lower risk of LTFU than those on other regimens (p.13), while Kaung Nyunt et al. (96) found the reverse (p.11). No conclusions were made on these findings, and further research was proposed.

The cohort year of this study is the year that the test and treat initiative was adopted in Nigeria (30). Despite the challenges, it is noteworthy to mention that the majority (74%) of the study population started ART based on this criterion; for all patients to start ART irrespective of their clinical and immunological stages. This may be a probable explanation for the time to ART start not being a significant predictor of LTFU.

4.1.3. Relevance of the Framework

Understanding LTFU involves a multifactorial approach and demands a comprehensive knowledge of the influencing factors. As highlighted in the adapted conceptual framework determinants of LTFU among HIV-infected children in ART care, as shown in ***Figure 7***, it is crucial to analyse the socio-demographic and clinical factors. The framework helped select variables, analyse data, and interpret results. The framework was straightforward and linked important socio-demographic and clinical variables in ways that are easy to interpret. However, it would be essential to analyse the healthcare factors when determining the predictors of LTFU among children in Nigeria. I propose adapting the framework to include more clinical variables and healthcare-related factors.

4.1.4. Potential Limitations of this Study

Before interpreting the results of this study, certain limitations must be considered. Firstly, using routinely collected patient data and a large sample size provides a diverse representation of the characteristics and outcomes of children on ART in Nigeria. However, data quality was a limitation. The use of medical records from healthcare facilities collected for patient care is prone to missing, inconsistent and inaccurate data, measurement and misclassification errors, in comparison to data collected for a research study. Expressly, patients with missing drug duration were excluded from the study. Anthropometric measurements such as weight and height were missing for more than three-quarters (82%) of the study participants. Also, clinical data such as WHO staging, CD4 count, and drug regimen likely to influence LTFU were missing for 31%, 62%, and 37% of the children at ART start, respectively. CD4 per cent is recommended for children below five years, but the database had CD4 counts for all ages. Adjusting BMI using the single imputation method made no essential change to the results. Using a single imputation method can create bias in the results while not confronting the uncertainty of the dataset. Caution is required to interpret this study's CD4 count and drug regimen.

Additionally, mortality estimates may have been under-reported as death status was not verified but based on the recorded data in the EMR/NDR. It is possible that patients reported as LTFU may be receiving treatment in another healthcare facility (silent treatment) or dead; therefore, overestimating the LTFU rate. LTFU children were not traced to determine their actual status as that was beyond the scope of this study and would have given added information to healthcare facilities on interventions for patient retention on ART. Lastly, the data from NDR and NOMIS were sufficient to answer the quantitative predictors; however, a qualitative study would be needed to identify the qualitative predictors of LTFU.

CHAPTER FIVE

5.1. Conclusion and Recommendations

5.1.1. Conclusion

Regardless of the scale-up of the ART program in Nigeria, especially among children, this study estimated that 55% of children on ART in Nigeria were LTFU after five years on ART. The differences observed between the results of this study and that of other studies in Nigeria and other countries can be attributed to the different study settings, LTFU measurement, study design, sample size and follow-up period. The findings from this study have significant program implications because the high rate of LTFU is greater than WHO's recommended target of <15% and this happened when the test and treat strategy for children was fully implemented in Nigeria. However, the high rate of LTFU is a recurrent challenge in the HIV program, including among adults. Several efforts have been put in place by the national HIV/AIDS program and other implementing partners to track children that are LTFU and achieve the political declaration on HIV/AIDS made in 2021 for all children living with HIV to achieve 75% and 85% viral suppression by 2023 and 2025, respectively. However, these efforts need to be strengthened. Some of the findings from this study could contribute to reducing the increased rate of LTFU among children in the country.

Firstly, the incidence rate of LTFU increased steadily from three months after the start of ART to the end of the follow-up period (five years). This increase occurred even though there was the implementation of the test and treat strategy and decentralisation of ART services to secondary and primary healthcare centres. This suggests that caregivers may have moved to healthcare facilities close to their homes to access HIV services or may not access services due to financial constraints or the country's current security challenges.

Secondly, it can be concluded that the high rate of LTFU among paediatrics on ART in Nigeria is well founded on factors such as the child's age, WHO staging, CD4 count, and caregiver's employment status. These factors are interrelated across diverse levels. For example, older children with advanced HIV disease, opportunistic infections and informally employed caregivers may have died, and the caregivers believe there is no reason to return to the healthcare facility to report the death. Also, informal employment can be time-consuming and tasking; the caregivers may forget to give the children medications, forget to take them to the healthcare facilities for follow-up visits, be demoralised by the long waiting times in the healthcare facilities or turn to traditional medicines. Due to economic hardship, visiting healthcare facilities may be burdensome to people. Families may prioritise other purchases in the home and not consider spending money for specific tests or transportation to the healthcare facility as necessary because the child looks healthy.

Thirdly, this study found that a child's age was a predictor of LTFU and concluded that the higher hazard of LTFU among the older age group (5–9 years) could be because of the start of preschool education. Also, children are more aware and curious about the things happening around them and may start questioning their caregivers on reasons for daily medications and frequent hospital visits. This may discourage the caregivers for fear of HIV status disclosure and stigma. Furthermore, the stigma and discrimination of PLHIV are significant issues that need to be addressed in Nigeria. However, PLHIV need to be more knowledgeable of their rights and demand enforcement of the bill against PLHIV discrimination.

