Improving HIV Antiretroviral Therapy Adherence in Nigeria: implications for client and public health

Oladipupo Oluwaseun Shobowale
Nigeria

Master in International Health
September 2011 – March 2015

KIT Health (Royal Tropical Institute)
Vrije Universiteit Amsterdam
Amsterdam, The Netherlands

April 2015

Word Count: 12,970

Improving HIV Antiretroviral Therapy Adherence in Nigeria: implications for client and public health

A thesis submitted in partial fulfillment of the requirement for the degree of

Master in International Health

by

Oladipupo Oluwaseun Shobowale
Nigeria

Declaration:
Where other people's work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.
The thesis: **Improving HIV Antiretroviral Therapy Adherence in Nigeria: implications for client and public health**, is my own work.

Signature:.....

Master in International Health (MIH)
September 2011 – March 2015
KIT (Royal Tropical Institute)/Vrije Universiteit Amsterdam
Amsterdam, The Netherlands

April 2015

Organised by:

KIT (Royal Tropical Institute), Development Policy & Practice
Amsterdam, The Netherlands

In co-operation with:

Vrije Universiteit Amsterdam/Free University of Amsterdam (VU)
Amsterdam, The Netherlands

Table of Contents

Table of Contents.....i
List of Figures.....iv
List of Tables.....iv
Dedication.....v
List of Abbreviations.....vi
Abstract viii
Introduction 1
Chapter 1: Background Information.....2
1.1. Geography and Population.....2
1.2. Socio-demographic Overview.....2
1.3. Socio-economic Overview.....2
1.4. Health Situation.....2
1.5. Health System.....3
1.6. HIV Epidemic in Nigeria.....3
1.7. HIV Treatment and Care in Nigeria.....4
Chapter 2: Overview, Problem Statement, Justification, Objectives and Methodology.....6
2.1. Adherence: Definition, Concept and Terminology.....6
2.2. ART Adherence and Treatment Outcomes.....6
2.3. Problem Statement and Justification of Study.....7
2.4. Objectives.....8
2.4.1. General Objective.....8
2.4.2. Specific Objectives.....9
2.5. Methodology.....9
2.5.1. Search Strategy and Keywords.....9
2.5.2. Inclusion and Exclusion Criteria.....9
2.6. Framework for ART Adherence.....9
Chapter 3: Patterns of ART Adherence in Nigeria.....12
3.1. National Guidelines on ART in Nigeria.....12
3.2. Measurement of Adherence.....12
3.3. Adherence Rates in Sub-Sahara Africa.....13
3.4. Adherence Rates in Nigeria.....13
Chapter 4: Factors influencing ART Adherence.....15
4.1. Individual/Client-related Factors.....15
4.1.1. Sociodemographic Indices.....15
Age.....15
Sex.....15
Education.....15
Marital status.....16
Occupation, income and poverty.....16

4.1.2. HIV and ART-related Knowledge, Attitudes and Belief.....16
4.1.3. Perceived Health Status or Wellbeing and Cessation of Symptoms.....16
4.1.4. Disclosure of HIV Status.....17
4.1.5. Forgetfulness.....17
4.2. Social/Community-related Factors.....17
4.2.1. Stigma and Discrimination.....17
4.2.2. Social Support.....18
4.2.3. Religion.....18
4.2.4. Traditional Medicine and Alternative Medicine.....19
4.2.5. Financial Problems.....19
4.2.6. Gender Issues.....19
4.3. Condition (HIV)-related Factors.....20
4.3.1. Severity of HIV Infection (WHO-clinical staging) and Rate of Progression.....20
4.3.2. Severity of Symptoms.....20
4.3.3. HIV-related Disability.....20
4.3.4. HIV-Comorbidities.....21
4.4. Medication-related Factors.....21
4.4.1. Complexity of Drug Regimen.....21
4.4.2. ART Drug Side Effect.....22
4.4.3. Dietary Restrictions.....22
4.5. Health System-related and Structural Factors.....23
4.5.1. Quality of Care.....23
Patient-provider relationship.....23
Provision of privacy.....23
Waiting times and follow-up appointments.....23
Staff Skills/Inadequately trained healthcare providers.....24
Inadequate monitoring, counseling and follow-up schedule.....24
4.5.2. Limited Availability of ART drugs and ART-related Services.....24
4.5.3. Poor Access to Care Facilities: distance and financial.....25
Chapter 5: ART Adherence Interventions.....26
5.1. Classification of ART Adherence Interventions.....26
5.2. Adherence Intervention Studies from Nigeria, Sub-Sahara Africa and other Low and Middle-income Countries.....26
5.2.1. Affective Intervention Strategies.....27
Counseling.....27
Motivational Interviewing.....27
Peer support.....27
Psychiatric and psychological treatment.....27

5.2.2. Behavioural Intervention Strategies.....28
DOT/DAART.....28
Communication (SMS) technology.....28
Other reminder tools.....29
5.2.3. Biological Intervention Strategies.....29
Nutritional support and food supplementation.....29
Fixed Dose Combination (FDC).....29
5.2.4. Cognitive Intervention Strategies.....30
Client education.....30
Media methods.....30
5.2.5. Structural Intervention Strategies.....30
Home-based care (HBC).....30
Treatment supporters.....31
5.2.6. Combination of Intervention Strategies.....31
Chapter 6: Discussion.....33
6.1. Patterns of Adherence in Nigeria.....33
6.2. Factors influencing ART Adherence.....34
Individual/Client-related factors.....34
Social/Community-related factors.....34
Condition (HIV)-related factors.....35
Medication-related factors.....36
Health system-related and structural factors.....36
ART adherence framework.....37
Interaction of ART adherence factors.....37
6.3. ART Adherence Interventions.....37
6.4. Potential Relevant Adherence Interventions: Nigeria.....39
Chapter 7: Conclusions and Recommendations.....40
7.1. Conclusion.....40
7.2. Recommendations.....40
References.....43
Annexes.....70
Annex 1: Nigeria Health Indicators.....70
Annex 2: New HIV infections and AIDS-related death between 2008-2012.....71
Annex 3: Summary of ART Adherence Studies done in Nigeria (2004-2014).....72
Annex 4: Summary of ART Adherence Intervention Studies done in Nigeria.....75
Annex 5: ART Adherence Assessment/Measurement Methods: literature review.....77

List of Figures

Figure 1: Nigeria: Geopolitical Zones……..2

Figure 2: Relationship between Virological Failure and ART Adherence…7

Figure 3: Adapted Framework on ART Adherence……..……11

Figure 4: Matrix: Potentially Relevant ART Adherence Interventions for Nigeria……39

Figure 5: New HIV infections and AIDS-related death between 2008-2012……..71

List of Tables

Table 1: Classification of ART adherence intervention strategies……26

Table 2: Nigeria Health Indicators……70

Table 3: Summary of ART Adherence Studies done in Nigeria……72

Table 4: Summary of ART Adherence Intervention Studies done in Nigeria……75

DEDICATION

To my Father:

Sir Olasunkanmi Joseph Shobowale

You were everything to me. Miss you more everyday and I would have done anything to spend more time with you- just to hear your voice and gaze in your eyes. Nothing can heal the pain of your sudden death. You left and that void is yet to be filled.

I wish I could pay back the constant labor of love and support. Like you always told me, "when the going gets tough, the tough get going"…. I am keeping my head up Dad and I hope I've made you proud enough despite the struggles.

I LOVE YOU DAD! Love you more than words can say!

This is for you Pa.

LIST OF ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral (drug)
AUD	Alcohol Use Disorders
AUDIT	Alcohol Use Disorders Identification Test
AZT	Zidovudine
CBC	Community-based Care
CD4	Cluster of Differentiation 4
CES-D	Centre for Epidemiologic Studies Depression Scale
DAART	Directly Administered Antiretroviral Therapy
DOT	Directly Observed Therapy
EDM	Electronic Drug Monitoring
EFV	Efavirenz
FCT	Federal Capital Territory
FDC	Fixed Dose Combination
FTC	Emtricitabine
GARPR	Global AIDS Response Country Progress Report
HC	Health Centre
HCT	HIV Counselling and Testing
HBC	Home-Based Care
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HRH	Human Resources for Health
IPV	Intimate Partner Violence
LACA	Local Government Action Committee on AIDS
LMIC	Low and Middle-Income Country
LTFU	Loss-to-Follow-Up
MEMS	Medication Event Monitoring System
MI	Motivational Interviewing
MNS	Mental, Neurological and Substance Use (disorder)
MSM	Men who have sex with Men
NACA	National Agency for the Control of AIDS
NARHS	National HIV/AIDS and Reproductive Health Survey
NCD	Non-communicable Disease
NHIS	National Health Insurance Scheme
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitors
NSP	National Strategic Plan
NVP	Nevirapine
OI	Opportunistic Infection

PI	Protease Inhibitors
PHC	Primary Health Care
PLHIV	People Living with HIV
PCRP	Presidential Comprehensive Response Plan
QOL	Quality of life
RCT	Randomized Control Trial
SACA	State Action Committee on AIDS
SAT	Self-administered Therapy
SMS	Short Messages Service
SOC	Standard of Care
SSA	Sub-Sahara Africa
TasP	Treatment as prevention
TB	Tuberculosis
TDF	Tenofovir
TDM	Therapeutic Drug Monitoring
TWOT	Twice-weekly Observed Therapy
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
WOT	Once-weekly Observed Therapy

ABSTRACT

Background: Antiretroviral therapy (ART) adherence remains crucial to achieving therapeutic success in the management of HIV infection.

Objective: To explore the patterns of ART adherence, assess the factors influencing ART adherence and identify effective interventions geared towards improving ART adherence among adult people living with HIV (PLHIV) in Nigeria.

Methods: An explorative descriptive literature review was done to identify relevant information according to the study objectives. An ART adherence framework was adapted from Wekesa and Sabate to analyse the factors influencing adherence.

Findings: A wide variation of ART adherence rates (14.9% to >95%) was observed in the studies conducted in Nigeria. Evident factors influencing ART adherence identified were forgetfulness, financial problems, stigma and discrimination, social support, availability of ART drugs, complexity of drug regimen, drug side effects and aspects of access to ART such as cost and distance. Relevant adherence intervention strategies were identified and included: enhanced counselling, peer support, communication technology (SMS), fixed dose combination and home-based care.

Conclusions: Multiple interacting factors affect ART adherence among PLHIV. Furthermore, from study findings, major research gaps were identified such as lack of studies in PLHIV sub-populations (e.g. men who have sex with men and elderly PLHIV), cost analysis studies on adherence interventions and studies assessing long-term adherence.

Recommendations: Need for further research in highlighted areas, adoption of outlined interventions, and expanded funding for constant supply of ART drugs and subsidization of ART-related services.

Key words: Adherence, adherence factors, antiretroviral therapy, adherence intervention strategies, people living with HIV, Nigeria

Word Count: 12,970

INTRODUCTION

The Human Immunodeficiency Virus (HIV) epidemic remains a significant global threat and sub-Sahara Africa (SSA) accounts for the highest global HIV infection burden of about 71% of all people living with HIV (PLHIV) [1]. Nigeria has an estimated 3.2 million people infected with HIV and accounts for the second highest burden of HIV globally after South Africa [2]. Over the past nine years, trend analyses of HIV prevalence from national sentinel surveillance data indicate that the HIV epidemic is stabilizing at about 4% [2].

With the advent and global scale-up of antiretroviral therapy (ART), and in cases where there is good access and tolerance to treatment, PLHIV can survive for many years, living healthy normal lives. Nevertheless, PLHIV thus require lifelong ART and ancillary care which in 'real-life' situations is often complicated with multiple challenges related to factors such as access to healthcare services, social insecurity, religious beliefs, and stigma and discrimination, to mention a few. These potentially result in a broad range of adverse treatment outcomes in PLHIV.

The benefits of ART cannot be over-emphasized. ART leads to a reduction in viral load, which aids immune reconstitution and significant clinical improvement, reduces the risks of opportunistic infections (OIs), lowers mortality rates and also improves the quality of life (QOL) of PLHIV [3-6]. Recently, the "treatment as prevention (TasP)" approach using ART in PLHIV to prevent transmission to uninfected partners is increasingly acknowledged and being adopted as a preventive strategy in the global HIV response [7-8].

Available evidence over the past decades shows that adherence to ART regimens is central to the success of the therapeutic management of HIV infection [9-10]. Poor adherence has implications for both individual and public health. These include treatment failure, disease progression, morbidity and mortality, increased risk of drug resistance and higher risks of HIV transmission (including drug resistant HIV strains) [11-12]. This causes huge financial and economic losses at individual, family, community and country levels [12-13].

This thesis aims to explore the patterns of ART adherence, assess the factors influencing adherence and identify effective responses to associated adherence challenges among PLHIV in Nigeria. Findings from this study will be used to propose recommendations regarding potentially relevant strategies for improving adherence among PLHIV in Nigeria.

CHAPTER 1. Background Information

1.1 Geography and Population

Nigeria is situated in West Africa bordering between Benin Republic to the west, Cameroun and the Republic of Chad to the east, the Niger Republic to the north and in the south by the Atlantic Ocean. Nigeria occupies a total surface area of 923,768 square kilometres [14]. The 2006 Census reported a population figure of 140,431,790 and a growth rate of 3.2% [14]. Current estimations show that Nigeria is the most populous African country with over 177 million people [2,15].

1.2. Socio-demographic Overview

Nigeria is made up of 36 states and the Federal Capital Territory (FCT). The states comprise of 774 local government areas [14]. Nigeria is divided into six geopolitical zones (see Figure 1). These include: North East, North West, North Central, South West, South East and South South [14]. There are over 374 ethnic groups in Nigeria with three major tribes: Yoruba (SW), Hausa (North) and Igbo (SE) [14]. Languages spoken include English (official language), Hausa, Yoruba and Igbo and over 500 other indigenous languages [14]. About 50% of the population live in urban areas with an urbanization growth rate estimated at 3.75% [17]. The predominant religions are Christianity, Islam and indigenous traditional religions.

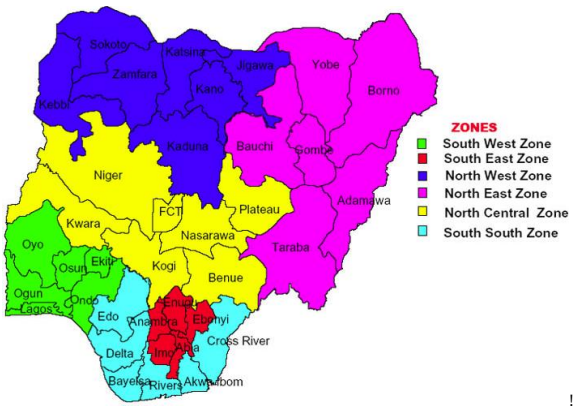

Figure 1. Nigeria Geopolitical Zones [16]

1.3. Socio-economic Overview

Nigeria is a lower-middle income country [18]. Despite the country's immense natural resources, over 54% of the population live below the international poverty line [17]. Total adult literacy level is 51.1% [17]. Recent data from the World Bank shows that Nigeria has a Gross Domestic Product per Capita of $3,005.5 [19] and GINI index of 48.8 [20]. Nigeria is currently ranked 156 out of 169 on the Human Development Index (HDI) [21]. Gender inequality issues are still predominant in Nigeria [22].

1.4. Health Situation

Nigeria still has poor health status indicators (*see Annex 1*) which has been described as, "one of the worst in world" [23]. Over the years, Nigeria has made little and slow progress towards reaching both national

targets and agreed international standards (e.g. millennium development goals) [2]. Communicable diseases (infectious diseases and vaccine preventable diseases) still remain the leading cause of morbidity and mortality [23]. Furthermore, there is a rising burden of noncommunicable diseases (NCD) in the Nigerian populace [23].

1.5. Health System

The Nigerian health system is composed of public and private sectors, and the provision of health care is delivered via the functions of the three tiers of the Nigerian government: the local government is responsible for the primary health care system. The state and federal government are responsible for secondary (district/general hospitals- first level of speciality care) and tertiary (specialist and teaching hospitals) care. The total expenditure on health (as percentage of Gross Domestic Product) is 6.1% [24]. To date, the National Health Insurance Scheme (NHIS) covers less than 5% of the national population, mostly civil servants employed in government parastatals living in urban areas [25]. Community-based health insurance is in the elementary stages and has been implemented in only a few states (Lagos, Kwara and Anambra) [26]. Private expenditure on health constitutes 68.2% of the total health expenditure and of this, 95.7% is out-of-pocket [24]. Private health care providers constitute more than 70% of the health care system [27] and public-private partnership is still in its early development stages.

1.6. HIV Epidemic in Nigeria

Nigeria has a generalized HIV epidemic [2]. The first case of AIDS was reported in 1986. Since then the prevalence of HIV rose significantly from 1.8% in 1991 to about 5.8% in 2001. Subsequent HIV sentinel surveys showed a decline in prevalence from 5.0% in 2003 to 4.4% in 2005 and 4.1% in 2010. The current HIV prevalence as derived from the National HIV/AIDS and Reproductive Health Survey (2012 NARHS plus II) is 3.4% [28]. Trends from NARHS show that the HIV epidemic is reversing (HIV prevalence from 2007 NARHS was 3.6%) [2].