Lastly, it is noteworthy to mention the importance of data quality in the HIV program because this would help program implementers take the right decisions concerning children on ART.

5.1.2. Recommendations

Based on the significant challenges identified by this study, the following recommendations are proposed to reduce LTFU and improve the management and retention of paediatrics on ART in Nigeria.

5.1.2.1. Recommendations to Healthcare Facilities

Child-centred interventions should be implemented to improve children's long-term retention on treatment. Firstly, drawing from the success of the PMTCT program in establishing a mother-baby pair, the clinic visits of children on ART can be aligned with those of their caregivers with tailored adherence counselling, including ARV side effects, barriers to clinic visits and possible solutions for the caregivers. Adherence counselling should also emphasise the importance of continuing ARV irrespective of the child's health status. With the current engagement of case managers for HIV testing at various healthcare facilities in Nigeria, these people can be leveraged for intensive continuous tracking of LTFU children.

Healthcare facilities should integrate paediatric and adult HIV services to create an organised system of HIV care, such as initiatives on adherence programs, like family-centred care for families with children on ART—to enhance their retention in treatment. Although some healthcare facilities have after-school clinics for adolescents, this should be expanded to provide tailored paediatric HIV services, including after-hours and weekend clinics for children in schools and employed caregivers.

Furthermore, healthcare facilities should design a coordinated system of HIV care which includes implementing strategies to reduce provider-related stigma and improving the capacity of the monitoring and evaluation (M&E) and data entry officers for accurate reporting of HIV program data—also engaging in task shifting to prevent overstretching and burnout of healthcare facility staff.

5.1.2.2. Recommendations to Implementing Partners and the National HIV/AIDS program

Additionally, HIV data collection, reporting and surveillance need to be improved. The pertinent stakeholders are the FMoH, the national HIV/AIDS program and implementing partners, with the former leading the process. This would involve retraining the healthcare facility and state data entry and M&E officers on M&E processes, including data quality assurance and routine data quality assessments (DQA) or spot checks. Also, this can include training facility and state programs and M&E officers to continuously review the patient data and understand the distribution of the disease and patterns of LTFU. The findings can be shared with relevant stakeholders for the synergy of the M&E system. The monthly M&E review meetings can be leveraged for the training and routine supervisory visits for the DQA and spot checks to avoid incurring additional costs.

Furthermore, healthcare facilities with a high incidence of LTFU should be identified and provided with the necessary support to return and retain patients on treatment, prioritising older paediatrics and those with advanced HIV disease. The existing network of PLHIV, healthcare facility case managers, and community healthcare workers can be leveraged to expand the tracking of lost patients by providing support to caregivers.

This study determined that not all patients were started on ART within 14 days. The national HIV/AIDS program should actively enforce the implementation of the test and treat strategy and use the new national guideline for HIV care and treatment to reduce the treatment delay and high rate of LTFU. Clinicians at the healthcare facilities should be retrained, with the distribution of job aids and the required guidelines to all healthcare facilities. These can be integrated into the routine training of clinicians by implementing partners of the ART program, in collaboration with the FMoH and the national HIV/AIDS program.

5.1.2.3. Recommendations to the Federal Government of Nigeria

The study identified that stigma and discrimination might be reasons for LTFU among paediatrics. Therefore, the act on anti-discrimination against PLHIV should be re-enacted and enforced in all states by the government of Nigeria, with full implementation of the national HIV/AIDS stigma strategy.

The government needs to be involved and support the respective agencies to implement the recommendations to the healthcare facilities, implementing partners, and the HIV/AIDS program. In addition to existing strategies, implementing these recommendations will propel the country towards achieving the UNAIDS 95-95-95 targets, SDG goals and political declarations on HIV/AIDS for children.

5.1.2.4. Recommendations for Further Research

Qualitative research would be needed in Nigeria for a deeper dive and to understand the reasons behind the contrasting evidence of caregivers’ age, sex, marital status, and drug regimen of the child as predictors of LTFU.

References

1. World Health Organisation. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV guidelines. 2015 [cited 2022 Aug 8]; Available from: https://apps.who.int/iris/bitstream/handle/10665/186275/9789241509565_eng.pdf

2. MedCalc. Cox regression [Internet]. [cited 2022 Jul 27]. Available from: https://www.medcalc.org/manual/cox-regression.php

3. MedCalc. Kaplan-Meier survival analysis [Internet]. [cited 2022 Jul 27]. Available from: https://www.medcalc.org/manual/kaplan-meier.php

4. World Health Organisation. Consolidated HIV strategic information guidelines [Internet]. 2020 [cited 2022 Jun 9]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331697/9789240000735-eng.pdf

5. U.S. Agency for International Development (USAID). Orphans and Vulnerable Children [Internet]. [cited 2022 Aug 8]. Available from: https://www.usaid.gov/global-health/health-areas/hiv-and-aids/technical-areas/orphans-and-vulnerable-children

6. Encyclopaedia Britannica. Nigeria - History, population, flag, map, languages, capital, & facts [Internet]. [cited 2022 Jun 21]. Available from: https://www.britannica.com/place/Nigeria

7. Federal Ministry of Health Nigeria. National Health Policy: Promoting the health of Nigerians to accelerate socio-economic development. 2016 [cited 2022 May 23]; Available from: https://naca.gov.ng/wp-content/uploads/2019/10/National-Health-Policy-Final-copy.pdf