There is a wide variation in HIV prevalence at regional and state levels with the South South zone accounting for the highest HIV prevalence of 5.5% and the South East, 1.8%. Rivers state had the highest prevalence of 15.2% while Ekiti State had the lowest prevalence of 0.2%. HIV prevalence in rural areas has been reported to be higher than in urban areas (4 vs. 3%) [2]. HIV prevalence among key populations in Nigeria is significantly higher than in the general population and they have been reported to contribute to a significant proportion (about 23%) of new HIV

infections [2]. An estimate of 220,394 new infections occurred in 2013 and the number of AIDS-related death was 210,031 [2].

The main mode of transmission is via heterosexual sex. Nevertheless, other modes of transmission include mother-to-child transmission and transfusion of infected blood and blood products [2]. Key drivers of the HIV epidemic in Nigeria have been outlined and these include: multiple concurrent sexual partnerships, transactional and intergenerational sex, inadequate access to healthcare services, poor quality of healthcare services, poverty, HIV-related stigma and discrimination and gender inequality [2].

1.7. HIV Treatment and Care in Nigeria

Nigeria started the ART programme in 2002. The number of ART programme sites has increased significantly over the years, from 190 in 2006 to 491 in 2012, and 820 in 2013 [2,29], covering the 36 states (and the FCT) and encompassing all levels of care [2]. It is pertinent to mention that ART services are mainly offered at secondary and tertiary levels of care [2,30]. Not all PLHIV eligible for ART have access to treatment [2,31]. Reports indicate that about 1,476,741 PLHIV require anti-retroviral drugs [2]. However, less than a third of these are on treatment [31].

The 2010-2015 National Strategic Plan (NSP) target is to ensure that at least 80% of eligible PLHIV have access to comprehensive, quality HIV and AIDS treatment and related care (such as prevention and treatment of opportunistic infections) by 2015 [2]. The Presidential Comprehensive Response Plan (PCRP) was developed recently to bridge existing gaps in the slow progress in achieving the 2011 United Nations Political Declaration on HIV and AIDS [2]. According to the global AIDS response country progress report (GARPR) [2], this comprises mainly of "bridging the funding resource gap and accelerating the implementation of key interventions".

The national guideline for the treatment and care of HIV was rolled out to enhance all aspects of care such as: HIV and AIDS diagnosis, ART in adults and adolescents, ART monitoring and follow-up, management of co-infections (e.g. tuberculosis (TB)), adverse drug reaction and complications, ART adherence, care and support and preventive management (e.g. post-exposure prophylaxis, TB and OIs). While the coverage of HIV services has slightly improved nationwide, persisting challenges include- limited human and material capacity, poor linkage

from HCT sites, stock out of ART drugs, and reliance on external donor funding are still evident and is extended to the general health system [2].

The National Agency for the Control of AIDS (NACA) provides the overall national coordination on the HIV and AIDS response in Nigeria and utilizes a multisectoral approach [2]. The state and local government area responses are coordinated by State Action Committee on AIDS (SACA) and Local Government Action Committee on AIDS (LACA) who interact with the different ministries, private sector, civil society organizations (including faith and community based organizations) and development partners (local and international) [2].

CHAPTER 2. Overview, Problem statement, Justification, Objectives and Methodology

This chapter presents a short overview on ART adherence, problem statement and justification for the study, objectives and methodology.

2.1. Adherence: Definition, Concept and Terminology

Adherence can be explained as the extent to which a client who has started treatment continues with the planned, instructed or agreed mode of treatment under minimal supervision [32]. Furthermore, adherence to an ART regimen involves different elements such as taking prescribed drugs in the correct doses, at the right time, with the right dietary instructions and complying with follow-up appointments. Past studies have used varying definitions for ART adherence. Fogarty and colleagues in a review reported that only few studies clearly defined adherence in operational terms and many of the studies included in the review used varying definitions and adherence levels [33].

WHO defined adherence as the "extent to which a person's behaviour in terms of taking medications, following a diet, and/or executing lifestyle changes follows agreed or corresponds to recommendations from a health care provider" [34]. Another definition by Weinreich and Bean [35] states adherence as "a measure of completeness and consistency of drug intake". Jani [36] defined medication adherence in HIV infection/disease as the "ability of the person living with HIV to be involved in choosing, starting, managing and maintaining a combination medication regimen to control viral replication and improve immune function".

2.2. ART Adherence and Treatment Outcomes

The benefit of ART in the therapeutic management of HIV infection has been documented over a broad range of ART regimen in various settings [9,37-38]. As outlined previously, there is accumulating evidence on the association between ART adherence and therapeutic success [9-13]. Furthermore, ART adherence has been demonstrated as a good predictor of clinical outcome and survival in PLHIV [9]. Paterson and colleagues indicated the relationship between ART adherence and virologic failure (*see Figure 2*) [9]. Similarly, another study by Nachega et al. demonstrated a linear dose-response relationship between adherence levels and sustained viral suppression [39]. In all treatment failure-related aspects, client adherence is most vital and modifiable [12,40].

Adherence levels of 95% or higher has been considered as a key factor to ensure treatment effectiveness in the context of inducing viral

suppression, reducing the likelihood of drug resistance, disease progression and death among PLHIV in many studies [9-13,40-42]. Other studies indicate that virologic suppression is possible with lower levels of adherence (<95%) when using some ART drugs such as boosted Protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) [12,43-44]. Nonetheless, high levels of adherence (≥95%) have been considered necessary in the early phases of ART [45-46].

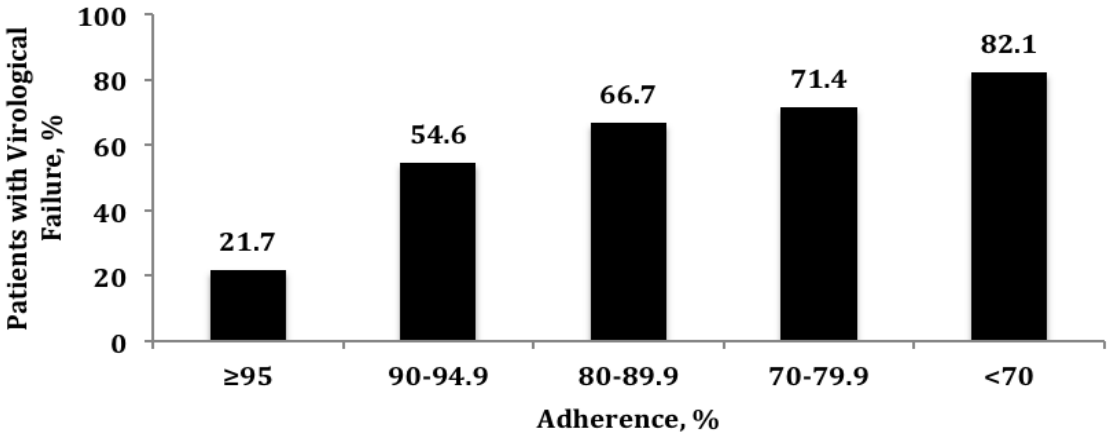

Figure 2. Relationship between Virological Failure and ART Adherence Levels [9]

2.3. Problem Statement and Justification of Study

The HIV epidemic in Nigeria remains a significant national public health threat. Despite the scale-up of ART services in the past decade, sub-optimal adherence still poses a threat to achieving optimal treatment outcomes. Findings from a retrospective review study conducted in Nigeria in 2010 indicated adherence rates ranging from 44% to >95% with a significant number of these studies reporting low adherence rates in different parts of the country [47]. Data from the recent GARPR document showed that in 2012, only 73.4% of PLHIV (adults and children)[1] were on treatment 12 months after initiation of antiretroviral therapy [2]. This is much lower compared to rates from Rwanda, a low-income country, where 92.7% of PLHIV were still on treatment after 12-36 months [48] and 95.3% after 12 months in Ghana [49].

There is also a growing concern on the rising numbers of PLHIV on second-line drugs in Nigeria [40]. This is worrying in view of the high cost implication and limited available options for second-line and third-line ART drugs in Nigeria and other SSA countries [40,50-51]. Furthermore, recent

[1] Disaggregated data not available from report

reports indicate that the availability of third-line drugs and salvage therapy for treatment failure is virtually non-existent in Nigeria [52]. The relevance of ART adherence to the reduction of HIV transmission via TasP approaches among PLHIV in Nigeria and globally cannot be ignored. Accumulating research has shown that optimal adherence is central to the success of TasP [53].

Adherence has been reported to be a determinant of treatment and virological failure and this significantly contributes to mortality and morbidity (including opportunistic infections) in PLHIV on ART [9,42,54-55]. Between 2008 and 2012, the number of AIDS-related deaths and new infections has increased (*see Annex 2*) [29]. According to the UNAIDS GAP report [31], Nigeria accounted for the highest number of AIDS-related deaths globally (14%) in 2013. Furthermore, while AIDS-related mortality is decreasing in other SSA countries, there has been no decline in AIDS-related death over the past 9 years (since 2005) in Nigeria [31]. This has been attributed partly to limited access of PLHIV to ART. Nonetheless, data from large ART program studies conducted have shown that poor adherence, poor retention and high numbers of clients loss-to-follow-up (LTFU) in ART programs may be responsible for the dismal health outcomes among PLHIV in Nigeria [56-58]. Similar findings have been reported in other studies from national HIV programs showing high levels of attrition among PLHIV in ART programs [59].

Despite past studies showing that adherence may be better in developing countries compared to developed countries [60], there are still concerns about the maintenance of long-term adherence in PLHIV as this may wane and not persist over time [12,61]. To my knowledge, only one study [47][2] done in 2010 has reviewed ART adherence studies among PLHIV in Nigeria. Thus, new evidence on the current patterns and responses to ART adherence among PLHIV in Nigeria may be needed.

2.4. Objectives

2.4.1. General Objective

This study seeks to explore the patterns of ART adherence among adult PLHIV in Nigeria, assess the factors that influence ART adherence and identify effective interventions directed towards improving ART adherence, in order to inform and make appropriate recommendations to

[2] Retrospective literature review of Nigerian studies done between 2002-2009

improve policy, planning and implementation towards enhancing treatment outcomes, QOL and reducing HIV transmission.

2.4.2. Specific Objectives

1. To describe the patterns of ART adherence in Nigeria.
2. To identify and assess the factors that influence ART adherence in Nigeria.
3. To identify effective ART adherence interventions to improve ART adherence among PLHIV.
4. To make recommendations for ART adherence improvement among PLHIV in Nigeria.

2.5. Methodology

This thesis is an explorative descriptive literature study of adherence to ART among adult PLHIV in Nigeria.

2.5.1. Search Strategy and Keywords

Published and unpublished, peer-reviewed and grey literature will be obtained via databases (MEDLINE, EMBASE), search engines (PubMed, Scopus, Google Scholar), and relevant websites (UNAIDS, WHO, Global Fund, UNICEF).

Keywords, texts and MeSH terms used were: (adult) AND (antiretroviral OR antiretroviral therapy OR antiretroviral therapy, highly active OR ARV OR HIV OR human immunodeficiency virus OR acquired immunodeficiency syndrome OR AIDS) AND (adheren* OR complian* OR patient compliance OR medication adherence) OR (retention OR loss to follow up OR attrition) AND (intervention) AND (nigeria, sub-Sahara Africa, low and middle-income countries).

2.5.2. Inclusion and Exclusion Criteria

Studies done from the year 2004 to date were included in this literature study. Other relevant articles or studies before 2004 were included incidentally based on relevance to the study topic. Studies were limited to those in English.

2.6. Framework for ART Adherence

For the purpose of exploring factors influencing ART adherence, a conceptual framework was adapted from Wekesa [62] outlining the factors - individual, community/socioeconomic, medication and structural-influencing ART adherence among PLHIV in SSA (*see Figure 3*). The framework was chosen because it provides a biosocial approach to

exploring factors influencing adherence. It emphasizes the dynamic interaction between the clinical and social processes influencing adherence and the outcomes of these interactions over time.

The framework posits the concept that ART adherence is founded on multi-level interactions between individual and non-individual (social or community, structural and medication) factors and emphasizes the idea that adherence is not exclusively determined by the individual but as a result of complex interaction between these factors and specific circumstantial processes. The components of the framework are not seen as mutually exclusive, but as linked and mutually reinforcing in some situations. Furthermore, similar models have been used in other studies to explore the factors influencing adherence [41,63].

The original framework did not explore how condition-related factors specifically affect adherence in the context of severity of HIV symptoms, HIV disease staging, HIV-related disabilities and comorbidities (e.g. noncommunicable diseases and mental health disorders); therefore this was borrowed from Sabate [34] and included in the framework.

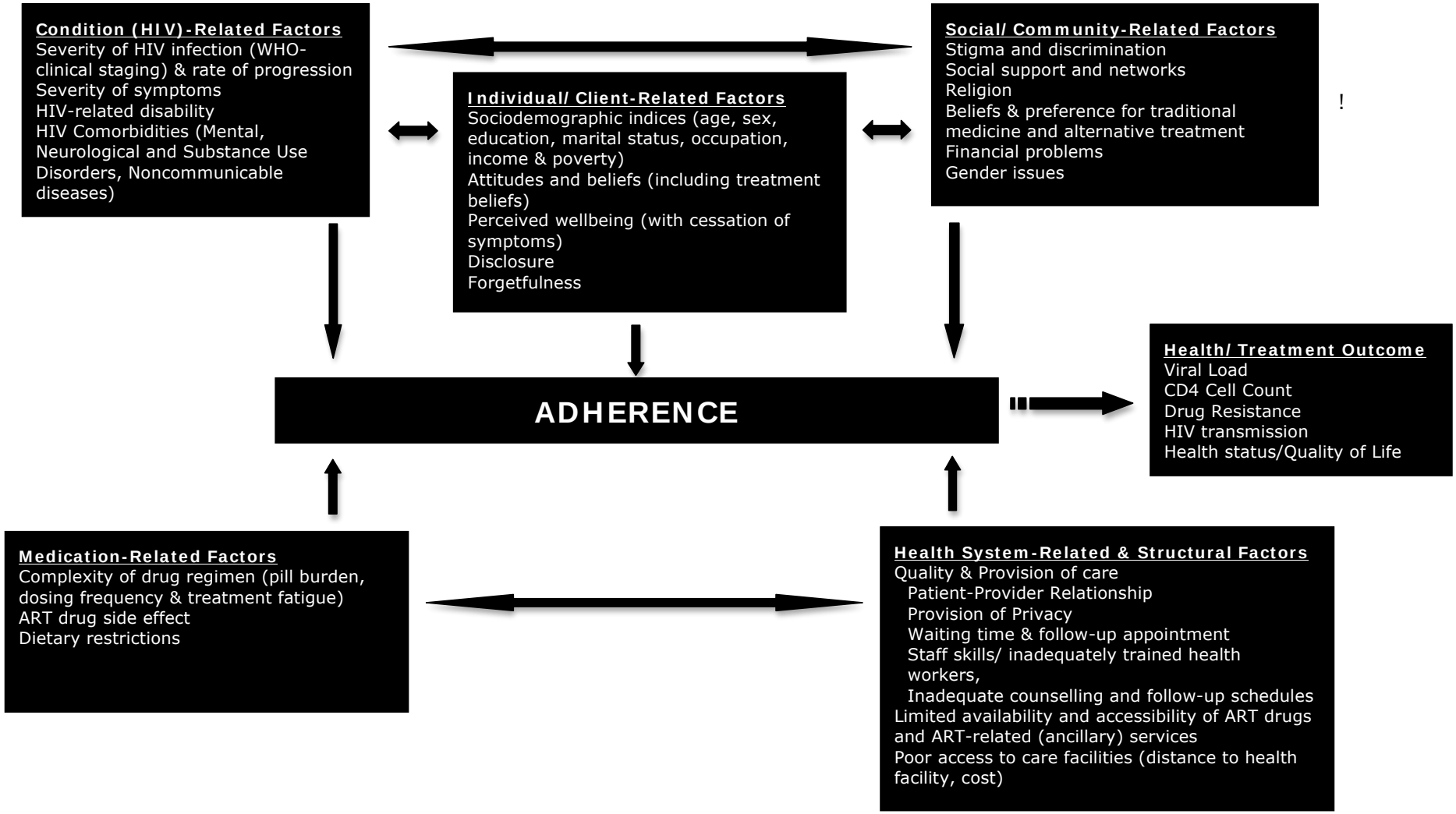

Figure 3. Adapted Framework on ART Adherence [34,62]

CHAPTER 3. Patterns of ART Adherence in Nigeria

This chapter gives an overview of the national guidelines on ART in Nigeria, adherence measurement approaches and describes the patterns of ART adherence from studies identified in Nigeria.

3.1. National Guidelines on ART in Nigeria

ART involves the use of a combined regimen of 3 (or more) ARV drugs. Combined drug regimens can inhibit viral replication by acting at different points and/or via different mechanisms in the HIV life cycle [64-65] resulting in significant suppression of viral load and improved clinical outcomes.

The national guideline [64] states the following as preferred options for first-line ART regimen in ART naïve adults:

i. Zidovudine (AZT) + Lamivudine (3TC) + Efavirenz (EFV)
ii. AZT + 3TC + Nevirapine (NVP)
iii. Tenofovir (TDF) + 3TC or Emtricitabine (FTC) + EFV
iv. TDF + 3TC or FTC + NVP

Furthermore, there are specific and varying recommendations for various patient categories and clinical conditions e.g. second-line ART regimen, pregnancy, TB and/or HBV co-infection, ART naïve women of childbearing age, ARV-exposed women for PMTCT and renal failure. These guidelines are in accordance with the WHO guidelines. Nevertheless, it is crucial to mention that Nigeria has not yet adopted the latest WHO recommendation [66] on the CD4 cell count eligibility criteria of ≤500 cells/mm^3 for ART initiation.

3.2. Measurement of Adherence

Across a broad range of diseases, Berg and Arnsten [67], explained medication adherence as an "individual, complex and dynamic behaviour" that is often associated with difficulties and challenges in measurement. Adequate monitoring through accurate measurements has been proposed as vital in preventing adverse outcomes such as ART failure and the development of drug resistance [68]. There are different approaches to the measurement of ART adherence in PLHIV [11,33] and the broad range of available methods complicates measurement [11,67], owing to the fact that there is no standard approach (gold standard) for monitoring adherence.

Annex 5 offers a detailed literature review on adherence measurement methods in PLHIV. In summary, adherence measurement methods

include self-reporting, pill count, pharmacy refill records, provider estimation, electronic drug monitoring (EDM), biological markers and therapeutic drug monitoring (TDM) [11,33,67]. Several approaches for categorizing adherence measurement methods have been outlined in the literature. Fogarty et al. [33] and Watt [69] described these methods as subjective and objective approaches. Meanwhile, Garcia et al. [70] categorized these approaches into two classes: (1) patient-derived method e.g. self-reporting (with the use of questionnaires and interviews) and, (2) independent drug monitoring methods e.g. pill counts, pharmacy refill records, medication event monitoring system (MEMS) or EDM, TDM.

A limitation of patient-derived method is the overestimation of adherence [11,60,70-71]. Independent monitoring methods have been indicated to be more accurate. Nonetheless, some limitations have been highlighted in existing literature (*see Annex 5*).

3.3. Adherence Rates in Sub-Sahara Africa

Over the past years, a substantial number of ART adherence studies emerged from SSA. A possible explanation for this trend is the increase in access to ART in these countries, that in addition harbours >70% of all PLHIV on ART globally [72]. Research evidence from the SSA region has shown varying rates in ART adherence based on the place, study timing and quality (including methodology) [60,73]. Nevertheless, in SSA, the level of adherence has been demonstrated to be higher than that found in North America [60]. Mills et al. in a meta-analysis reported that a pooled estimate of 77% PLHIV from SSA achieved adequate adherence as compared to 55% of PLHIV in North American settings [60]. Consistent findings of higher adherence have been reported in low-HDI countries compared to high-HDI countries [73]. Furthermore, a recent meta-analysis on self-reported adherence to ART in SSA also reported high adherence rates [74].

3.4. Adherence Rates in Nigeria

ART adherence studies from Nigeria show mixed rates of adherence (*see Annex 3 for more detailed information and explanations*), varying from low (14.9%) to high adherence rates (≥95%) among PLHIV [75-113]. Nwauche and colleagues [82] reported an adherence rate of 49.2% among PLHIV in a subsidized ART program in the South South zone. Two recent studies conducted in a rural district hospital [83] and tertiary health facility [84] in the same zone reported adherence rates of 50.4% and 59.9%. Other studies conducted in the same zone also demonstrated low adherence rates [85-86]. In the South East zone, Okoronkwo et al.

reported a very low adherence rate of 14.9% among respondents in their study [75]. Another study also reported a low adherence rate of 24.7% among study participants [76]. Nevertheless two studies from the same zone reported higher adherence rates [77-78]. Two studies from the South West zone reported adherence rates of 44% [89] and 46% [94] among PLHIV in ART programs. Other studies from the same zone reported rates ranging between 26.9%-95.5% (*see Annex 3*). Studies conducted in the North West and North Central zones reported adherence rates between 62% to ≥95% [100-113]. There was a lack of studies from the North East zone.

Studies conducted among pregnant women reported adherence levels of 78.3% in the South East zone [79] and 80.6% in the South West zone [95] respectively. Differences in the pattern of adherence rates was observed in the geopolitical zones as some studies done in the South West and South South zones reported much lower rates compared to North West and North Central zones (*see Annex 3*). Majority of these studies were cross-sectional studies with only few cohort studies done [94,99-100,102]. Furthermore, in most of the studies, patient-derived methods were utilized to assess adherence with only a few combining this method with independent monitoring methods such as pill counts [75,86,106], pharmacy refill [91-92,111] and biologic markers such as viral load and CD4 cell counts [87,99,100,102].

Based on the observation that self-report was used in most of the identified studies, the differences between studies could not have been due to the measurement approach. Findings on adherence patterns observed are comparable to rates from past systematic reviews and meta-analysis on African studies. However, rates observed in some studies [75-76] are much lower than that reported in meta-analysis studies.

CHAPTER 4. Factors influencing ART Adherence

This chapter identifies and outlines the factors influencing ART adherence among PLHIV in Nigeria with the aid of the adapted conceptual framework. The chapter is structured around the following groups of factors derived from the framework: individual/client-related, social/community-related, condition-related, medication-related, and health system-related and structural factors.

4.1 Individual/Client-related Factors

4.1.1.Sociodemographic Indices

Age

Studies conducted in Nigeria have demonstrated a relationship between age and ART adherence [58,76,98,108-110]. Uzochukwu et al. reported that PLHIV over the age of 35 years were more likely to be adherent than those younger than 35 years old [76]. This was consistent with findings from a retrospective study of a large ART program cohort, which reported that PLHIV younger than 35 years of age were at a higher risk of non-adherence [58]. Furthermore, some of these studies reported a positive correlation between older age and ART adherence [98,108-109]. However, several other Nigerian studies did not find any association [84,89,105,113].

Sex

Studies from Nigeria on the relationship between sex and ART adherence are inconclusive, as some studies found no association between clients being male or female and adherence [86,89,105], while those that have reported an association show contradicting findings [58,75-76,108-109,111].

Education

Some Nigerian studies have shown that education level is associated with adherence [76,79,82,86,89,104-106], either positively or negatively. Pennap et al. reported that adherence was higher among literate clients [105]. Consistent findings have also been reported in other studies demonstrating low educational status to be associated with non-adherence [79,82,86,106]. Other studies have shown a negative association between educational level and adherence [76]. However, some studies did not find any association between adherence and educational status [84,87,111,113]. Education has furthermore been reported to have a significant effect on other factors associated with ART

adherence [75-76]. For example, clients who were highly educated had the tendency to be non-adherent due to busy schedules [75].

Marital status

Studies investigating the relationship between ART adherence and marital status have demonstrated a positive association [82,95,105], while other studies have not found any association [75,84,89,113]. Consistent findings on non-association have also been reported in other studies from SSA [114-115]. Furthermore, a study conducted in Uganda showed a negative association between marital status and ART adherence [116].

Occupation, income and poverty

Some studies from Nigeria have reported an association between occupation, higher income and increased adherence [82,89]. Nevertheless, other studies have not found any association [86]. A recent systematic review on the effect of employment status on ART adherence showed employment to favour ART adherence [117]. Conversely, poverty (often linked to unemployment) has been shown to significantly and adversely influence adherence over time [47,86]. This could result in client being unable to pay for food, transportation to healthcare facilities or for other HIV-related treatment expenses.

4.1.2.HIV and ART-related Knowledge, Attitudes and Belief

Knowledge, beliefs and perception of HIV and ART are critical in ensuring good adherence in PLHIV. Studies from Nigeria [77,87,92,95,98,105,108] and SSA [41,60,118] have demonstrated that beliefs of illness, efficacy of treatment regimens and the knowledge of the consequences of non-/poor adherence significantly influence adherence. Olowookere et al. reported in a Nigerian cross-sectional study that more than a third of respondents had a negative attitude toward ART as a result of doubts about their HIV status [92]. Similar findings from another study done in South Africa indicated that study participants (PLHIV) stopped taking their medications due to non-acceptance of their HIV status and belief in the non-existence of HIV [119]. Furthermore, one third of the respondents in the study conducted by Olowookere et al. were of the view that lifetime ART will consequently lead to fatigue [92]. Other studies from Tanzania [120] and South Africa [121] have also reported that PLHIV stopped taking their medication due to ideas that ART is dangerous and not helpful.

4.1.3.Perceived Health Status or Wellbeing and Cessation of Symptoms

Studies from Nigeria have shown that associated improvement in health of PLHIV after initiating ART motivates, improves and sustains adherence

[83-84]. Oku et al. reported that PLHIV who perceive that their health status improved after initiating ART, were more likely to be adherent compared to those who did not observe any improvements [83-84]. This is in keeping with findings from other studies done in South Africa [119] and Zambia [122]. However, other Nigerian studies have reported that ART adherence declines after recovery [79,91,97,111]. In a particular study, some PLHIV reverted to alternative medicine after initial recovery out of desperation for a permanent cure of HIV infection [94].

4.1.4.Disclosure of HIV Status

Non-disclosure of HIV status can be a barrier to ART adherence. PLHIV often experience fear in disclosing their HIV status to their sexual partners, spouses, friends and family members, and this has been associated with poor adherence [63,79,91,97,108-109,112,119]. This occurs as a result of the direct and indirect consequences of the stigma and discrimination attached to HIV infection [123-124], as stigma has been shown to be a major barrier to disclosure among PLHIV in Nigeria [47,76,92,97]. Studies from SSA also indicate that non-disclosure is associated with inadequate social support [125-126] and this can affect adherence. Conversely, in Nigeria, studies have demonstrated that disclosure of HIV status to partners/spouse and/or family members is associated with good adherence [56,108] and this is consistent with findings from studies done in other SSA countries [122,127-128]. Furthermore, disclosure has been found to stimulate social support, which in turn is associated with good ART adherence [95,126,129-130].

4.1.6.Forgetfulness

Forgetfulness has been consistently cited as a reason for suboptimal adherence in numerous studies [47,75-77,79,83-85,88,91,98,104-105,107,113]. This has been linked to busy schedules [75-76], cognitive impairment related to psychological comorbidities [101,107] and older age [75].

4.2. Social/Community-related Factors

4.2.1.Stigma and Discrimination

There is strong evidence that stigma and discrimination influence ART adherence [47,60,129,131]. PLHIV can experience stigma and discrimination both in communities and healthcare facilities [131]. In addition, they tend to experience different forms of stigma, which can take the form of public attitude stigma, disclosure stigma, personalized stigma, negative self-image stigma [97] and provider stigma [132-134].

As outlined previously, stigma and discrimination can affect adherence through multiple pathways such as through non-disclosure of HIV status [123-124] and through its effect on adaptive coping and social support [131]. Furthermore, consequences of stigma on mental wellbeing have been established as a barrier to ART adherence [135]. Findings from the 2011 Nigerian HIV-Stigma index study indicate that HIV-related stigma is still highly prevalent [136]. Studies from Nigeria have consistently indicated that stigma is a barrier to optimal ART adherence [47,76,86,90,92,94,97,103,106,113,137].

Evidence from Nigeria indicate that PLHIV sometimes spend considerable time travelling to distant facilities in order to avoid being seen going for treatment in their immediate environment or communities as a result of HIV-associated stigma [77,138]. In addition, PLHIV often miss medications or timely administration of medications especially when in public places in order to avoid being seen as taking HIV-related medication [95]. Sekoni et al. reported that in Nigeria, disclosure on HIV status was limited to family members [97]. This is similar to findings from Kenya [123] and Zambia [139], where PLHIV carefully confined the disclosure of their status to selected people for the fear of stigma, discrimination and abandonment.

4.2.2.Social Support

There is overwhelming evidence supporting the importance of social support in achieving optimal ART adherence [88-90,95-96,98]. Family and community members can either facilitate adherence through providing treatment-related support or as a barrier through stigmatizing PLHIV [90,127,140]. Even in situations where PLHIV are faced with numerous challenges, PLHIV are at a better chance of adhering to their treatment requirements when there is an existing (family and/or community) support structure [120]. Studies from Nigeria have shown that PLHIV with some form of social support from family members or those accessing social support groups were more adherent to treatment compared to PLHIV who did not have access to any form of social support [89-90]. This is consistent with findings from other studies from South Africa [129-130] and Ethiopia [141].

4.2.3.Religion

Religious beliefs and practices have been indicated to influence adherence [108,142]. Religious fasting has been indicated in some Nigerian studies to negatively affect ART adherence [91,108]. Nevertheless, a study demonstrated high adherence rates among Muslims during the Ramadan

fasting period [102]. PLHIV often times are non-adherent due to religious commitments and situations where they avoid being seen taking medication, such as in religious gatherings [83,91,103].

4.2.4.Traditional Medicine and Alternative Treatment

There is accumulating evidence that there is a high prevalence of the use of complimentary and alternative medicine among PLHIV in Nigeria [143]. In some cases, PLHIV often assess both ART facilities and traditional healers and consequently stop taking ART medication [83]. Other studies reported that clients often default from treatment after feeling better and seek help from traditional and faith healers [94]. In line with the above, two Nigerian studies by Oku et al., reported a positive association between medication adherence and non-use of herbal medicines [83-84]. Similar findings have also been reported in other Nigerian studies [80,88,106] and a study conducted in South Africa [129].

4.2.5.Financial Problems

Financial constraints have been documented over time as a significant factor affecting ART in Nigeria [76,82-84,86,93]. Oku et al. [84-85] reported that despite ART being offered free of charge, user fees were often required and necessary at healthcare facilities for other treatment related-issues such as laboratory investigations, treatment of OIs and registration (opening of folders). In the same study, it was demonstrated that payment for ART services significantly decreased ART adherence.

4.2.6.Gender Issues

Gender inequality has been reported to negatively influence ART adherence, this especially affects women as they mostly suffer the consequences of inequality [125]. This is consistent with studies in three SSA countries (Botswana, Tanzania and Uganda) conducted by Hardon et al. where men were reported to have restricted the access of women to ART programs [41]. Studies from Nigeria show that women sometimes face challenges regarding adherence in cases when they have to perform traditional rituals such as widowhood rites [94].

Studies conducted among pregnant women [144] and non-pregnant women living with HIV [145] in Nigeria revealed that disclosure of status potentially stimulated intimate partner violence (IPV) and this can negatively influence adherence. Similar findings have been observed in other studies from Kenya [146], Tanzania [147] and Uganda [148], while other studies have not seen any association [149-150].

4.3. Condition (HIV)-related Factors

4.3.1.Severity of HIV Infection (WHO-clinical staging) and Rate of Progression

There are indications from studies conducted in Nigeria that the severity of HIV infection affects adherence in the context of LTFU and attrition from ART programs [56-58]. Charurat and colleagues demonstrated that PLHIV with CD4 cell counts <100 cells/mm^3 and also those with CD4 cell counts >350 cells/mm^3 were at a higher risk of LTFU [58]. Furthermore, there were increased odds for poor adherence to ART in PLHIV with CD4 counts between 200-350 cells/mm^3 (OR 1.18, 95%, CI 1.06-1.32, *p .003*) and those with >350 cells/mm^3 (OR 1.25, 95%, CI: 1.05-1.49, *p.01*) [58]. Similar findings were also reported in PLHIV with low CD4 cell counts and detectable viral load [57]. Odafe et al. reported that PLHIV with advanced disease (WHO clinical stage III and IV) and CD4 cell counts <200 cells/mm^3 had a higher risk of attrition from ART [56]. Similar findings were also highlighted in other studies from outside Nigeria [151-153]. In addition, the presence of opportunistic infections has been shown to negatively influence ART adherence [153-154].

4.3.2.Severity of Symptoms

HIV symptoms spanning from physical (fever, nausea) to psycho-cognitive (depression, anxiety, concentration and problem solving problems) domains have been reported to also influence adherence either positively or negatively [34,155]. While some studies in Nigeria have reported that the association between HIV symptoms and subsequent improvement with ART enhances optimal adherence [83], there is evidence that the severity of symptoms such as sleep quality and memory functioning can negatively influence adherence [156-157].

4.3.3.HIV-related Disability

PLHIV have the potential of experiencing a wide range of disabilities related to HIV infection [158]. This spans disabilities in body structure and function to activity limitation and restriction in participating in usual normal activities (according to the WHO International Classification of Functioning, Disability and Health (ICF)) [158]. There is a dearth of research from Nigeria on the association between HIV-related disabilities, unrelated disabilities and ART adherence. Nevertheless, evidence from other countries in SSA and in developing countries indicates that this can negatively influence adherence [34,158-160]. This may also occur through the effect of multiple factors such as lack of social support, poverty, access to health facilities and stigma and discrimination [159-

160].

4.3.4.HIV-Comorbidities

Chronic comorbidities (NCDs and mental health disorders) have been shown to be highly prevalent among PLHIV [161-162]. HIV infection has direct and indirect effects on multiple organ systems and is usually associated with a diverse range of co-morbidities [161-163]. PLHIV have been shown to have higher risks of developing NCDs as compared to HIV-negative individuals, due to HIV infection itself, ART and in association with improved survival and ageing [161,163-165]. Recent trends show that a significant proportion of PLHIV who are on ART now die from non-AIDS related causes as HIV-related mortality is on the decline [164].

Overwhelming evidence indicates that mental, neurological and substance use (MNS) disorders are associated with poor and non-adherence [166-168]. Few studies originating from Nigeria have shown that certain psychological factors (e.g. depression) influence ART adherence [83-85,88,96,101,107]. Olisah et al. reported that depressed PLHIV showed significantly poorer adherence compared with controls [101]. Similar findings were also reported in another study that found adherence to be lower among PLHIV with alcohol use disorders (AUD) compared with those without AUD [107]. Falang et al. demonstrated that non-alcohol intake was a good predictor for good adherence among PLHIV in their study [108]. Another study by Farley et al. reported that elevated CES-D[3] was associated with poor adherence. However, there was no association between AUDIT[4] scores and adherence [112]. Adewuya and colleagues also reported that psychological distress was associated with lower medication adherence among PLHIV [96].