8. CIA.gov. Nigeria - The World factbook [Internet]. [cited 2022 Jun 22]. Available from: https://www.cia.gov/the-world-factbook/countries/nigeria/#government

9. Statista. Demographics of Nigeria - statistics & facts [Internet]. [cited 2022 Jun 21]. Available from: https://www.statista.com/topics/6477/demographics-of-nigeria/#dossierKeyfigures

10. World Population Review. Nigeria population 2022 (Demographics, maps, graphs) [Internet]. [cited 2022 Jun 21]. Available from: https://worldpopulationreview.com/countries/nigeria-population

11. PopulationPyramid.net. Population of Nigeria 2021 - Population pyramid [Internet]. [cited 2022 Jun 21]. Available from: https://www.populationpyramid.net/nigeria/2021/

12. World Culture Encyclopedia. Culture of Nigeria - history, people, clothing, traditions, women, beliefs, food, customs, family [Internet]. [cited 2022 Jun 21]. Available from: https://www.everyculture.com/Ma-Ni/Nigeria.html#ixzz6rkQUc71H

13. Budget Office of the Federation - Federal Republic of Nigeria. Economic recovery & growth plan 2017-2020 [Internet]. [cited 2022 Jun 22]. Available from: https://budgetoffice.gov.ng/index.php/economic-recovery-growth-plan-2017-2020

14. World Bank. Nigeria overview: Development news, research, data [Internet]. [cited 2022 Jun 22]. Available from: https://www.worldbank.org/en/country/nigeria/overview

15. National Bureau of Statistics. Poverty and inequality in Nigeria 2019 reports [Internet]. [cited 2022 May 29]. Available from: https://nigerianstat.gov.ng/elibrary/read/1092

16. Abubakar I, Dalglish SL, Angell B, Sanuade O, Abimbola S, Adamu AL, et al. The Lancet Commissions. The Lancet Nigeria Commission: investing in health and the future of the nation. www.thelancet.com [Internet]. 2022 [cited 2022 May 24]; Available from: https://doi.org/10.1016/S0140-6736(21)02488-0

17. World Economics. Nigeria GDP 2021 economic data [Internet]. [cited 2022 Jun 22]. Available from: https://www.worldeconomics.com/Country-Size/Nigeria.aspx

18. Statista. Employment in Nigeria - statistics & facts [Internet]. [cited 2022 Jun 22]. Available from: https://www.statista.com/topics/9043/employment-in-nigeria/#dossierKeyfigures

19. National Population Commission Nigeria. Nigeria Demographic and Health Survey 2018. DHS Program ICF Rockville, Maryland, USA [Internet]. 2019 [cited 2022 Jun 22]; Available from: https://dhsprogram.com/pubs/pdf/FR359/FR359.pdf

20. UNICEF. Situation of women and children in Nigeria [Internet]. [cited 2022 Jul 7]. Available from: https://www.unicef.org/nigeria/situation-women-and-children-nigeria

21. UNICEF. Nigeria education [Internet]. [cited 2022 Jul 7]. Available from: https://www.unicef.org/nigeria/education

22. UNICEF. Towards an AIDS-free generation - Children and AIDS stocktaking report, 2013 [Internet]. [cited 2022 Jul 8]. Available from: https://data.unicef.org/resources/towards-an-aids-free-generation-children-and-aids-stocktaking-report-2013/

23. Federal Government of Nigeria. Second national strategic health development plan 2018-2022. Ensuring healthy lives and promoting the wellbeing of Nigerian populace at all ages. 2018 [cited 2022 Jun 23]; Available from: https://www.health.gov.ng/doc/NSHDP%20II%20Final.pdf

24. World Health Organisation. HIV/AIDS [Internet]. [cited 2022 May 6]. Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-aids

25. UNAIDS. Issues new fast-track strategy to end AIDS by 2030 - EGPAF [Internet]. [cited 2022 Jan 9]. Available from: https://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf

26. UNAIDS. Ending inequalities and getting on track to end AIDS by 2030 — A summary of the commitments and targets within the United Nations General Assembly's 2021 political declaration on HIV and AIDS [Internet]. [cited 2022 Jun 21]. Available from: https://www.unaids.org/sites/default/files/media_asset/2021-political-declaration_summary-10-targets_en.pdf

27. UNAIDS. Global HIV & AIDS statistics — Fact sheet [Internet]. [cited 2022 Feb 7]. Available from: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

28. UNICEF. Paediatric care and treatment [Internet]. [cited 2022 Jun 10]. Available from: https://data.unicef.org/topic/hivaids/paediatric-treatment-and-care/

29. UNAIDS. UNAIDS data 2021 [Internet]. [cited 2022 Jun 24]. Available from: https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf

30. National AIDS and STI Control Programme. National guidelines for HIV prevention treatment and care. 2016 [cited 2022 Jul 8]; Available from: https://naca.gov.ng/wp-content/uploads/2017/08/National-HIVAIDS-Prevention-and-Treatment-Guidelines_2016.pdf

31. Ugochukwu EF. Clinical spectrum of paediatric HIV in Nnewi, Nigeria. West African Journal of Medicine [Internet]. 2006 Jan 1 [cited 2022 Jul 15];25(1):10–4. Available from: https://www.ajol.info/index.php/wajm/article/download/28238/5006