Chronic comorbidities in PLHIV can influence adherence in many domains. This includes associated disabilities [158], polypharmacy [169-171], double stigma and most especially when these conditions are undiagnosed or effective treatment is unavailable [159].

4.4. Medication-related Factors

4.4.1.Complexity of Drug Regimen (pill burden, dosing frequency)

The complexity of drug regimen has been shown to influence adherence

[3] Centre for Epidemiologic Studies Depression Scale (CES-D) is a 20-item self-report measure screening tool for depression (has good specificity, sensitivity and high internal consistency)
[4] Alcohol Use Disorders Identification Test (AUDIT) is a 10-question screening test/tool for harmful alcohol consumption (developed by the World Health Organization)

among PLHIV [172-174] as this can lead to pill or treatment fatigue. Oku et al. in two recent Nigerian studies reported that pill burden had a significant negative influence on adherence [83-84]. PLHIV who were on more than two pills were found less likely to be adherent to ART. Consistent findings have also been demonstrated in other studies and reviews conducted in Nigeria [47,82,108]. A study conducted in Zambia also reported that pill burden significantly affects ART adherence [122]. Furthermore, dosing schedules also influence adherence [175-176]. For example, complex daily dosing schedules are associated with poor and/or non-adherence [175-178].

Improved and higher adherence has been reported in studies on fixed dose combinations [179-180]. Pill fatigue has also been documented in PLHIV with comorbidities (*see 4.3.4*) [169,171].

4.4.2.ART Drug Side Effect

Side effects have been consistently reported as a major reason for interrupted ART medication consumption and stoppage of medication in Nigerian studies [76,81-82,86,91,106] as well as studies from other low and middle income countries (LMIC) [124,172]. Furthermore, some studies included in a systematic review of ART adherence in SSA have reported similar findings [60]. Of note are side effects such as depression from EFV, rash and loss of appetite [106]. Sekoni et al. in a study reported a high adherence level among PLHIV in their study and the availability of ART drugs with minimal side effects was identified as one of the reasons for the high motivation to be adherent to ART [97].

The neuropsychiatric side effect of EFV, notably depression, has been shown overtime to affect adherence among PLHIV [181]. Poor adherence occurs in cases where PLHIV cannot cope with side effects [33,111,182-183]. However, a study conducted in Nigeria on side effect coping practices did not find a significant increase in non-adherence as a coping strategy among study participants [184]. Lipodystrophy[5] as a result of ART drugs has also been shown to affect adherence and this may be due to associated stigma related to physical appearance [97].

4.4.3.Dietary Restrictions

Some studies from Nigeria indicate that ART drugs with dietary (including fluid) restrictions may affect adherence [83-84]. Consistent reports and findings have been highlighted in a study done in India [172].

[5] Lipodystrophy is a type of tissue disorder characterized by changes (abnormal) in fat distribution

4.5. Health System-related and Structural Factors

4.5.1. Quality of Care

Patient-provider relationship

Good patient-provider relationship and effective communication has been underscored as vital to achieving optimal outcomes in ART programs [185-187]. This fosters increased trust and confidence in the health provider and treatment plan [11]. In cases where there is distrust, lack of involvement of patient in treatment process (decision-making), unfriendliness and inadequate communication between provider and clients, there is often a higher risk for non-or poor adherence to ART [185,187]. In addition, unpleasant experience with healthcare systems is associated with suboptimal adherence among PLHIV [188-189]. Studies from Nigeria indicate that good relationships between clients and health providers enhance adherence [87,98,104,111]. Conversely, patients often poorly adhere to their medication due to language barriers and miscommunication from care providers [82]. Furthermore, healthcare providers can also act as a barrier to ART adherence when the predisposition and attitude to clients is poor such as stigma and discrimination [132-134]. This has been highlighted in several Nigerian studies [190-192]. In addition, frequent change in healthcare personnel managing PLHIV has been linked to adherence problems [173].

Provision of privacy

A positive perception of privacy in the context of the environment where care is accessed significantly influences adherence to treatment [122]. Conversely, lack of privacy and confidentiality has been indicated as a barrier to ART adherence [63,173]. A study by Skovdal et al. reported privacy-related difficulties in healthcare facilities [193]. This is consistent with findings from other studies in Nigeria [89-90]. In some cases, clients have to share the room with other clients who are being seen by other doctors and this can hinder optimal adherence in terms of LTFU or the ability to communicate freely [41]. Erah and Arute indicated in their study that clients were dissatisfied with privacy in the context of the area where ART drugs where dispensed [86].

Waiting times and follow-up appointments

Studies from Nigeria [75,98] and other SSA countries [41,194-195] have reported that long or extended waiting time is a huge challenge to PLHIV on ART. Consistent findings have been shown in other studies (SSA) in the context of ART medication adherence and attending follow-up

appointments [119]. This may be partly due to the overburdening of health workers in ART facilities [41].

Staff Skills/Inadequately trained healthcare providers
The availability of staff experienced in the treatment and care of PLHIV has been shown to facilitate adherence [41,98]. Research has shown that when this is not the case, adherence can be hampered [125,196].

Inadequate monitoring, counselling and follow-up schedules
Studies have shown that adequate follow-up and regular adherence counselling are facilitators of good adherence [41,77,89-90,106], while conversely inadequacies can be a barrier to optimal adherence among PLHIV [41,89]. Furthermore, there may be a need to individualize adherence counselling which may already be compounded by overburdening of HIV-related care services due to shortages in health workers [41]. Some studies have shown that PLHIV tend to run out of medication [77]. This highlights possible inadequacies in follow-up appointment frequency (including medication refill).

4.5.2.Limited Availability of ART Drugs and ART-related Services
Non-availability of ART drugs and other HIV care-related drugs have also been reported to be associated with non-adherence to ART in many studies from Nigeria [47,76,82,88,104]. Between 2004 and 2005, the national ART program suffered from shortage of ART drugs [47]. Subsequently, studies conducted afterwards reported that drug stock out during this period might have affected ART adherence among PLHIV [76,82,104]. This was not reported in some studies [86]. To date, many programs often experience shortage of drugs and in some situations encounter difficulties in getting their regular supply of drugs.

Availability of free ART has been found to be associated with good adherence [47,76-77,86,106-107,110]. Furthermore, the provision of free ancillary or HIV-related services has also been reported to facilitate optimal adherence to ART [76,89]. Continuous access to health care services and medications by clients also influences treatment adherence [47,86,106]. The lack of capacity e.g. human, infrastructure, limits the ability of healthcare structures in providing quality care to PLHIV and this acts as a barrier to accessing key services, which ultimately affects adherence [47]. In many settings, clients often encounter challenges in getting laboratory results on time, which may delay necessary changes in treatment and care as required [89]. These factors altogether potentially discourage PLHIV and can affect adherence.

4.5.3.Poor Access to Care Facilities: distance and financial

Studies have reported an association between distance to ART facilities and the risk for suboptimal adherence in Nigeria [76,79,91,105,109]. This is in keeping with findings from other resource-limited settings [60,120,197]. Direct and indirect costs (*see 4.2.5*) such as transportation to healthcare facility have also been documented as limiting adherence [83-86,105]. This is consistent with findings from other studies done in Nigeria [47,82]. A systematic review has shown cost of treatment (e.g. drugs and transportation) to be an important factor adversely influencing adherence in SSA countries [60].

CHAPTER 5. ART Adherence Interventions

This chapter identifies, outlines and discusses effective ART adherence interventions that have been done in Nigeria and other SSA countries.

5.1. Classification of ART Adherence Interventions

There is a wide body of evidence on the effectiveness of strategies for enhancing adherence to ART. Barnighausen and colleagues [45] in a systematic review of evaluation studies conducted in SSA outlined the categories of adherence interventions among PLHIV. These include: behavioural, cognitive, affective, biological, structural and/or combination of interventions (*see Table 1*).

Strategy	Rationale	Type of intervention
Affective	To improve ART adherence via social and emotional (psychological) support	Counselling Peer support Psychiatric/Psychological treatment (e.g. antidepressants)
Behavioural	To improve ART adherence via direct behavioural modification	Reminders tools (medication diaries, pill boxes, SMS, alarms, beepers, pagers) Directly Observed Therapy (DOT)/Directly Administered Antiretroviral Therapy (DAART)
Biological	To improve ART adherence via enhancing physical/somatic capabilities to administer ART medication	FDC (fixed dose combinations) Food rations/vitamin or micronutrient supplement
Cognitive	To improve ART adherence via teaching, instruction or clarification methods on ART and HIV infection	Counselling/Group education Media education materials (TV, Video, Audio, reading materials)
Structural	To improve ART adherence via changes in service delivery structures	Community delivery of ART Community mobilization (peer support and treatment supporters)
Combination	To improve ART adherence via a combination of outlined strategies (as above)	

Table 1. Classification of Adherence Intervention Strategies (adapted from Barnighausen et al. [45])

5.2. Adherence Intervention Studies from Nigeria, Sub-Sahara Africa and other Low and Middle-income Countries

Findings from the literature review indicate a limited number of ART adherence intervention studies originating from Nigeria to date

[40,78,198-203] (*see Annex 4)*. Nonetheless, there is a fairly large body of evidence from other SSA countries and LMICs. Available evidence from Nigeria will be outlined first under each of the categories. Additional studies identified from other SSA countries will be added subsequently.

5.2.1. Affective Intervention Strategies

Counselling
Adherence counselling has been indicated as the mainstay of adherence management among PLHIV over the years [11,204-205]. A randomised controlled trial (RCT) study conducted in Kenya by Chung and colleagues, composing of four arms (counselling, alarms, counselling + alarm and no intervention) around the time of ART initiation and over 18 months found out that intensive adherence counselling especially at ART initiation was associated with sustained long-term adherence and lower risks of virological failure among study participants [206]. In addition, a recent network meta-analysis showed that intensified adherence counselling was highly effective in increasing ART adherence in SSA countries [207].

Motivational Interviewing (MI)
Motivational interviewing is a form of counselling that aims at addressing and resolving ambivalence or indecision in the context of building motivation towards behaviour change. A pilot study conducted in Nigeria by Holstad and colleagues [198] assessing the effectiveness of motivational interviewing (MI) and risk reduction behaviour as a group intervention among women showed that the MI intervention group had higher ART adherence levels after 6 months (*see Annex 4*).

Peer support
Peer support is also an established effective method of improving adherence among PLHIV [208]. Further literature search for interventions indicate that affective strategies such as peer support for ART adherence have essentially been used as part of combined (multi-component) interventions [209]. This will be discussed in detail subsequently.

Psychiatric and psychological treatment
The use of psychotropic medication (e.g. antidepressants) and/or psychotherapeutic interventions (cognitive behavioural therapy, interpersonal therapy) has also been shown to improve ART adherence and treatment outcomes among PLHIV in SSA [210-214] and other parts of the world [215-216].

5.2.2. Behavioural Intervention Strategies

DOT/DAART

Taiwo and colleagues [199] in a Nigerian randomised controlled trial (RCT) of patient-nominated DOT-ART treatment supporters reported initial improvements in adherence. However, improvements were not sustained in the long-term and there were no significant increases in other study outcomes such as CD4 counts and viral suppression at the end of the study. Another study from Nigeria conducted by Idoko et al. [200] investigated the effects of DOT/DAART on adherence. Three intervention groups were included in the study: daily observed therapy (DOT), twice weekly observed therapy (TWOT) and once weekly observed therapy (WOT) and compared with self-administered therapy (SAT). Findings from this study reported non-significant increases in adherence across time points in the study [45,200]. Nevertheless, treatment outcomes (viral load and CD4 cell counts) were much better in intervention groups (DOT, TWOT, WOT) than in self-administered group (SAT). Other studies from Kenya [217], Mozambique [218] and South Africa [219] on DOT/DAART have consistently shown similar results. Sarna et al. observed increased adherence with DOT-ART and this was specifically the case among PLHIV with depression [217]. Nachega et al. indicated increased CD4 cell counts and survival at 6 months of follow-up in the DOT-ART group [219].

Findings from two systematic reviews on DOT/DAART RCTs [220-221] suggest that this intervention has not been consistently associated with increased adherence and virological suppression as compared to self-administered ART. Nonetheless, there are indications that DOT/DAART may be more effective in certain populations such as PLHIV with TB co-infection, drug users, prison settings [222] and other PLHIV at high risk of sub-optimal adherence [221].

Communication (SMS) technology

Studies investigating the effect of mobile phone technology (in this case, short messages service (SMS)) on adherence have reported promising findings [223]. RCT on the effect of the use of weekly SMS reminders done in Kenya revealed that PLHIV involved in the study were more likely to achieve high adherence levels (>90%) at 48 weeks compared to the control group [224]. Furthermore it was reported that they had a lower chance of treatment interruption. Another study from Kenya [225] also reported significant adherence improvement and reduction in viral load among PLHIV enrolled in the study (weekly interactive SMS plus follow-up

calls for study participants who did not respond in 2 days). Uzma et al. [226] demonstrated similar results in another study conducted in Pakistan. SMS technology has also been shown to improve HIV-related service delivery for PLHIV in Uganda [227]. Other positive findings have been reported in China [228]. Despite the encouraging results from these studies, a study done in Cameroon did not detect any significant effect of the intervention on adherence [229].

Another SMS-related intervention study from Brazil done by Da Costa and colleagues [230] only detected significant improvements on ART adherence over four months. A pilot study in India showed that after SMS intervention ended, it had an effect on adherence for at least six months [231]. A more recent study from India found no significant effect of SMS intervention on ART adherence or time to virological failure after two years [232].

Other reminder tools
Ukwe et al. in a study conducted in Nigeria showed that the use of pillboxes increased adherence among study participants (*see Annex 4*) [78]. As mentioned previously, Chung et al. did not find any improvement in adherence with the use of alarm devices nor was this associated with lowering the risks of virological failure [206]. Roux [233] in a study using diary cards as an adherence enhancing intervention reported non-significant effects of this strategy although it was well accepted among the study participants.

5.2.3. Biological Intervention Strategies

Nutritional support and food supplementation
There is evidence from studies conducted in the Republic of Niger that food assistance may be effective in improving adherence among PLHIV with food insecurity [234]. This has also been reported in studies from Zambia [235]. Nevertheless, other studies conducted in Malawi did not find any significant effect of food supplementation on adherence to ART [236-237].

Fixed Dose Combination (FDC)
Studies on the use of FDCs have shown improvements in ART adherence [238-239]. Furthermore, there is evidence supporting the value of FDCs in the context of ART regimen simplification (with regards to ease of drug administration) in enhancing ART adherence [189,240].

5.2.4. Cognitive Intervention Strategies

Client Education
Client education is an established form of intervention usually after HIV infection diagnosis [241]. Some studies have demonstrated the effectiveness of Client education on ART adherence, while others have not shown increased adherence [209,222,242-243]. Nevertheless, it is of note that educational interventions significantly increase client knowledge level on HIV infection, preventive methods and ART [209,242]. Educational sessions are often combined with counselling and may often be indistinguishable [207,242].

Media methods
Media methods (e.g. TV, radio) have been highlighted in some studies as an effective intervention in other aspects of HIV care such as uptake of HIV testing and diagnosis [222], nonetheless, this has not been extensively studied in the context of ART adherence in SSA [222]. There have been indications from some studies on the potential effectiveness of mass media methods (i.e. on ART drugs complimented with health education on adherence) in aiding disclosure and increasing adherence [244], and this should be explored in resource-limited settings such as in SSA [222,244-245].

5.2.5. Structural Intervention Strategies

Home-based care (HBC)
A study carried out in Botswana, Lesotho, Namibia and South Africa revealed that PLHIV who had access to community-based care (CBC) services, specifically HBC services had higher ART adherence levels and better improvements in health-related QOL indicators (physical functioning, social functioning, cognitive functioning, emotional well-being, energy and fatigue and general health) compared to those who were not exposed to these services [246]. Furthermore, the same study showed that they (i.e. PLHIV accessing CBC services) had a higher and faster overall increase in CD4 cell counts. Studies from Uganda have also shown that HBC (with trained lay-workers) is as effective as management with higher cadre health professionals in facility-based care settings [247]. Kipp et al. indicated that PLHIV in CBC or health centres (managed by clinical officers, lay volunteers and treatment supporters) were more likely to be adherent to ART and achieve viral suppression over 6 months [247]. This strategy was also cost-effective. Authors of the same study further published study outcomes after 2 years and demonstrated

successful ART outcomes in CBC/health centre (HC), which was the same as findings from the hospital-based care cohort managed by doctors [248]. Similar findings of higher/enhanced ART adherence have also been reported by other studies from Uganda [249-250]. In addition to increased ART adherence, HBC has been reported to improve survival/reduce mortality [251-252] and is also an accepted and feasible strategy among PLHIV in resource-limited settings [253]. A qualitative study [254] on the effect of HBC on adherence done in Swaziland reported that this intervention played a vital role in the treatment of PLHIV in "hard-to-reach" areas. Furthermore, it was reported that care supporters in HBC were more actively engaged in addressing multiple aspects of factors influencing adherence such as poverty, stigma and perception of HIV and ART compared to that in clinic settings [254].

Treatment supporters

Many of the studies from SSA used "treatment supporters" in delivering ART adherence interventions and this showed promising results and treatment outcomes [241]. Treatment adherence support intervention has been used interchangeably with terms such as treatment buddy, treatment assistant or monitor [255]. Kunutsor et al. [256] indicated that treatment supporter intervention showed a higher likelihood for achieving optimal adherence compared to the control group. A study from Zambia reported optimal and increased adherence among PLHIV on ART who had treatment buddies [255]. Another study from Uganda also reported increased/higher levels of ART adherence and reduced virological failure rates among PLHIV with treatment supporters [257]. Chang et al. [258] reported long-term (96-192 weeks) improvements in loss-to-follow-up rates and decreased virologic failure among study participants (PLHIV) who had access to treatment support via peer health workers in their ART centre. Zuyderduin et al. [259] in a quasi-experimental study conducted in Botswana reported that buddy systems improved self-care behaviours such as disclosure, adherence to ART and TB treatment among women living with HIV. It is pertinent to highlight that the role/tasks of treatment supporters are different in studies that have been reviewed as this ranged from home (twice-weekly) and facility provision of counselling and education, social support and ART adherence assessment (pill-count and self-report).

5.2.6. Combination of Intervention Strategies

The combination of adherence intervention strategies has been reported to be more strongly associated with improving adherence to ART compared to single strategies [209]. Busari and colleagues in two

Nigerian studies [201-202] examined the effect of structured teaching programs (patient education and counselling) compared to standard clinic care among PLHIV who were on ART. Findings indicated that PLHIV who received the intervention (10 educational modules on adverse drug effects, benefits of treatment, self-efficacy and social support) had significant higher rates of adherence, higher CD4 cell counts, reduced frequency of OIs and lower mortality than in the comparison group. A recent RCT study done by Maduka and Tobin-West [40], in Nigeria among 104 non-adhering[6] PLHIV using monthly adherence counselling and twice-weekly SMS revealed that post-intervention, there was significant improvement in ART adherence among participants in the intervention group compared to the control group. Furthermore, there was a significant increase in CD4 cell count from 193 cells/mm^3 to 575 cells/mm^3. Mugusi et al. [260] in their study conducted in Tanzania reported improved adherence using a combination of strategies (regular counselling, regular counselling plus calendars, and regular counselling with treatment assistants). Over time, there was no difference in adherence levels, CD4 cell count and weight changes in the intervention groups. Of note in this study is the value of regular/persistent counselling. Chang et al. in a trial used peer health workers (also PLHIV) in the delivery of interventions on adherence counselling and health and HIV-related education (group and individual sessions), home-visits, pill counts and triggering referral if patient/clients need urgent care. Findings indicated a decreased risk of virologic failure on long-term ART (greater than 96 weeks) and loss-to-follow-up in the intervention group compared to the control group [258]. Findings from network meta-analysis studies indicate that adherence care packages including combined components of interventions such as enhanced adherence counselling, communication technology (SMS) and social support (with treatment supporters) was more effective in increasing ART adherence among PLHIV in SSA as compared to standard of care approaches [207].

[6] PLHIV with history of non-adherence (<95%) to ART at the commencement of study

CHAPTER 6. Discussion

This chapter discusses the findings from previous chapters (3-5), highlight and isolate significant findings. In addition, relevant adherence interventions for PLHIV in Nigeria will be synthesized and proposed based on findings from the literature review.

6.1. Patterns of Adherence in Nigeria

Findings from studies highlighted in chapter 3 show a wide variation in adherence levels among PLHIV on ART in Nigeria (14.9% to ≥95%). Although most of the studies used the self-report method in assessing adherence, the variation observed might be due to the differences in study population as this ranged from studies comprising of both men and women, women, pregnant women to depressed PLHIV. In addition, healthcare system levels where these studies were conducted varied, as some were done in rural primary health care (PHC) settings and others in tertiary healthcare centres. For example, some centres provided free ART and ancillary services, while others did not. The differences in the factors (chapter 4) affecting adherence in studies identified can also be considered as partly responsible for the variation in adherence rates. Furthermore, some aspects of study methodology may be accountable for the observed variation as many of the studies only evaluated certain aspects ART adherence, such as missed doses of ART drugs, and only a few taking into account other aspects such as correct ART dosing, timing and attendance of follow-up appointments. Lastly, there were differences in the time period of recall used in assessing adherence (ranging from 1-30 days).

Adherence studies including sub-populations such as men who have sex with men (MSM), people who inject drugs (PWID), sex workers, PLHIV in prison settings, HIV-related disabilities (and other disabilities) and elderly PLHIV are lacking from Nigeria. In addition, studies in PLHIV with MNS disorders (apart from depression) and chronic comorbidities are limited. Similarly, there is a dearth of studies originating from the North Eastern part of Nigeria. Only two studies evaluated ART adherence among pregnant women. This is quite worrying in the view of the future national adoption of the WHO option B+ recommendation[7] for pregnant women which has been documented to be associated with adherence challenges in some SSA countries [261-263]. Hardly did any study attempt to evaluate long-term ART adherence, as the majority of studies identified, were cross-sectional in nature. The limitations of cross-sectional studies

[7] Option B+ involves the initiation of ART (regardless of CD4 count) and continued (lifelong) ART in pregnant and breastfeeding women

in isolating causal association should be noted. Only two studies combined the former with a qualitative research component (focus group discussion).

The combination of adherence assessment methods has been indicated to be more efficient in adequately measuring adherence compared to single methods [34,71]. However, most studies used the self-report method, with only a few of the studies identified utilizing a combination of adherence assessment methods. Lastly, some studies outlined in this literature study utilized data before 2006, which was notably a period plagued by a nation-wide stock out of ART drugs, lasting between 2004-2005. This may have, to a reasonable extent, influenced study outcomes.

6.2. Factors influencing ART Adherence

Findings from chapter 4 underscored the important role of factors influencing ART adherence. In addition, the potential for these factors to either be a facilitator or barrier and the interaction of multiple factors in influencing adherence was also observed.

Individual/Client-related factors

Factors identified as facilitators of ART adherence in this review include: disclosure of HIV status, HIV and ART-related knowledge, older age. Other factors identified as potential barriers included negative beliefs about HIV and ART, poverty, unemployment and forgetfulness. Perceived health status and cessation of symptoms was found to either be a facilitator or barrier to optimal ART adherence. A prevalent factor identified in many of the studies was forgetfulness. Evidence on the influence of sociodemographic factors (e.g. sex, level of education and marital status) was inconclusive and deserves further research. Poverty is pervasive in Nigeria and reports from national newspapers indicate anecdotally of the existence of ART drug black markets where PLHIV sell their drugs to other clients in some parts of the country [264].

Social/community-related factors

Factors identified influencing adherence were stigma and discrimination, social support, religion, financial problems and gender issues. Of all these highlighted factors, financial problems, social support and stigma and discrimination were more evident in most studies. Ware et al. strongly emphasized the role of social support in ART adherence in the context of

utilizing this as a source of "social capital"[8] [127], where the PLHIV sees adherence as a way to pay back for support received. Furthermore, from the perspective of social capital theory, PLHIV were enabled to navigate day-to-day survival despite societal hardships and other HIV-related challenges. The concept of social capital has been indicated as an explanation for higher adherence levels observed in SSA compared to developed countries [127]. It was further highlighted that it also mitigated the detrimental effects of persistent stigma and discrimination. In situations where social capital is lacking, as may often be the case, it constitutes a huge barrier to optimal ART adherence. Findings from this study underscore the value of social support for PLHIV on the community level in Nigeria, which plausibly, may be more sustainable in the long-term than other factors strengthening adherence.

The challenge of stigma and discrimination has been described as a persistent problem that pervades every aspect of the Nigerian society and this has implications for PLHIV and more crucially, HIV key populations such as MSM who may suffer from "double stigma". The resultant effect on access to ART programs and, more specifically, ART adherence cannot be overlooked in view of the recent criminalization of same-sex relationships [31]. The anti-stigma and discrimination bill has been passed through the legislative arm of government but is yet to be signed into law by the President [2].

Condition-related factors

The severity of HIV infection, HIV symptoms, HIV-related disability and comorbidities were all highlighted as barriers to optimal ART adherence. The severity of HIV infection, which can also be translated into the categories of clients encountered in ART programs such as early presenters or late presenters (i.e. those with advanced HIV infection) has been shown to influence ART adherence [58]. PLHIV may present late for ART due to social factors as outlined in the framework. Likewise, the role of comorbid MNS disorders both in poor adherence and high-risk behaviours has been underscored in past studies. In addition, the effect of chronic comorbidities (noncommunicable diseases) on adherence via polypharmacy and effect of poor QOL cannot be overemphasized. These findings highlight the need for integrated service delivery arrangements that can stimulate early detection, diagnosis and management of comorbid conditions, thereby improving adherence. In addition, although ART programs have stipulated standards of care (SOC) for adherence

[8] Relationships and/or networks with a common background (e.g. norms and values) that facilitate cooperation to obtain assistance/benefits or desired results [127]

management, there may be a need to identify relevant interventions to be included in care packages based on the different categories of PLHIV accessing ART programs in Nigeria who may have different adherence management needs. Lastly, HIV-related disability and disability in PLHIV and its effects on ART adherence has not been thoroughly explored. Further research and new evidence are needed.

Medication-related factors

The complexity of drug regimens and ART drug side effects were identified as evident barriers to ART adherence in this study. A report by GNP+ [265] indicated that ART programs in Nigeria were not providing ART drugs in FDC formulations, which often resulted in PLHIV having to use higher pill counts daily. Recent evidence strongly supports the effectiveness of FDCs (single tablet regimens) in enhancing ART adherence and other treatment outcome indicators such as the QOL among PLHIV. Other issues such as poor packaging of ART drugs with misleading information were reported. Nigeria is yet to take steps in addressing these issues.

Health system-related factors

While ART drugs are subsidized in most ART programs in Nigeria, the cost of ART-related services and distance to treatment facilities were notable barriers to adherence in many studies where out-of-pocket payment for ART-related services (e.g. transportation and laboratory investigations) was existent. On the other hand, free or subsidized all-inclusive ART services were a significant facilitator of adherence in many studies. The availability and constant supply of ART drugs in Nigeria has been a persistent problem. In many cases, there have been reports of programs being out-of-stock on ART drugs. It is of note that, only few HIV treatment and care centres provide monitoring services such as viral load monitoring, CD4 cell count and other ancillary tests. This often results in delay in receiving test results and limits access to testing facilities due to distance and cost-related issues. The catastrophic effect of ART-related costs on Nigerian PLHIV in rural areas (and poor PLHIV) has been noted [266]. Furthermore, ART sites seldom provide drugs for the treatment of opportunistic infections. This is especially evident in peripheral ART sites (managed by state and local governments). A recent study revealed that treatment outcomes in decentralized sites in Nigeria might not be favourable compared to tertiary ART centres [267]. This can affect adherence among PLHIV, thus, reiterating the importance of effective and persistent strengthening of monitoring and evaluation of decentralized ART programs in Nigeria.

There have been indications on the challenges related to the retention of health workers in the health system and there is an urban-rural disparity [268]. This plausibly extends to ART programs. Increasing numbers of PLHIV on ART (both first line and second line ART drugs) potentially hamper the quality of care accessed in view of health workers being overwhelmed by the increasing numbers of clients enrolled in ART programs.

ART adherence framework

Reflecting back, it is noteworthy to mention that the adapted framework model was adequate in analysing the factors influencing ART adherence among PLHIV in Nigeria, as there were no significant findings that did not fit into the framework model throughout the literature review process. Furthermore, the process of adapting the framework (e.g. condition-related factors and other outlined factors) made the model more effective in identifying and addressing the factors highlighted in this study.

Interaction of ART adherence factors

Interactions between and within outlined factors were observed in this study. These included interactions between factor levels such as individual and social factors- perceived health status or wellbeing/cessation of symptoms and the use alternative/traditional treatment, disclosure of HIV status, fear and experience of stigma and social support, disclosure of HIV status and gender issues (e.g. IPV). Similarly, interactions between social and health system/structural factors were observed. These include: financial problems and poor access (cost), the effect of stigma and discrimination on patient-provider relationship. Other interactions noted include condition and medication-related factors e.g. chronic comorbidities and complexity of drug regimen, condition and social-related factors such as disability, stigma, poverty, poor access and social support. On the other hand, interactions within factor levels were observed. These include: individual factor component interactions such as age and forgetfulness; and social component interactions like: religion and stigma, stigma and social support.

6.3. ART Adherence Interventions

Findings from this literature study show that adherence interventions often relate to multiple intervention categories as opposed to those outlined by Barnighausen and colleagues. For example, peer support addresses affective, behavioural (DOT/DAART) and structural (treatment supporters) categories. Furthermore, Barnighausen et al. suggested that

adherence interventions developed and originally based on theories of behaviour in developed countries might be potentially non-valid in the SSA context [45]. Nonetheless, despite the evident gap in research evidence on adherence interventions from Nigeria, there is a considerable large body of evidence on effective adherence intervention strategies (increasing adherence and achieving the desired treatment outcomes as outlined in framework) from other SSA countries and LMICs. This disproves the idea of non-validity in SSA settings.

While these findings may be evidenced-based, some of the outlined interventions may not be relevant for and feasible in Nigeria and thus the need for proper reflection and adaptation. This is firstly related to context-specific population characteristics such as high numbers of PLHIV enrolled in ART programs (as Nigeria accounts for the second highest burden of PLHIV worldwide, and also possible increases with expanded ART coverage). The second reason centres around other system-related characteristics such as lack of resources and healthcare service delivery arrangements like provider cadres assigned to carry out the range of interventions across the different categories and sub-populations of PLHIV enrolled in ART programs. This may require additional training as the role of health care provider cadres in Nigeria centres mainly around basic monitoring and support of ART. A third reason is the fact that adherence is a dynamic behaviour, influenced by multiple factors. These are all crucial in order to inform policy makers and program managers, and this requires a public health approach in tackling such challenges as opposed to solely utilizing clinical approaches.

Chaiyachati et al. [241] concluded in a systematic review on adherence interventions that combining interventions might be more effective in enhancing adherence through the mechanisms of interventions working via different pathways (and factors). This is further strengthened by findings from a recent network meta-analysis showing the higher effectiveness of a combined package of interventions (cognitive and behavioural) compared to single interventions [207]. The feasibility of implementing interventions as part of a routine package of care in Nigeria is yet to be addressed due to a significant lack of cost benefit and cost-effectiveness studies on adherence interventions originating from the country. Moreover, there is limited evidence on such cost-analysis studies from SSA and other LMICs. There is also a lack of stigma and discrimination intervention studies addressing ART adherence from Nigeria and likewise in other SSA countries. The effect of (mass) media methods on the uptake of HIV testing has been shown to be effective

[222]. Nonetheless, the effect of this intervention on ART adherence is inconclusive.

ART is a long-term, lifelong process and this underscores the importance of sustainability of intervention strategies in ART programs. In addition, the effectiveness of some interventions (e.g. DOT/DAART) may be more relevant to certain sub-populations than to the general population. Lastly, the question arises as to what interventions are relevant in the context of 'TasP'. However, there are indications that enhanced counselling is effective in adherence-related TasP approaches [269-270].

6.4. Potential Relevant ART Adherence Interventions: Nigeria

Potential relevant ART adherence interventions for PLHIV in Nigeria were synthesized (*see Figure 4*) based on findings from literature review on the most evident factors influencing ART adherence in Nigeria and interventions addressing these factors (Nigeria and in other SSA countries). In addition, based on evidence [207,241] from reviewed literature, combining the outlined interventions[9] in this matrix may be more effective in enhancing adherence among PLHIV in Nigeria. For example, a combined package of enhanced counselling and HBC addresses all the highlighted prevalent factors from the literature review.

The additional value of proposed interventions in this synthesis is the potential capability of these interventions to address other outlined factors in the study, which were not included in this matrix.

Factors (Row) ↓	Key Interventions (Column) →	Enhanced counselling	Peer support	Communication technology (SMS)	FDC	Home-based care
Individual-related Factors						
Forgetfulness		x		x		
Social/Community-related Factors						
Financial problems			x			x
Stigma & Discrimination			x			x
Social support			x	x		x
Medication-related Factors						
Complexity of drug regimens		x			x	
Side effect		x			x	
Health System-related & Structural-related Factors						
Access	Distance					x
	Cost					x

Figure 4. Matrix: Potentially Relevant ART Adherence Interventions for Nigeria

[9] Each intervention has the innate capability to address multiple factors

CHAPTER 7. Conclusion and Recommendations

7.1. Conclusion

This study outlined and analysed the patterns and factors influencing ART adherence among PLHIV in Nigeria. In addition, effective adherence interventions conducted in Nigeria and other SSA (and LMIC) countries were identified.

There was a wide variation in pattern of adherence and possible explanations for this finding were highlighted (*see section 6.1*). Research-related gaps identified in this study were: lack of adherence studies among sub-populations including MSM, PWID, sex workers, elderly PLHIV, PLHIV with other MNS disorders (apart from depression) and chronic comorbidities, HIV-related disabilities, pregnant women living with HIV, and PLHIV in prison settings. In addition, studies assessing long-term ART adherence are unavailable. Similarly, there is a lack of qualitative studies on ART adherence in Nigeria. There is a need for further research in these areas. There was a dearth in cost-analysis studies of adherence interventions and likewise, interventions directed towards the TasP approach in Nigeria.

Multiple factors influencing adherence were identified in *chapter 4* (with the aid of the adapted framework). Prevalent factors identified as influencing adherence among PLHIV in Nigeria include: forgetfulness, poverty and financial problems, stigma and discrimination, social support, complexity of drug regimens, ART drug side effect, poor access (cost and distance), availability of ART drugs and free/subsidized ART-related services. Lastly, interactions were observed between and within components of outlined factors on ART adherence and the effects of these interactions were noted.