32. Ojukwu J, Ogbu C. Paediatric HIV/AIDS in Abakaliki. Nigerian Journal of Paediatrics [Internet]. 2005 Mar 22 [cited 2022 Jul 15];30(4):128–34. Available from: https://www.ajol.info/index.php/njp/article/view/12075

33. Oniyangi O, Awani B, Iregbu K. The pattern of paediatric HIV/AIDS as seen at the National Hospital Abuja Nigeria. Nigerian Journal of Clinical Practice [Internet]. 2007 Sep 13 [cited 2022 Jul 15];9(2):153–8. Available from: https://www.ajol.info/index.php/njcp/article/view/11291

34. World Health Organization. Manual on paediatric HIV care and treatment for district hospitals [Internet]. 2011 [cited 2022 Jul 16]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44511/9789241501026_eng.pdf

35. National Agency for the Control of AIDS. Federal Republic of Nigeria Global AIDS response - Country progress report. 2015 [cited 2022 Jun 28]; Available from: https://naca.gov.ng/wp-content/uploads/2016/11/Nigeria_GARPR_2015_Report_0.pdf

36. Federal Republic of Nigeria. National HIV and AIDS strategic plan 2017-2021. [cited 2022 Jun 23]; Available from: https://naca.gov.ng/wp-content/uploads/2018/05/National-HIV-and-AIDS-Strategic-Plan-FINAL1.pdf

37. Federal Republic of Nigeria. National HIV and AIDS strategic framework 2017-2021. [cited 2022 May 19]; Available from: https://www.childrenandaids.org/sites/default/files/2017-11/NATIONAL-HIV-AND-AIDS-STRATEGIC-FRAMEWORK.pdf

38. Federal Ministry of Health Nigeria. Nigeria HIV/AIDS indicator and impact survey (NAIIS) 2018: Technical report. Abuja, Nigeria. October 2019 [Internet]. [cited 2022 Jan 9]. Available from: https://naiis.ng/resource/NAIIS-Report-2018.pdf

39. National Agency for the Control of AIDS. Modes of HIV transmission in Nigeria: Application of the incidence patterns model. 2020 [cited 2022 Jul 7]; Available from: https://naca.gov.ng/wp-content/uploads/2021/07/Mode-of-Transmission-of-HIV-IPM_Report_Nigeria-2020.pdf

40. UNAIDS. Confronting inequalities. Lessons for pandemic responses from 40 years of AIDS. 2021 [cited 2022 Jun 10]; Available from: https://www.unaids.org/sites/default/files/media_asset/2021-global-aids-update_en.pdf

41. HIV.gov. HIV care continuum [Internet]. [cited 2022 Jun 8]. Available from: https://www.hiv.gov/federal-response/policies-issues/hiv-aids-care-continuum

42. Dalhatu I, Onotu D, Odafe S, Abiri O, Debem H, Agolory S, et al. Outcomes of Nigeria's HIV/AIDS treatment program for patients initiated on antiretroviral treatment between 2004-2012. PLOS ONE [Internet]. 2016 Nov 1 [cited 2022 Jan 20];11(11):e0165528. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0165528

43. Sabate E. Adherence to long-term therapies: Evidence for action. Geneva: World Health Organization, 2003. [Internet]. [cited 2022 Jun 8]. Available from: https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf

44. Federal Ministry of Health Abuja - Nigeria. National guidelines for HIV and AIDS treatment and care in adolescents and adults. 2010 [cited 2022 Feb 7]; Available from: https://www.shccin.org/wp-content/uploads/2017/09/National-Guideline-for-treatment-and-care-of-HIV_AIDS-in-adults-and-Adolescents-2010.pdf

45. Maduka O, Tobin-West C. Adherence counseling and reminder text messages improve uptake of antiretroviral therapy in a tertiary hospital in Nigeria. Nigerian Journal of Clinical Practice [Internet]. 2013 Sep 10 [cited 2022 Mar 2];16(3):302–8. Available from: https://www.ajol.info/index.php/njcp/article/view/93968

46. Meloni ST, Chang C, Chaplin B, Rawizza H, Jolayemi O, Banigbe B, et al. Time-dependent predictors of loss to follow-up in a large HIV treatment cohort in Nigeria. Open Forum Infectious Diseases [Internet]. 2014 Sep 1 [cited 2022 May 19];1(2). Available from: https://academic.oup.com/ofid/article/1/2/ofu055/1464584

47. UNICEF. A child was infected with HIV every two minutes in 2020 [Internet]. [cited 2022 May 18]. Available from: https://www.unicef.org/nigeria/press-releases/child-was-infected-hiv-every-two-minutes-2020-unicef

48. World Health Organisation. Global report on early warning indicators of HIV drug resistance - Technical Report. 2016 [cited 2022 Jul 15]; Available from: https://apps.who.int/iris/bitstream/handle/10665/246219/9789241511179-eng.pdf

49. Eguzo K, Lawal A, Umezurike C, Eseigbe C. Predictors of loss to follow-up among HIV-infected patients in a rural South-Eastern Nigeria Hospital: A 5-year retrospective cohort study. Annals of Medical and Health Sciences Research. 2015;5(6):373.