Effective adherence interventions from Nigeria and other SSA countries like enhanced counselling, peer support, communication technology (SMS), use of FDC and HBC were identified and discussed. Potentially relevant interventions addressing highlighted (prevalent) factors among PLHIV in Nigeria were synthesized and proposed. Lastly, the need to combine highlighted adherence interventions was emphasized in order to effectively enhance ART adherence in Nigerian PLHIV.

7.2. Recommendations

Based on the findings of this literature study, the following recommendations are hereby made to the following stakeholders:

Federal Government

1. Increase budgetary allocation and funding for the constant supply and availability of ART drugs (in FDC formulations) and likewise, expanding subsidization arrangements of ART-related services through the PCRP and similar arrangements.
2. Enact and enforce HIV-related anti-stigma and discrimination laws in all states of the Federation.

Ministry of Health, NACA and ART Program Managers

1. Encourage, fund and conduct further research. This should include the following areas:
   (a) Adherence studies in specific sub-populations of PLHIV such as MSM, sex workers, PWID, older PLHIV, PLHIV in prison settings, PLHIV with MNS disorders and other chronic comorbidities and pregnant women living with HIV.
   (b) Research studies designed to evaluate long-term ART adherence.
   (c) Qualitative research studies on ART adherence among PLHIV and other relevant stakeholders.
   (d) Cost analysis (cost-effectiveness and cost-benefit) studies on adherence intervention strategies.
   (e) Further research to delineate the factors responsible for non-adherence in the LTFU sub-group.
   (f) Continuous (and strengthening of) monitoring and evaluation of decentralized ART programs.
2. Consider and adopt proposed interventions in *section 6.4* (i.e. enhanced counselling, peer support, SMS, FDC and HBC) and develop a package of outlined adherence interventions.
3. Review and develop effective service delivery integration and task shifting arrangements in ART programs.
4. Set up monitoring systems, quality assurance mechanisms and watchdogs to ensure reduction of provider-related stigma and other forms of HIV-related stigma against PLHIV in ART programs.
5. Strengthen tracking systems for PLHIV in ART programs in order to reduce the rate of LTFU among PLHIV and ensure early active follow-up when this is flagged.

Civil Society Organization (CSO)

1. Coordinate efforts and ensure community mobilization and engagement towards setting-up social and peer support structures and home-based care services for PLHIV on ART.

2. Coordinate with and engage community leaders and members (including the youth), religious leaders, faith bodies in tackling and addressing stigma and discrimination-related challenges for PLHIV on ART in the community.

REFERENCES

1. World Health Organization. Global Health Observatory (GHO) data: HIV/AIDS [Internet]. 2014 [cited 2014 Jul 15]. Available from: http://www.who.int/gho/hiv/en/
2. National Agency for the Control of AIDS. Federal Republic of Nigeria. Global AIDS Response Country Progress Report (GARPR). Nigeria [Internet]. 2014 [cited 2014 Jul 15]. Available from: http://www.unaids.org/sites/default/files/en/dataanalysis/knowyourresponse/countryprogressreports/2014countries/NGA_narrative_report_2014.pdf
3. Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. The Lancet 2010;376(9740):532–39.
4. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1- infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. The Lancet 2002;360(9327):119–29.
5. Mills EJ, Bakanda C, Birungi J, Chan K, Ford N, Cooper CL, et al. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. Ann Intern Med. 2011;155(4):209-16.
6. Mannheimer SB, Matts J, Telzak E, Chesney M, Child C, Wu AW, et al. Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. AIDS Care 2005;17(1):10–22.
7. Idoko J, Folayan MO. The use of antiretroviral therapy for the prevention of new HIV infection in populations at high risk for HIV sero-conversion in Nigeria: perspectives paper. African Journal of Reproductive Health 2014: Special Edition on HIV/AIDS: Special Edition 3(18):127-34.
8. Granich R, Kahn JG, Bennett R, Holmes CB, Garg N, Serenata C, et al. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011–2050. PLoS One 2012;7(2):e30216.
9. Paterson DL, Swindells S, Mohr J, Brester, M, Vergis EN, Squler C, et al. Adherence to protease inhibitor Therapy and Outcomes in Patients with HIV Infection. Ann Intern Med. 2000;133(1):21-30.
10. Turner BJ. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. Journal of Infectious Diseases 2002;185(2):143-51.
11. Adefolalu AO, Nkosi ZZ. The complex nature of adherence in the

management of HIV/AIDS as a chronic medical condition. Diseases 2013;1(1):18-35.
12. Nachega JB, Mills EJ, Schechter M. Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of knowledge and research priorities. Current Opinion in HIV and AIDS 2010;5(1):70-77.
13. Stricker SM, Fox KA, Baggaley R, Negussie E, de Pee S, Grede N, Bloem MW. Retention in Care and Adherence to ART are Critical Elements of HIV Care Interventions. AIDS and Behavior 2014;18:465–75.
14. National Population Commission (NPC) [Nigeria] and ICF International. Nigeria Demographic and Health Survey 2013 [Internet]. Abuja, Nigeria, and Rockville, Maryland, USA: NPC and ICF International. 2014 [cited 2014 Sept 10]. Available from: https://dhsprogram.com/pubs/pdf/FR293/FR293.pdf
15. Population Reference Bureau. World Population Data Sheet. 2014 [cited 2014 Sept 10]. Available from: http://www.prb.org/pdf14/2014-world-population-data-sheet_eng.pdf
16. Nigeria Geopolitical Zones Picture. [image on the Internet]. [cited 2014 Sept 10]. Available from: http://collections.infocollections.org/whocountry/index/assoc/s7928e/p08.jpg
17. UNICEF. At a glance: Nigeria. Statistics [Internet]. 2014 [updated 2013 Dec 27; cited 2014 June 20]. Available from: http://www.unicef.org/infobycountry/nigeria_statistics.html.
18. World Bank. World Development Indicators, Data by country: Nigeria. The World Bank [Internet]. 2014 [cited 2014 Jul 10]. Available from: http://data.worldbank.org/country/nigeria
19. World Bank. GDP per capita (current US$), World Development Indicators, The World Bank [Internet]. 2014 [cited 2014 Jul 10]. Available from: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD
20. World Bank. GINI index, World Development Indicators, The World Bank [Internet]. 2014 [cited 2014 Jul 10]. Available from: http://data.worldbank.org/indicator/SI.POV.GINI
21. UNDP. Human Development Report. The Rise of the South: Human Progress in a Diverse World. Nigeria [Internet]. 2013 [cited 2014 Jul 11]. Available from: http://hdr.undp.org/sites/default/files/Country-Profiles/NGA.pdf
22. British Council. Gender in Nigeria report. Improving the lives of girls and women in Nigeria. Issues Policies Action [Internet]. 2012 [cited

2014 Jul 11]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/67333/Gender-Nigeria2012.pdf
23. Federal Ministry of Health. Nigeria. National Strategic Health Development Plan (NSHDP) 2010 – 2015. 2010 [cited 2014 Jul 12]. Available from: http://www.health.gov.ng/doc/NSHDP.pdf
24. WHO. Nigeria statistics summary (2002 - present). Global Health Observatory Data Repository. 2013 [cited 2014 Jul 12]. Available from: http://apps.who.int/gho/data/node.country.country-NGA
25. Lawan UM, Iliyasu Z, Daso AM. Challenges to the scale-up of the Nigerian National Health Insurance Scheme: public knowledge and opinions in urban Kano, Nigeria. Annals of Tropical Medicine and Public Health 2012;5(1):34.
26. Odeyemi IAO. Community-based health insurance programmes and the national health insurance scheme of Nigeria: challenges to uptake and integration. International Journal for Equity in Health 2014;13(1):20.
27. Kombe G, Fleisher L, Kariisa E, Arur A, Sanjana P, Paina L, et al. Nigeria Health System Assessment 2008. Health Systems 20/20 report. Bethesda, MD: Abt Associates Inc. Health Systems 20/20 [Internet]. 2009 [cited 2014 Jul 12]. Available from: http://www.healthsystemassessment.com/wp-content/uploads/2012/06/Nigeria_HSA_FINAL_June2009.pdf
28. Federal Ministry of Health. Nigeria. National HIV&AIDS and Reproductive Health Survey (NARHS Plus II, 2012) [Internet]. 2013 [cited 2014 Jul 14]. Available from: http://nascp.gov.ng/demo/wp-content/uploads/2014/02/NARHS-Plus-2012-Final-18112013.pdf
29. National Agency for the Control of AIDS. Federal Republic of Nigeria. Global AIDS Response Country Progress Report (GARPR). Nigeria [Internet]. 2012 [cited 2014 Jul 15]. Available from: http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/Nigeria%202012%20GARPR%20Report%20Revised.pdf
30. National HIV/AIDS Division, Federal Ministry of Health [Nigeria] and MEASURE Evaluation. Assessment of Primary Health Care Facilities for Decentralization of HIV/AIDS Services in Nigeria 2012. Federal Ministry of Health, Abuja, Nigeria [Internet]. 2014 [cited 2014 Jul 16]. Available from: http://www.cpc.unc.edu/measure/publications/tr-13-93
31. UNAIDS. The GAP report [Internet]. 2014 [cited 2014 Sept 10]. Available from:

http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf
32. Adherence (n.d.). The American Heritage®Stedman's Medical Dictionary, Houghton Mifflin Company [Internet] Dictionary.com. [cited 2014 Sept 10]. Available from: http://dictionary.reference.com/browse/adherence
33. Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: A review of published and abstract reports. Patient Education Counselling 2002;46(2):93-108.
34. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization, 2003. [cited 2014 Sept 12] Available from: http://whqlibdoc.who.int/publications/2003/9241545992.pdf
35. Weinreich S, Benn C. AIDS - Meeting the Challenge: data, facts, background. Geneva: World council of churches; 2004.
36. Jani AA. Adherence to HIV treatment regimens: Recommendations for best practices. 2002 [cited 2014 Sept 13]. Available from: http://www.apha.org/NR/rdonlyres/A030DDB1-02C8-4D80-923B-7EF6608D62F1/0/BestPracticesnew.pdf
37. Wood E, Hogg RS, Yip B, Harrigan R, O'Shaughnessy MV, Montaner JSG. The impact of adherence on CD4 cell count responses among HIV-Infected patients. Journal of Acquired immune Deficiency Syndromes 2004;35(3):261-68.
38. Conway B. The role of adherence to antiretroviral therapy in management of HIV infection. Journal of Acquired immune Deficiency Syndromes 2007;45(1):14-18.
39. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase inhibitor–based HIV therapy and virologic outcomes. Ann Internal Med. 2007;146(8):564-73.
40. Maduka O, Tobin-West CI. Adherence counselling and reminder text messages improve uptake of antiretroviral therapy in a tertiary hospital in Nigeria. Niger J Clin Pract.2013;16(3):302-8.
41. Hardon A, Davey S, Gerrits T, Catherine H, Irunde H, Kgatlwane J, et al. From access to adherence: the challenges of antiretroviral treatment. Studies from Botswana, Tanzania and Uganda, pp. 1-1349. 2006 [cited 2014 Sept 15]. Available from: http://www.who.int/medicines/publications/challenges_arvtreatment15Aug2006.pdf
42. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between Adherence to Antiretroviral Therapy and Human Immunodeficiency Virus Drug Resistance. Clinical Infectious

Diseases 2003;37:1112–18.
43. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. Clin Infect Dis. 2006;43(7):939–41.
44. Martin M, Del Cacho E, Codina C, Tuset M, De Lazzari,E, Mallolas J, et al. Relationship between adherence levels, type of the antiretroviral regimen, and plasma HIV type 1 RNA viral load: A prospective cohort study. AIDS Research and Human Retroviruses 2008;24(10):1263-68.
45. Bärnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. The Lancet infectious diseases 2011;11(12):942-51.
46. Lima VD, Bangsberg DR, Harrigan PR, Deeks SG, Yip B, Hogg RS, Montaner JS. Risk of viral failure declines with duration of suppression on highly active antiretroviral therapy irrespective of adherence level. J Acquir Immune Defic Syndr. 2010; 55(4):460–65.
47. Monjok E, Smesny A, Okokon IB, Mgbere O, Essien EJ. Adherence to antiretroviral therapy in Nigeria: an overview of research studies and implications for policy and practice. HIV/AIDS (Auckl). 2010;2:69-76.
48. Ministry of Health. Rwanda. National Annual Report on HIV/AIDS [Internet]. 2012 [cited 2014 Sept 20]. Available from: http://rbc.gov.rw/IMG/pdf/national_annual_report_on_hiv_aids_july_2010_june_2011.pdf [Assessed]
49. Ghana AIDS Commission. Ghana. Country AIDS Response Progress Report [Internet]. 2014 [cited 2014 Sept 20]. Available from: http://www.unaids.org/sites/default/files/en/dataanalysis/knowyourresponse/countryprogressreports/2014countries/GHA_narrative_report_2014.pdf
50. Ouattara EN, Ross EL, Yazdanpanah Y, Wong AY, Robine M, Losina E, et al. Clinical impact and cost-effectiveness of making third-line antiretroviral therapy available in sub-Saharan Africa: A model-based analysis in Cote d'Ivoire. JAIDS.2014;66(3):294-302.
51. Pujades-Rodríguez M, O'Brien D, Humblet P, Calmy A. Second-line antiretroviral therapy in resource-limited settings: the experience of Medecins Sans Frontieres. AIDS 2008;22(11):1305-1312.
52. Adelaja A. Coalition faults Nigerian Government on HIV treatment. Premium Times [Internet]. 2014 Jan 11 [cited 2014 Oct 10]. Available from: http://www.premiumtimesng.com/politics/153153-coalition-faults-nigerian-government-hiv-treatment-2.html

53. Nachega JB, Uthman OA, Mills EJ, Quinn TC. Adherence to antiretroviral therapy for the success of emerging interventions to prevent HIV transmission: A wake up call. J AIDS Clin Res.2012;S4.
54. Parienti JJ, Massari V, Descamps D, Vabret A, Bouvet E, Larouzé B, Verdon R. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine-or efavirenz-based antiretroviral therapy. Clinical Infectious Diseases 2004;38(9):1311-1316.
55. DeFino M, Clark J, Mogyoros D, Shuter J. Predictors of virologic success in patients completing a structured antiretroviral adherence program. Journal of the Association of Nurses in AIDS Care 2004;15(5):60-67.
56. Odafe S, Torpey K, Khamofu H, Ogbanufe O, Oladele EA, Kuti O, et al. The pattern of attrition from an antiretroviral treatment program in Nigeria. PLoS One 2012; 7(12):e51254.
57. 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 Infect Dis. 2014;1(2): ofu055.
58. Charurat M, Oyegunle M, Benjamin R, Habib A, Eze E, Ele P, et al. Patient retention and adherence to antiretrovirals in a large antiretroviral therapy program in Nigeria: a longitudinal analysis for risk factors. PLoS One 2010;5:e10584.
59. Ugoji C, Ake-Uzoigwe R, Ladele M, Akolo C, Mendy G, Dakum P, et al. Correlates of Patient Retention in HIV Care and Treatment Programs in Nigeria. Poster abstract presented at: IAPAC, 8th International Conference on treatment and prevention adherence; 2013 Jun 2-4; Miami.
60. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA.2006;296(6):679-90.
61. Bangsberg DR, Mills EJ. Long-term adherence to antiretroviral therapy in resource-limited settings: a bitter pill to swallow. Antivir Ther. 2013;18:25-28.
62. Wekesa E. ART adherence in resource poor settings in sub-Saharan Africa: A multidisciplinary review. 2007 [cited 2014 Sept 20]. Available from: http://uaps2007.princeton.edu/papers/70123
63. Reda AA, Biadgilign S. Determinants of adherence to antiretroviral therapy among HIV-infected patients in Africa. AIDS Research and Treatment 2012.
64. Federal Ministry of Health. National guidelines for HIV and AIDS treatment and care in adolescents and adults. 2010 [cited 2014 Oct

20]. Available from: http://www.who.int/hiv/pub/guidelines/nigeria_art.pdf.
65. Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. The Lancet 1999;353(9156):863-68.
66. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013 [cited 2014 Oct 20]. Available from: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf.
67. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. J Acquir Immune Defic Syndr. 2006;43(1):79-87.
68. Colebunders R, Moses KR, Laurence J, Shihab HM, Semitala F, Lutwama F, et al. A new model to monitor the virological efficacy of antiretroviral treatment in resource poor countries. Lancet Infect. Dis. 2006;6(1):53–59.
69. Watt MH. Understanding patients' adherence to antiretroviral therapy: a mixed methods study in Arusha, Tanzania [PhD thesis]. University of North Carolina. 2007 [cited 2014 October 10]. Available from: http://dc.lib.unc.edu/cdm/ref/collection/etd/id/1646.
70. Garcia, R., Schooley, R., Badaro, R. An adherence trilogy is essential for long term HAART success, The Brazilian JID.2003;7(5):307-14.
71. Martin LR, Williams SL, Haskard KB, DiMatteo MR. The challenge of patient adherence. Therapeutics and Clinical Risk Management 2005;1(3):189.
72. World Health Organization. Global update on the health sector response to HIV. 2014 [cited 2014 October 10]. Available from: http://apps.who.int/iris/bitstream/10665/128494/1/9789241507585_eng.pdf?ua=1
73. Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodríguez E, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav.2011;15(7):1381-96.
74. Okafor CE, Ekwunife OI. Self-reported adherence to antiretroviral therapy in sub-Saharan Africa: A meta-analysis. International Journal of Public Health and Epidemiology 2014;3(3):17-25.
75. Okoronkwo I, Okeke U, Chinweuba A, Iheanacho P. Nonadherence Factors and Sociodemographic Characteristics of HIV-Infected