50. Balogun M, Meloni ST, Igwilo UU, Roberts A, Okafor I, Sekoni A, et al. Status of HIV-infected patients classified as lost to follow up from a large antiretroviral program in southwest Nigeria. PLoS ONE [Internet]. 2019 Jan 1 [cited 2022 Jul 11];14(7):e0219903. Available from: https://doaj.org/article/deab5fbadcc34250af72579dc1782900

51. Ojeniran MA, Emokpae A, Mabogunje C, Akintan P, Hoshen M, Weiss R. How are children with HIV faring in Nigeria?- A 7 year retrospective study of children enrolled in HIV care. BMC Pediatrics [Internet]. 2015 Jul 22 [cited 2022 Jul 11];15(1):1–7. Available from: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-015-0405-9

52. Abolodje E, Audu E, Bello SO, Audu ES, Ikrama HI, Moses Kelechi I. The pattern of loss to follow-up among HIV-infected clients in a tertiary health facility in north central Nigeria. Sri Lanka Journal of Child Health [Internet]. 2020 [cited 2022 Jul 11];49(2):170–4. Available from: http://dx.doi.org/10.4038/sljch.v49i2.8966

53. Onubogu CU, Ugochukwu EF. A 17 year experience of attrition from care among HIV infected children in Nnewi south-east Nigeria. BMC Infectious Diseases [Internet]. 2021 Dec 1 [cited 2022 Jul 11];21(1):1–11. Available from: https://link.springer.com/articles/10.1186/s12879-021-06099-3

54. Aliyu A, Adelekan B, Andrew N, Ekong E, Dapiap S, Murtala-Ibrahim F, et al. Predictors of loss to follow-up in art experienced patients in Nigeria: A 13 year review (2004-2017). AIDS Research and Therapy [Internet]. 2019 Oct 8 [cited 2022 Jul 8];16(1):1–9. Available from: https://aidsrestherapy.biomedcentral.com/articles/10.1186/s12981-019-0241-3

55. Ugwu R, Eneh A. Factors influencing adherence to paediatric antiretroviral therapy in Portharcourt, south-south Nigeria. Pan African Medical Journal [Internet]. 2014 May 6 [cited 2022 Mar 2];16(1). Available from: https://www.ajol.info/index.php/pamj/article/view/103291

56. Hong SY, Winston A, Mutenda N, Hamunime N, Roy T, Wanke C, et al. Predictors of loss to follow-up from HIV antiretroviral therapy in Namibia. PLoS ONE. 2022 Apr 1;17(4 April).

57. Ubesie AC, Iloh KK, Ayuk CA, Ibeziako SN, Emodi JI, Obumneme-Anyim I. Outcomes of Paediatrics HIV care at the University of Nigeria teaching Hospital, Ituku-Ozalla, Enugu after ten years of service. Nigerian Journal of Paediatrics [Internet]. 2017 Mar 10 [cited 2022 Jul 11];44(1):22–5. Available from: https://www.ajol.info/index.php/njp/article/view/152768

58. Janssen S, Wieten RW, Stolp S, Cremers AL, Rossatanga EG, Klipstein-Grobusch K, et al. Factors associated with retention to care in an HIV clinic in Gabon, Central Africa. PLOS ONE [Internet]. 2015 Oct 16 [cited 2022 Jul 8];10(10):e0140746. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140746

59. Braitstein P, Katshcke A, Shen C, Sang E, Nyandiko W, Ochieng VO, et al. Retention of HIV-infected and HIV-exposed children in a comprehensive HIV clinical care programme in Western Kenya. Tropical Medicine & International Health [Internet]. 2010 Jul 1 [cited 2022 Jul 16];15(7):833–41. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-3156.2010.02539.x

60. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review. PLoS Medicine. 2007 Oct;4(10):1691–701.

61. World Health Organisation. Patient monitoring guidelines for HIV care and antiretroviral therapy (ART). 2006 [cited 2022 Aug 6]; Available from: https://apps.who.int/iris/bitstream/handle/10665/43382/9241593881_eng.pdf

62. Hibstie YT, Kibret GD, Talie A, Temesgen B, Melkamu MW, Alebel Id A. Nearly one in every six HIV-infected children lost from ART follow-up at Debre Markos referral Hospital, northwest Ethiopia: A 14-year retrospective follow-up study. 2020; Available from: https://doi.org/10.1371/journal.pone.0239013

63. Sifr Z, Ando T, Semeon W, Rike M, Ashami K. Level of attrition from antiretroviral therapy among human immune deficiency virus-infected children: The cases of Sidama zone, southern Ethiopia. HIV/AIDS - Research and Palliative Care. 2021;13:813–22.

64. Abuogi LL, Smith C, McFarland EJ. Retention of HIV-infected children in the first 12 months of anti-retroviral therapy and predictors of attrition in resource limited settings: A systematic review. PLOS ONE [Internet]. 2016 Jun 1 [cited 2022 Aug 6];11(6):e0156506. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0156506

65. Hagströmer O, Lundstedt L, Balcha TT, Björkman P. Decentralised paediatric HIV care in Ethiopia: a comparison between outcomes of patients managed in health centres and in a hospital clinic. http://dx.doi.org/103402/gha.v6i022274 [Internet]. 2013 [cited 2022 Aug 6];6(1):22274. Available from: https://www.tandfonline.com/doi/abs/10.3402/gha.v6i0.22274

66. Jones M, Stander M, van Zyl M, Cameron D. Recall of lost-to-follow-up pre-antiretroviral therapy patients in the Eastern Cape: Effect of mentoring on patient care. South African Medical Journal [Internet]. 2012 Aug 22 [cited 2022 Aug 6];102(9):768–9. Available from: http://www.samj.org.za/index.php/samj/article/view/5957/4426

67. Bernays S, Jarrett P, Kranzer K, Ferrand RA. Children growing up with HIV infection: The responsibility of success. The Lancet. 2014;383(9925):1355–7.

68. Berheto TM, Haile DB, Mohammed S. Predictors of loss to follow-up in patients living with HIV/AIDS after initiation of antiretroviral therapy. North American Journal of Medical Sciences [Internet]. 2014 Sep 1 [cited 2022 Aug 6];6(9):453. Available from: https://www.najms.org/article.asp?issn=1947-2714;year=2014;volume=6;issue=9;spage=453;epage=459;aulast=Berheto

69. Ojikutu B, Higgins-Biddle M, Greeson D, Phelps BR, Amzel A, Okechukwu E, et al. The association between quality of HIV care, loss to follow-up and mortality in pediatric and adolescent patients receiving antiretroviral therapy in Nigeria. PLOS ONE [Internet]. 2014 Jul 30 [cited 2022 Aug 7];9(7):e100039. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0100039

70. Flannelly LT, Flannelly KJ, Jankowski KRB. Independent, dependent, and other variables in healthcare and chaplaincy research. http://dx.doi.org.vu-nl.idm.oclc.org/101080/088547262014959374 [Internet]. 2014 Oct 1 [cited 2022 Jul 4];20(4):161–70. Available from: https://www-tandfonline-com.vu-nl.idm.oclc.org/doi/abs/10.1080/08854726.2014.959374

71. World Health Organisation. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance: African Region [Internet]. 2005 [cited 2022 Jul 20]. Available from: https://apps.who.int/iris/handle/10665/69058

72. Islam Khan S, Sayed Md Latiful Hoque A. SICE: an improved missing data imputation technique background and related works. 2020;7:37. Available from: http://creativecommons.org/licenses/by/4.0/.

73. Hosmer DW, Lemeshow S, Sturdivant RX. Applied logistic regression [Internet]. Applied Logistic Regression: Third Edition. New York: John Wiley & Sons, Incorporated; 2013 [cited 2022 Aug 8]. 1–510 p. Available from: https://onlinelibrary.wiley.com/doi/book/10.1002/9781118548387

74. Meloni S, Chaplin B, Chang C, Rawizza H, Okonkwo P, Kanki P. Patterns of adherence and loss to follow-up in pediatric patients on ART in Nigeria. Curr HIV Res [Internet]. 2015 May 13 [cited 2022 Jul 28];13(3):210–8. Available from: https://www.researchgate.net/publication/276297399_Patterns_of_Adherence_and_Loss_to_Follow-Up_in_Pediatric_Patients_on_ART_in_Nigeria

75. Kiragga AN, Castelnuovo B, Schaefer P, Muwonge T, Easterbrook PJ. Quality of data collection in a large HIV observational clinic database in sub-Saharan Africa: Implications for clinical research and audit of care. J Int AIDS Soc. 2011;14(1).

76. Kawonga M, Blaauw D, Fonn S. Aligning vertical interventions to health systems: a case study of the HIV monitoring and evaluation system in South Africa [Internet]. 2012. Available from: http://www.health-policy-systems.com/content/10/1/2

77. Meloni S, Eisen G, Banigbe B. Scale-up of networked HIV treatment in Nigeria: Creation of an integrated electronic medical records system. Article in International Journal of Medical Informatics [Internet]. 2014 [cited 2022 Aug 7]; Available from: http://dx.doi.org/10.1016/j.ijmedinf.2014.09.006

78. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. Current HIV/AIDS Reports 2009 6:4 [Internet]. 2009 Oct 14 [cited 2022 Aug 9];6(4):194–200. Available from: https://link.springer.com/article/10.1007/s11904-009-0026-8

79. Wiener L, Mellins CA, Marhefka S, Battles HB. Disclosure of an HIV diagnosis to children: history, current research, and future directions. J Dev Behav Pediatr [Internet]. 2007 Apr [cited 2022 Aug 9];28(2):155–66. Available from: https://pubmed.ncbi.nlm.nih.gov/17435473/

80. Chandiwana N, Sawry S, Chersich M, Kachingwe E, Makhathini B, Fairlie L. High loss to follow-up of children on antiretroviral treatment in a primary care HIV clinic in Johannesburg, South Africa. Medicine [Internet]. 2018 Jul 1 [cited 2022 Aug 4];97(29). Available from: /pmc/articles/PMC6086461/

81. Kassa SF, Worku WZ, Atalell KA, Agegnehu CD. Incidence of loss to follow-up and its predictors among children with HIV on antiretroviral therapy at the University of Gondar comprehensive specialized referral Hospital: A retrospective data analysis. HIV AIDS (Auckl) [Internet]. 2020 [cited 2022 Aug 4];12:525. Available from: /pmc/articles/PMC7547131/

82. Menshw Snr T, Birhanu S, Gebremaryam T, Yismaw W, Endalamaw A. Incidence and predictors of loss to follow-up among children attending ART clinics in northeast Ethiopia: A retrospective cohort study. HIV AIDS (Auckl) [Internet]. 2021 [cited 2022 Aug 3];13:801. Available from: /pmc/articles/PMC8364847/