Adults Receiving Antiretroviral Therapy in Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. ISRN AIDS. 2013.
76. Uzochukwu BSC, Onwujekwe OE, Onoka AC, Okoli C, Uguru NP, Chukwuogo OI. Determinants of non-adherence to subsidized anti-retroviral treatment in southeast Nigeria. Health Policy Plan. 2009;24:189-96.
77. Onyeonoro UU, Ebenebe UE, Ibeh CC, Nwamoh UN, Ukegbu AU, Emelumadu OF. Adherence to antiretroviral therapy among people living with human immunodeficiency virus/acquired immunodeficiency syndrome in a tertiary health facility in South Eastern Nigeria. J HIV Hum Reprod. 2013;1(2):58-63.
78. Ukwe CV, Ekwunife OI, Udeogaranya OP, Iwuamadi UI. Self-reported adherence to HAART in South-Eastern Nigeria is related to patients' use of pillbox. SAHARA J (Journal of Social Aspects of HIV/AIDS Research Alliance) 2010;7(1).
79. Igwegbe AO, Ugboaja JO, Nwajiaku LA. Prevalence and determinants of non-adherence to antiretroviral therapy among HIV-positive pregnant women in Nnewi, Nigeria. International Journal of Medicine and Medical Sciences 2010;2(8):238-45.
80. Ekwunife OI, Oreh C, Ubaka CM. Concurrent use of complementary and alternative medicine with antiretroviral therapy reduces adherence to HIV medications. International Journal of Pharmacy Practice 2012;20(5):340-43.
81. Nwankwo UV, Nduka OS, Ilodigwe EE, Ogbonna B, Uzodinma US, Okonta JM. Assessment of highly active antiretroviral therapy (HAART) adherence among HIV patients in a tertiary health institution in Nigeria. African Journal of Pharmacy and Pharmacology 2014;8(47):1192-99.
82. Nwauche CA, Erhabor O, Ejele OA, Akani CI. Adherence to antiretroviral therapy among HIV-infected subjects in a resource-limited setting in the Niger Delta of Nigeria. African Journal of Health Sciences 2006;13(3–4):13–17.
83. Oku AO, Owoaje ET, Oku OO, Monjok E. Prevalence and determinants of adherence to highly active anti-retroviral therapy amongst people living with HIV/AIDS in a rural setting in South-South Nigeria: original research article. African journal of reproductive health 2014;18(1):133-44.
84. Oku AO, Owoaje ET, Ige OK, Oyo-ita A. Prevalence and determinants of adherence to HAART amongst PLHIV in a tertiary health facility in south-south Nigeria. BMC infectious diseases 2013;13(1):1-9.
85. Oku AO, Owoaje ET, Oku OO, Monjok E. Prevalence and

determinants of adherence to highly active antiretroviral therapy (HAART) amongst a cohort of HIV positive women accessing treatment in a tertiary health facility in southern Nigeria. Journal of HIV/AIDS and Infectious Diseases 2013;2(102):1-8.
86. Erah PO, Arute JE. Adherence of HIV/AIDS patients to antiretroviral therapy in a tertiary health facility in Benin City. Afr J Pharm Pharmacol. 2008;2(7):145–52.
87. Agu K, Ochei U, Oparah A, Onoh O. Treatment outcomes in patients receiving combination antiretroviral therapy in Central Hospital, Benin City, Nigeria. Tropical Journal of Pharmaceutical Research 2010;9(1):1-10.
88. Asekomeh EG, Ebong OO, Onwuchekwa AC. Effects of psychosocial parameters on adherence of adult Nigerians to antiretroviral Therapy. Nigerian Journal of Psychiatry 2010;8(1).
89. Afolabi M, Ijadunola K, Fatusi A, Olasode O. Determinants of adherence to antiretroviral drugs among people living with HIV/AIDS in the Ife-Ijesa zone of Osun state, Nigeria. African Journal of Primary Health Care and Family Medicine 2009;1(1):1-6.
90. Afolabi BA, Afolabi MO, Afolabi AA, Odewale MA, Olowookere SA. Roles of family dynamics on adherence to highly active antiretroviral therapy among people living with HIV/AIDS at a tertiary hospital in Osogbo, south-west Nigeria. African Health Sciences 2014;13(4):920-26.
91. Olowookere SA, Fatiregun AA, Akinyemi JO, Bamgboye AE, Osagbemi GK. Prevalence and determinants of nonadherence to highly active antiretroviral therapy among people living with HIV/AIDS in Ibadan, Nigeria. J Infect Dev Ctries. 2008;2(5):369–72.
92. Olowookere SA, Fatiregun AA, Adewole IF. Knowledge and attitudes regarding HIV/AIDS and antiretroviral therapy among patients at a Nigerian treatment clinic. The Journal of Infection in Developing Countries 2012;6(11):809-16.
93. Ogundahunsi OA, Daniel OJ, Oladapo OT. Adherence to antiretroviral drugs among AIDS patients in Sagamu, Nigeria. Int J Biomed Health Sci 2008;4(2):41-45.
94. Daniel OJ, Oladapo OT, Ogundahunsi OA, Fagbenro S, Ogun SA, Odusoga OA. Default from antiretroviral treatment program in Sagamu, Nigeria. Afr J Biomed Res. 2008;11:221–24.
95. Ekama SO, Herbertson EC, Addeh EJ, Gab-Okafor CV, Onwujekwe DI, Tayo F, Ezechi OC. Pattern and determinants of antiretroviral drug adherence among Nigerian pregnant women. Journal of pregnancy 2012.

96. Adewuya AO, Afolabi MO, Ola BA, Ogundele OA, Ajibare AO, Oladipo BF, Fakande I. The effect of psychological distress on medication adherence in persons with HIV infection in Nigeria. Psychosomatics 2010;51(1):68-73.
97. Sekoni A, Obidike O, Balogun M. Stigma, medication adherence and coping mechanism among people living with HIV attending General Hospital, Lagos Island, Nigeria. African Journal Of Primary Health Care & Family Medicine 2012;4(1):1-10.
98. Kasumu LO, Balogun MR. Knowledge and attitude towards antiretroviral therapy and adherence pattern of HIV patients in southwest Nigeria. Int J Infect Control 2014;10(3):1-8.
99. Idigbe EO, Adewole TA, Eisen G, Kanki P, Odunukwe NN, Onwujekwe DI, et al. Management of HIV-1 infection with combination of Nevirapine, Stavudine, and Lamivudine; a preliminary report on the Nigerian antiretroviral program. J Acquir Immune Defic Syndr. 2005;40(1):65–69.
100. Agu KA, Omonaiye O, Oqua D, Sani T, Isah MA, Olayemi S, et al. Medication adherence and cluster of differentiation 4 (CD4) cells response in patients receiving antiretroviral therapy. Journal of AIDS and HIV Research 2013;5(5):163-69.
101. Olisah VO, Baiyewu O, Sheikh TL. Adherence to highly active antiretroviral therapy in depressed patients with HIV/AIDS attending a Nigerian University hospital clinic. Afr. J. Psychia.2010;13(4):275-79.
102. Habib AG, Shepherd JC, Eng MKL, Babashani M, Jumare J, Yakubu U, et al. Adherence to antiretroviral therapy (ART) during Muslim Ramadan Fasting. AIDS Behav. 2009;13(1):42-45.
103. Habib AG, Abdulmumini M, Dalhat MM, Hamza M, Iliyasu G. Antiretroviral Therapy Among HIV Infected Travellers to Hajj Pilgrimage. Journal of travel medicine 2010;17(3):176-81.
104. Iliyasu IS, Kabir M, Abubakar IS, Babashani M, Zubair ZA. Compliance to antiretroviral therapy among AIDS patients in Amino Kano Teaching Hospital, Kano, Nigeria. Nig J Med. 2005;14(3):290–94.
105. Pennap GR, Abdullahi U, Bako IA. Adherence to highly active antiretroviral therapy and its challenges in people living with human immunodeficiency virus (HIV) infection in Keffi, Nigeria. Journal of AIDS and HIV Research 2013;5(2):52-58.
106. Bello SI. HIV/AIDS patients' adherence to antiretroviral therapy in Sobi Specialist hospital, Ilorin, Nigeria. Glob J Med Res. 2011;11(2):16-25.
107. Shittu RO, Issa BA, Olanrewaju GT, Odeigah LO, Sule AG.

Adherence to Highly Active Antiretroviral Therapy, in Depressed Peoples Living with HIV/AIDS in Nigeria, West Africa. J Antivir Antiretrovir. 2013;6:006-012.
108. Falang KD, Akubaka P, Jimam NS. Patient factors impacting antiretroviral drug adherence in a Nigerian tertiary hospital. J Pharmacol Pharmacother.2012;3(2):138-42.
109. Salami AK, Fadeyi A, Ogunmodede JA, Desalu O. Factors influencing adherence to antiretroviral medications in Ilorin, Nigeria. Journal of the International Association of Physicians in AIDS Care (JIAPAC) 2010;9(3):191-95.
110. Shaahu VN, Lawoyin TO, Sangowawa AO. Adherence to highly active antiretroviral therapy (HAART) at a Federal Medical Center. Afr J Med Sci. 2008;37:29–36.
111. Agu KA, Okojie O, Oqua D, King RC, Omonaiye O, Onuoha C, et al. Medication Adherence and Risk factors for non-adherence among patients taking Highly Active Antiretroviral Therapy. West African Journal of Pharmacy 2011;22(1):19-26.
112. Farley J, Miller E, Zamani A, Tepper V, Morris C, Oyegunle M, et al. Screening for hazardous alcohol use and depressive symptomatology among HIV-infected patients in Nigeria: prevalence, predictors, and association with adherence. Journal of the International Association of Physicians in AIDS Care (JIAPAC) 2010;9(4):218-26.
113. Mohammed MD, Sarki R. Adherence to antiretroviral drugs in North-Central zone of Nigeria. East and Central African Journal of Pharmaceutical Sciences. 2004;7(3):52–55.
114. Obirikorang C, Selleh PK, Abledu JK, Fofie CO. Predictors of adherence to antiretroviral therapy among HIV/AIDS patients in the upper west region of Ghana. ISRN AIDS, 2013.
115. Wakibi SN, Ng'ang'a Z, Mbugua GG. Factors associated with non-adherence with highly active antiretroviral therapy in Nairobi, Kenya. AIDS Res Ther. 2011;8(1):43.
116. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugyenyi PN, Bangsberg DR. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. International journal of STD & AIDS 2005;16(1):38-41.
117. Nachega JB, Uthman OA, Peltzer K, Richardson LA, Mills EJ, Amekudzi K, Ouédraogo A. Association between antiretroviral therapy adherence and employment status: systematic review and meta-analysis. Bulletin of the World Health Organization 2015;93(1):29-41.
118. Nakiyemba A, Aurugai DA, Kwasa R, Oyabba T. Factors that

facilitate or constrain adherence to antiretroviral therapy among adult in Uganda: a pre-intervention study. In: Hardon A, Davey S, Gerrits T, Hodgkin C, Irunde H, Kgatlwane J, Kinsman J, Nakiyemba A, Laing R. (eds.) *From access to adherence: the challenges of antiretroviral treatment*. Geneva: World Health Organization. 2006. pp. 236-301.

119. Dahab M, Charalambous S, Hamilton R, Fielding K, Kielmann K, Churchyard GJ, Grant AD. "That is why I stopped the ART": patients' & providers' perspectives on barriers to and enablers of HIV treatment adherence in a South African workplace programme. BMC public health 2008;8(63):63
120. Roura M, Busza J, Wringe A, Mbata D, Urassa M, Zaba B. Barriers to sustaining antiretroviral treatment in Kisesa, Tanzania: A follow-up study to understand attrition from the antiretroviral program. AIDS Patients Care STDS. 2009;23(3):203-10.
121. Fielding KL, Charalambous S, Stenson AL, Pemba LF, Martin DJ, Wood R, Churchyard GJ, Grant AD. Risk factors for poor virological outcome at 12 months in a workplace-based antiretroviral therapy programme in South Africa: A cohort study. BMC Infect Dis.2008;8(1):93.
122. Sanjobo N, Frich JC, Fretheim A. Barriers and facilitators to patients adherence to antiretroviral treatment in Zambia: a qualitative study. Journal of Social Aspects of HIV/AIDS 2008;5(3):136-43.
123. Miller AN, Rubin DL. Factors Leading to Self-Disclosure of a Positive HIV Diagnosis in Nairobi, Kenya People Living With HIV/AIDS in the Sub-Sahara. Qualitative Health Research 2007;17(5):586-98.
124. Weiser S, Wolfe W, Bangsberg D, Thior I, Gilbert P, Makhema J, et al. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. Journal of Acquired Immunity Deficiency Syndromes 2003;34(3):281-88.
125. Kagee A, Remien RH, Berkman A, Hoffman S, Campos L, Swartz L. Structural barriers to ART adherence in Southern Africa: challenges and potential ways forward. Global Public Health 2011;6(1):83-97.
126. Nsimba SED, Irunde H, Comoro C. Barriers to ARV adherence among HIV/AIDS positive persons taking antiretroviral therapy in two Tanzania regions 8-12 months after program initiation. J AIDS Clinic Res 2010;1(3).
127. Ware NC, Idoko J, Kaaya S, Biraro IA, Wyatt MA, Agbaji O, Chalamilla G, Bangsberg DR. Explaining adherence success in Sub-Saharan Africa: an ethnographic study. Plos Med 2009:6(1):e1000011.
128. Tiyou A, Belachew T, Alemseged F, Biadgilign S. Predictors of

adherence to antiretroviral therapy among people living with HIV/AIDS in resource-limited settings of southwest Ethiopia. AIDS research and Therapy 2010;7:39.
129. Peltzer K, Preez NF, Ramlagan S, Anderson J. Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa. BMC Public Health 2010;10(1):1-10.
130. Nachega JB, Knowlton AR, Deluca A, Schoeman JH, Watkinson L, Efron A, et al. Treatment supporter to improve adherence to antiretroviral therapy in HIV-infected South African adults. A qualitative study. Journal of Acquired Immune Deficiency Syndromes 2006;43(1):127-33.
131. Katz IT, Ryu AE, Onuegbu AG, Psaros C, Weiser SD, Bangsberg DR, Tsai AC. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. Journal of the International AIDS Society 2013;16(3):2.
132. Nyblade L, Stangl A, Weiss E, Ashburn K. Combating HIV stigma in health care settings: what works? J Int AIDS Soc. 2009;12(1):15.
133. Uys L, Chirwa M, Kohi T, Greeff M, Naidoo J, Makoae L, et al. Evaluation of a health setting-based stigma intervention in five African countries. AIDS Patient Care STDS. 2009;23(12):1059–66.
134. Feyissa GT, Abebe L, Girma E, Woldie M. Stigma and discrimination against people living with HIV by healthcare providers, Southwest Ethiopia. BMC public health 2012;12(1):522.
135. Ofovwe CE, Ofovwe C. Psychological Disorders among Human Immunodeficiency Virus-infected Adults in Southern Nigeria. African journal of reproductive health 2014;17(4):177-182.
136. HIV Leadership through Accountability Programme: GNP+, NEWPHAN. PLHIV Stigma Index Nigeria Country Assessment [Internet]. Amsterdam: GNP+. 2011 [cited 2014 Dec 20]. Available from: http://www.stigmaindex.org/sites/default/files/reports/Nigeria%20StigmaIndex%20final_HighRs.pdf
137. Omosanya OE, Elegbede OT, Agboola SM, Isinkaye AO, Omopariola OA. Effects of stigmatization/discrimination on antiretroviral therapy adherence among HIV-infected patients in a rural tertiary medical center in Nigeria. Journal of the International Association of Providers of AIDS Care (JIAPAC) 2014;13(3):260-63.
138. Adeneye AK, Adewole TA, Musa AZ, Onwujekwe D, Odunukwe NN, Araoyinbo ID, et al. Limitations to access and use of antiretroviral therapy (ART) among HIV positive persons in Lagos, Nigeria. World Health Popul. 2006;8(2):46-56.
139. Murray LK, Semrau K, McCurley E, Thea DM, Scott N, Mwiya M, et

al. Barriers to acceptance and adhere of antiretroviral therapy in urban Zambian women: qualitative study. AIDS Care 2009;21(1):78.
140. Oluwagbemiga AE. HIV/AIDS and family support systems: A situation analysis of people living with HIV/AIDS in Lagos State. SAHARA J (Journal of Social Aspects of HIV/AIDS Research Alliance) 2008;4(3):668-77.
141. Ambebir A, Woldemichael K, Getachew S, Girma B, Deribe K. Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in Southwest Ethiopia. BMC Public Health 2008;8(265):2458-65.
142. Scott K, Campbell C, Madanhire C, Skovdal M, Nyamukapa C, Gregson S. In what ways do communities support optimal antiretroviral treatment in Zimbabwe? Health promotion international 2014;29(4):645-54.
143. Idung AU, Udoh SB, Abasiubong F. Complimentary and alternative medicine use among HIV-infected patients on antiretroviral therapy in the Niger-Delta region, Nigeria. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 2014;13(1):26-31.
144. Ezechi OC, Gab-Okafor C, Onwujekwe DI, Adu RA, Amadi E, Herbertson E. Intimate partner violence and correlates in pregnant HIV positive Nigerians. Archives of gynecology and obstetrics 2009;280(5):745-52.
145. Iliyasu Z, Abubakar IS, Babashani M, Galadanci HS. Domestic violence among women living with HIV/AIDS in Kano, Northern Nigeria: original research article. African journal of reproductive health 2011;15(3):41-49.
146. Kiarie JN, Farquhar C, Richardson BA, Kabura BN, John FN, Nduati RW, John-Stewart GC. Domestic violence and prevention of mother-to-child transmission of HIV-1. AIDS 2006;20(13):1763–69.
147. Maman S, Mbwambo JK, Hogan NM, Kilonzo GP, Campbell JC, Weiss E, Sweat MD. HIV-positive women report more lifetime partner violence: findings from a voluntary counseling and testing clinic in Dar es Salaam, Tanzania. Am J Public Health 2002;92(8):1331–37.
148. Osinde MO, Kaye DK, Kakaire O. Intimate partner violence among women with HIV infection in rural Uganda: critical implications for policy and practice. BMC women's health 2011;11(1):50.
149. Antelman G, Fawzi MCS, Kaaya S, Mbwambo J, Msamanga GI, Hunter DJ, Fawzi WW. Predictors of HIV–1 serostatus disclosure: a prospective study among HIV-infected pregnant women in Dar es Salaam, Tanzania. AIDS 2001;15(14):1865–74.
150. Kissinger PJ, Niccolai LM, Magnus M, Farley TA, Maher JE,