83. HIV Justice Network. Nigeria passes law to stop discrimination related to HIV | UNAIDS [Internet]. 2015 [cited 2022 Aug 6]. Available from: https://www.hivjustice.net/news-from-other-sources/nigeria-passes-law-to-stop-discrimination-related-to-hiv-unaids/

84. AHF Nigeria. A popular version of Nigeria's HIV and AIDS anti-discrimination act, 2014. 2015 [cited 2022 Aug 6]; Available from: https://naca.gov.ng/wp-content/uploads/2016/11/Updated-Popular-Version-of-Nigerias-HIV-and-AIDS-Anti-Discrimination-Act-27-10-15.pdf

85. National Agency for the Control of AIDS. National HIV/AIDS stigma reduction strategy. 2016 [cited 2022 Aug 6]; Available from: https://naca.gov.ng/wp-content/uploads/2017/05/Stigma-Reduction-Strategy-Final-1-PDF.pdf

86. Saumu WM, Maleche-Obimbo E, Irimu G, Kumar R, Gichuhi C, Karau B. Predictors of loss to follow-up among children attending HIV clinic in a hospital in rural Kenya. Pan African Medical Journal [Internet]. 2019 Apr 30 [cited 2022 Jul 28];32(1). Available from: https://www.ajol.info/index.php/pamj/article/view/210496

87. Sengayi M, Dwane N, Marinda E, Sipambo N, Fairlie L, Moultrie H. Predictors of loss to follow-up among children in the first and second years of antiretroviral treatment in Johannesburg, South Africa. 2013 [cited 2022 Aug 6]; Available from: http://dx.doi.org/10.3402/gha.v6i0.19248

88. Melaku Z, Lulseged S, Wang C, Lamb MR, Gutema Y, Teasdale CA, et al. Outcomes among HIV-infected children initiating HIV care and antiretroviral treatment in Ethiopia. Trop Med Int Health [Internet]. 2017 [cited 2022 Aug 10];22(4):474–84. Available from: https://pubmed.ncbi.nlm.nih.gov/28066962/

89. Machine EM, Gillespie SL, Homedes N, Selwyn BJ, Ross MW, Anabwani G, et al. Lost to follow-up: failure to engage children in care in the first three months of diagnosis. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2016 Nov 1;28(11):1402–10.

90. Ekouevi DK, Azondekon A, Dicko F, Malateste K, Touré P, Eboua FT, et al. 2-month mortality and loss-to-program in antiretroviral-treated children: The IeDEA pediatric West African Database to evaluate AIDS (pWADA), 2000-2008 [Internet]. 2011. Available from: http://www.iedea-

91. McNairy ML, Lamb MR, Carter RJ, Fayorsey R, Tene G, Mutabazi V, et al. Retention of HIV-infected children on antiretroviral treatment in HIV care and treatment programs in Kenya, Mozambique, Rwanda, and Tanzania. Journal of Acquired Immune Deficiency Syndromes [Internet]. 2013 Mar 1 [cited 2022 Aug 4];62(3). Available from: https://journals.lww.com/jaids/Fulltext/2013/03010/Retention_of_HIV_Infected_Children_on.18.aspx

92. Bhatta L, Klouman E, Deuba K, Shrestha R, Karki DK, Ekstrom AM, et al. Survival on antiretroviral treatment among adult HIV-infected patients in Nepal: A retrospective cohort study in far-western Region, 2006-2011. BMC Infectious Diseases [Internet]. 2013 Dec 26 [cited 2022 Aug 6];13(1):1–9. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-13-604

93. Assemie MA, Fentahun Muchie K, Ayele TA. Incidence and predictors of loss to follow up among HIV-infected adults at Pawi General Hospital, northwest Ethiopia: competing risk regression model. BMC Res Notes [Internet]. 2018;11:287. Available from: https://doi.org/10.1186/s13104-018-3407-5

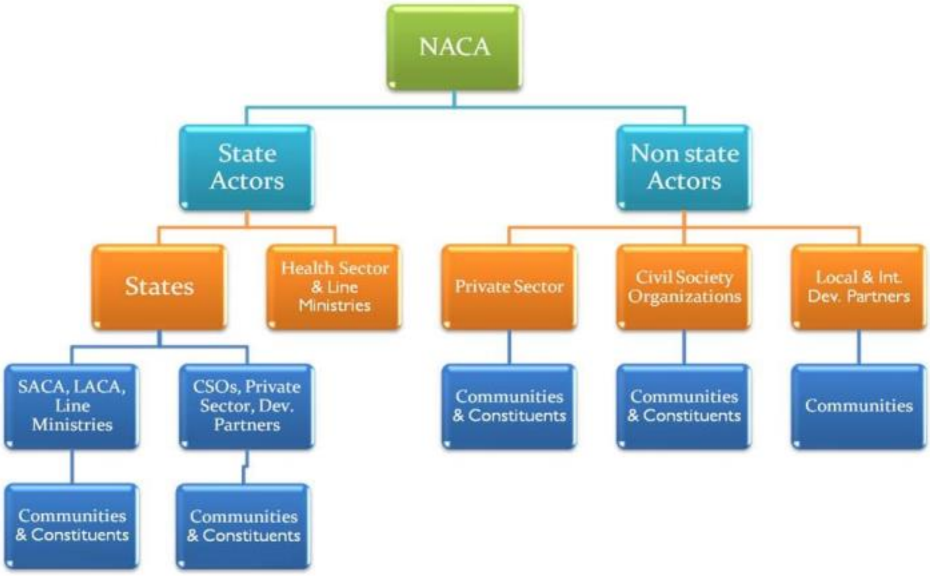
94. Phiri N, Haas AD, Msukwa MT, Tenthani L, Keiser O, Tal K. "I found that I was well and strong": Women's motivations for remaining on ART under option B+ in Malawi. PLoS One [Internet]. 2018 Jun 1 [cited 2022 Aug 7];13(6). Available from: https://pubmed.ncbi.nlm.nih.gov/29874247/

95. Oshikoya KA, Lawal S, Oreagba IA, Awodele O, Olayemi SO. Adverse events in HIV-infected children on antiretroviral therapy at a teaching Hospital in Lagos, Nigeria: A retrospective study. Adv Pharmacoepidem Drug Safety 1:117 [Internet]. 2012 [cited 2022 Aug 9]; Available from: 10.4172/2167-1052.1000117

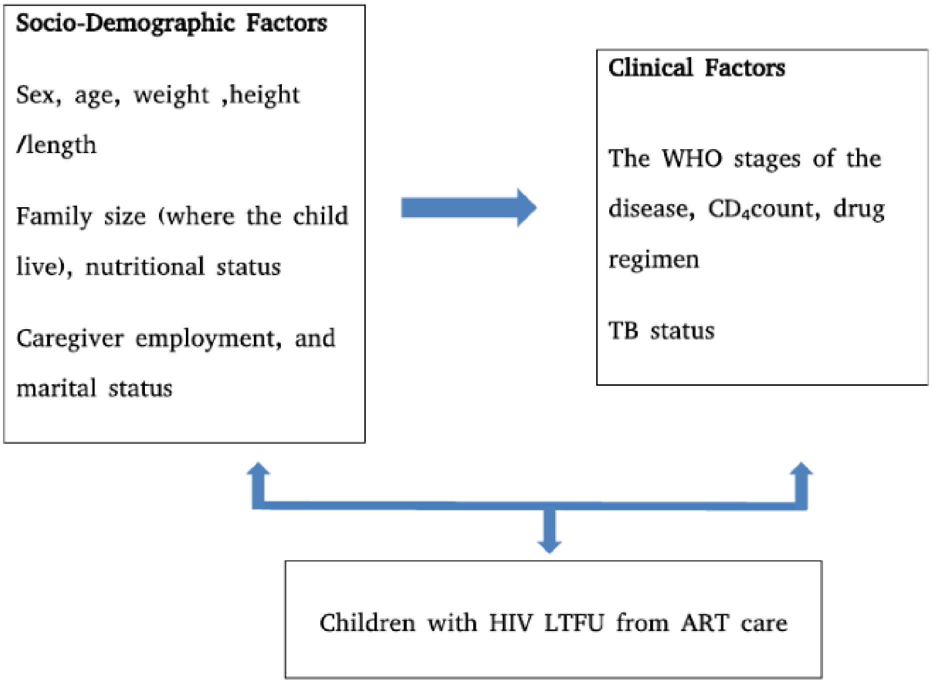
96. Kaung Nyunt KK, Han WW, Satyanarayana S, Isaakidis P, Hone S, Khaing AA, et al. Factors associated with death and loss to follow-up in children on antiretroviral care in Mingalardon specialist Hospital, Myanmar, 2006–2016. PLoS ONE. 2018 Apr 1;13(4).

Appendices

Appendix 1: Structure of the HIV response coordination in Nigeria (Source: Nigeria GARPR, 2015) (35)



Appendix 2: Conceptual framework for determinants of LTFU among HIV-infected children in ART care (Source: Sifr et al., 2021) (63)



Appendix 3: KIT (Royal Tropical Institute) Waiver

KIT Royal Tropical Institute

RESEARCH ETHICS COMMITTEE

Contact: Rob Kuijpers
r.kuijpers@kit.nl

To: Oluwaseun Chidera Okunuga
By E-mail: o.okunuga@student.kit.nl
Cc.: Lakis, Chantale <c.lakis@kit.nl>; Gerstel, Lisanne <l.gerstel@kit.nl>

Amsterdam, 15-06-2022

Subject Decision Research Ethics Committee S-193

Dear Oluwaseun Chidera Okunuga,

The Research Ethics Committee (REC) of Royal Tropical Institute has reviewed your application for a waiver for a "Predictors of Lost to Follow Up (LTFU) among Paediatrics living with HIV in Nigeria" (S-193) study that was originally submitted on 08-06-2022

Your proposal has been exempted from full ethical review based on the following considerations:

a. Only anonymized data will be used. This data does not contain any personal information through which individuals could be identified;
b. The data is stored in a safe place and can only be accessed by the researcher;
c. the data use has been approved by the data owner;
d. informed consent has not been given but it would not be feasible or practicable to ask informed consent to the participants to whom the data belong (anymore);
e. the research has important social, educational or scientific value;
f. the research poses no more than minimal risks to participants and does not give rise to the disclosure of the participant's identity.

The Committee requests you to inform the Committee if substantive changes to the protocol are made, important changes to the research team take place or researchers are added to the research team. Moreover, the Committee requests you to send the final report of the research containing a summary of the study's findings and conclusions to the Committee, for research managing and training purposes of the REC.

Wishing you success with the research,

Rob Kuijpers

Chair of the KIT REC

The Netherlands

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