Richardson-Alston G, et al. Partner notification for HIV and syphilis: effects on sexual behaviors and relationship stability. Sex Transm Dis. 2003;30(1):75–82.
151. Braitsein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. The Lancet 2006;367(9513):817–24.
152. Wandeler G, Keiser O, Pfeiffer K, Pestilli S, Fritz C, Labhardt ND, et al. Outcomes of antiretroviral treatment programs in rural Southern Africa. J Acquir Immune Defic Syndr.2012;59(2):9–16.
153. Lawn SD, Myer L, Harling F, Orrell C, Bekker LG, Wood R. Determinants of mortality and non death losses from an antiretroviral treatment service in South Africa: implications for program evaluation. Clin Infect Dis. 2006;43(6):770–76.
154. Rai S, Mahapatra B, Sircar S, Raj PY, Venkatesh S, Shaukat M, Rewari BB. Adherence to antiretroviral therapy and its effect on survival of HIV-infected individuals in Jharkhand, India. PloS one 2013;8(6):e66860.
155. Gay C, Portillo CJ, Kelly R, Coggins T, Davis H, Aouizerat BE, et al. Self-reported medication adherence and symptom experience in adults with HIV. Journal of the Association of Nurses in AIDS Care 2011;22(4):257-68.
156. Babson KA, Heinz AJ, Bonn-Miller MO. HIV medication adherence and HIV symptom severity: the roles of sleep quality and memory. AIDS Patient Care STDs 2013;27(10):544–52.
157. Robbins JL, Phillips KD, Dudgeon WD, Hand GA. Physiological and psychological correlates of sleep in HIV infection. Clin Nurs Res. 2004;13(1):33–52.
158. Hanass-Hancock J, Regondi I, van Egeraat L, Nixon S. HIV-related disability in HIV hyper-endemic countries: a scoping review. World Journal of AIDS 2013;3(3):257.
159. Nixon SA, Cameron C, Hanass-Hancock J, Simwaba P, Solomon PE, Bond VA, et al. Perceptions of HIV-related health services in Zambia for people with disabilities who are HIV-positive. Journal of the International AIDS Society 2014;17(1):18806.
160. "We Are Also Dying of AIDS" Barriers to HIV Services and Treatment for Persons with Disabilities in Zambia. Human Rights Watch. 2014 [cited 2014 Nov 5]. Available from: http://www.hrw.org/sites/default/files/reports/zambia0714_ForUpload_0.pdf
161. Haregu T, Oldenburg B, Sestwe G, Elliott J, Nanayakkara V. Epidemiology of Comorbidity of HIV/AIDS and Non-communicable

Diseases in Developing Countries: A systematic review. The Journal of Global Health Care Systems 2012;2(1):1-12.
162. Hirschhorn LR, Kaaya SF, Garrity PS, Chopyak E, Fawzi MCS. Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. AIDS 2012, 26 (1):65–75.
163. Nigatu T. Integration of HIV and noncommunicable diseases in health care delivery in low- and middle-income countries. Preventing Chronic Disease 2012;9:E93.
164. The antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1 infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis. 2010;50(10):1387-96.
165. Bendavid E, Ford N, Mills E. HIV and Africa's elderly: the problems and possibilities. AIDS 2012; 26(1):85-91.
166. Springer SA, Dushaj A, Azar MM. The Impact of DSM-IV Mental Disorders on Adherence to Combination Antiretroviral Therapy Among Adult Persons Living with HIV/AIDS: A Systematic Review. AIDS and Behavior 2012;16(8):2119–43.
167. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS Treatment Nonadherence: A Review and Meta-analysis. Journal of Acquired Immune Deficiency Syndromes 2011;58(2):181-87.
168. Malta M, Magnanini MM, Strathdee SA, Bastos FI. Adherence to antiretroviral therapy among HIV-infected drug users: a meta-analysis. AIDS and Behavior 2010;14(4):731-47.
169. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC. The Next Therapeutic Challenge in HIV: Polypharmacy. Drugs & aging 2013;30(8):613-28.
170. Maiese E, Malmenas M, Atkinson M. Impact of comorbidities on HIV medication persistence: a retrospective database study using US claims data. J Int AIDS Soc. 2012;15(6).
171. Monroe AK, Rowe TL, Moore RD, Chander G. Medication adherence in HIV-positive patients with diabetes or hypertension: a focus group study. BMC health services research 2013;13(1):488.
172. Cauldbeck M, O'Connor C, O'Connor M, Saunders J, Rao B, Mallesh V, et al. Adherence to antiretroviral therapy among HIV patients in Bangalore, India. AIDS Res Ther. 2009;6(7):1-8.
173. Glass TR, De Geest S, Weber R, Vernazza PL, Rickenbach M, Furrer H, et al. Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study. J Acquir Immune Defic Syndr. 2006;41(3):385–92.

174. Glass TR, Battegay M, Cavassini M, De Geest S, Furrer H, Vernazza PL, et al. The Swiss HIV cohort study. Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV Cohort Study. J Acq Immun Def Synd. 2010;54:197–203.
175. Frank I. Once-daily HAART: toward a new treatment paradigm. J Acq Immun Def. Synd. 2002;31:10-15.
176. Protopopescu C, Raffi F, Roux P, Reynes J, Dellamonica P, Spire B, et al. Factors associated with non-adherence to long-term highly active antiretroviral therapy: a 10-year follow-up analysis with correction for the bias induced by missing data. J. Antimicrob. Chemoth. 2009;64:599–606.
177. Mukherjee JS, Ivers L, Leandre F, Farmer P, Behforouz H. Antiretroviral therapy in resource-poor settings: Decreasing barriers to access and promoting adherence. J. Acq. Immun. Def. Synd. 2006;43:123-26.
178. Roca B, Lapuebula C, Vidal-Tregedor B. HAART with didanosine once versus twice daily: adherence and efficacy. Int J Infect Dis. 2005;9(4):195–200.
179. Jean-Baptiste R. Factors Associated with Adherence to Antiretroviral Therapy in Rwanda: A Multi-site Study. 2008 [cited 2014 Nov 20]. Available from: http://pdf.usaid.gov/pdf_docs/PNADN461.pdf
180. Van Galen KA, Nellen JF, Nieuwkerk PT. The Effect on Treatment Adherence of Administering Drugs as Fixed-Dose Combinations versus as Separate Pills: Systematic Review and Meta-Analysis. AIDS research and treatment 2014.
181. Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. AIDS and Behavior 2011;15(8):1803-18.
182. Kyajja R, Muliira JK, Ayebare E. Personal coping strategies for managing the side effects of antiretroviral therapy among patients at an HIV/AIDS clinic in Uganda. Afr J AIDS Res. 2010;9(3):205-11.
183. Ammassari A, Murri R, Pezzotti P, Trotta MP, Ravasio L, De Longis P, et al. Self reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr 2001;28(5):445–49.
184. Agu KA, Oparah AC, Ochei UM. Assessment of side effects coping practices of HIV-infected patients receiving antiretroviral therapy. Pharmacoepidemiology and drug safety 2012;21(12):1302-10.
185. Chesney MA. Factors affecting adherence to antiretroviral therapy. Clinical Infectious Diseases 2000; 30(2):171-176.

186. Ha JF, Longnecker N. Doctor-patient communication: a review. The Ochsner Journal 2010;10(1):38-43.
187. Stone VE, Clarke J, Lovell J, Steger KA, Hirschhorn LR, Boswell S, et al. HIV/AIDS patients' perspectives on adhering to regimens containing protease inhibitors. J Gen Intern Med 1998;13(9):586-593.
188. Osungbade KO, Shaahu VN, Owoaje EE, Adedokun BO. Patients' Satisfaction with Quality of Anti-Retroviral Services in Central Nigeria: Implications for Strengthening Private Health Services. Journal of Preventive Medicine 2013;1(3):11-18.
189. Sahay S, Reddy KS, Dhayarkar S. Optimizing adherence to antiretroviral therapy. The Indian journal of medical research 2011;134(6):835-49.
190. Reis C, Heisler M, Amowitz LL, Moreland RS, Mafeni JO, Anyamele C, Iacopino, V. Discriminatory attitudes and practices by health workers toward patients with HIV/AIDS in Nigeria. PLoS medicine 2005;2(8):246.
191. Umar AS, Oche MO, Adeoso AA. Discriminatory practices of health workers towards people living with HIV/AIDS in Sokoto, Nigeria. Journal of AIDS and HIV Research 2012;4(9):223-28.
192. Adebajo SB, Bamgbala AO, Oyediran MA. Attitudes of health care providers to persons living with HIV/AIDS in Lagos State, Nigeria. African journal of reproductive health 2003;7(1):103-12.
193. Skovdal M, Campbell C, Nhongo K, Nyamukapa C, Gregson S. Contextual and psychosocial influences on antiretroviral therapy adherence in rural Zimbabwe: towards a systematic framework for programme planners. International Journal of Health Planning and Management 2011;26(3):296–318.
194. Wouters E, Heunis C, van Rensburg D, Meulemans H. Patient satisfaction with antiretroviral services at primary health-care facilities in the Free State, South Africa-a two-year study using four waves of cross-sectional data. BMC Health Services Research 2008;8:210.
195. Thobias A. Exploration of factors associated with poor adherence among patients receiving antiretroviral therapy at Katutura State hospital communicable disease clinic in Khomas region in Namibia. [Master in Public Health thesis]. University of Western Cape. 2008 [cited 2014 November 15]. Available from: http://etd.uwc.ac.za/xmlui/handle/11394/2764
196. de Wet K, Wouters E, Engelbrecht M. Exploring task-shifting practices in antiretroviral treatment facilities in the Free State Province, South Africa. Journal of public health policy 2011;32:94-

101.
197. Wasti SP, Simkhada P, Randall J, Freeman JV, Van Teijlingen E. Factors influencing adherence to antiretroviral treatment in Nepal: a mixed-methods study. PloS one 2012;7(5):e35547.
198. Holstad MM, Essien EJ, Ekong E, Higgins M, Teplinskiy I, Adewuyi MF. Motivational groups support adherence to antiretroviral therapy and use of risk reduction behaviors in HIV positive Nigerian women: a pilot study. African journal of reproductive health 2012;16(3).
199. Taiwo BO, Idoko JA, Welty LJ, Otoh I, Job G, Iyaji PG, et al. Assessing the virologic and adherence benefits of patient-selected HIV treatment partners in a resource-limited setting. J Acquir Immune Defic Syndr. 2010;54(1):85–92.
200. Idoko JA, Agbaji O, Agaba P, Akolo C, Inuwa B, Hassan Z, et al. Direct observation therapy highly active antiretroviral therapy in a resource-limited setting: the use of community treatment support can be effective. Int J STD AIDS. 2007;18(11):760–63.
201. Busari O, Busari O, Oligbu G, Ashom D, Adeyemi A. HIV Study Group. Novel structured teaching of HIV patients in resource-limiting setting: effect of learning outcomes on adherence to HAART and immunological recovery. 17th Conference on Retroviruses and Opportunistic Infections; 2010 February 16-19; San Francisco, USA.
202. Busari O, Oligbu G, Busari O, Asham D, Adeyemi A. Effect of structured systematic (modular) teaching of HIV/AIDS patients on adherence to antiretroviral therapy (HAART): Report from a national HIV/AIDS treatment center in sub-Saharan Africa. 4th Annual HIV Treatment Adherence Conference of the International Association of Providers in AIDS Care; 2009 April 5-7; Miami, FL.
203. Udo DU, Itah A, Udofia UA. Promoting ART adherence and compliance through family and peer group support initiative. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2007 July 22–25; Sydney, Australia.
204. Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. *BMJ open 2013*;*3*(8):e002749.
205. Adherence to Antiretroviral Therapy in Adults: A Guide for Trainers. Nairobi: Population Council. 2004 [cited 2014 Dec 15]. Available from: http://www.popcouncil.org/uploads/pdfs/horizons/mombasaarvtrainingguide.pdf
206. Chung MH, Richardson BA, Tapia K, Benki-Nugent S, Kiarie JN, Simoni JM, et al. A Randomized Controlled Trial Comparing the

Effects of Counseling and Alarm Device on HAART Adherence and Virologic Outcomes. PLoS Medicine 2011;8(3):e1000422.
207. Mills EJ, Lester R, Thorlund K, Lorenzi M, Muldoon K, Kanters S, et al. Interventions to promote adherence to antiretroviral therapy in Africa: a network meta-analysis. The Lancet HIV 2014;1(3):e104-e111.
208. Hansana V, Sanchaisuriya P, Durham J, Sychareun V, Chaleunvong K, Boonyaleepun S, Schelp FP. Adherence to Antiretroviral Therapy (ART) among People Living With HIV (PLHIV): a cross-sectional survey to measure in Lao PDR. BMC public health 2013,13(1):617.
209. Ogunbanjo GA, Heyer A. Adherence to HIV Antiretrovirul therapy part II: which interventions are effective in improving adherence? Open forum. South African Family Practice 2006, 48(9):6-11.
210. Patel V. Araya R, Chatterjee S, Chisholm D, Cohen A, De Silva M, et al. Treatment and prevention of mental disorders in low-income and middle-income countries. The Lancet 2007;370(9591):991-1005.
211. Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Annals of Behavioral Medicine 2014*;*47*(3):259-69.
212. Bottonari KA, Tripathi SP, Fortney JC, Curran G, Rimland D, Rodriguez-Barradas M, et al. Correlates of antiretroviral and antidepressant adherence among depressed HIV-infected patients. AIDS patient care and STDs. 2012, 26(5):265-73.
213. Bolton P, Bass J, Neugebauer R, Verdeli H, Clougherty KF, Wickramaratne P, et al. Group Interpersonal Psychotherapy for Depression in Rural Uganda: A Randomized Controlled Trial. Journal of the American Medical Association 2003;289(23):3117-24.
214. Verdeli H, Clougherty K, Bolton P, Speelman L, Lincoln N, Bass J, et al. Adapting group interpersonal psychotherapy for a developing country: experience in rural Uganda. World Psychiatry 2003;2(2):114.
215. Dalessandro M, Conti CM, Gambi F, Falasca K, Doyle R, Conti P, et al. Antidepressant therapy can improve adherence to antiretroviral regimens among HIV-infected and depressed patients. Journal of Clinical Psychopharmacology 2007;27(1):58-61.
216. Crepaz N, Passin WF, Herbst JH, Rama SM, Malow RM, Purcell DW, Wolitski RJ. Meta-analysis of cognitive-behavioral interventions on HIV-positive persons' mental health and immune functioning. Health Psychology 2008;27(1):4.
217. Sarna A, Luchters S, Geibel S, Chersich MF, Munyao P, Kaai S, et al. Short-and long-term efficacy of modified directly observed

antiretroviral treatment in Mombasa, Kenya: a randomized trial. J Acquir Immune Defic Syndr. 2008;48(5):611–19.
218. Pearson CR, Micek MA, Simoni JM, Hoff PD, Matediana E, Martin DP, et al. Randomized control trial of peer-delivered, modified directly observed therapy for HAART in Mozambique. J Acquir Immune Defic Syndr. 2007; 46(2):238–44.
219. Nachega JB, Chaisson RE, Goliath R, Efron A, Chaudhary MA, Ram M, et al. Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy. AIDS. 2010; 24(9):1273–80.
220. Ford N, Nachega JB, Engel ME, Mills EJ. Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials. The Lancet 2009;374:2064–71.
221. Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, Shin SS. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. J Acquir Immune Defic Syndr. 2010;54(2):167-79.
222. Scanlon ML, Vreeman RC. Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIV/AIDS (Auckland, NZ) 2013;5:1.
223. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. The Cochrane database of systematic reviews 2012;3:CD009756.
224. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, DeWalque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS. 2011;25(6):825–34.
225. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. The Lancet 2010;376(9755):1838–45.
226. Uzma Q, Emmanuel F, Ather U, Zaman S. Efficacy of Interventions for Improving Antiretroviral Therapy Adherence in HIV/AIDS Cases at PIMS, Islamabad. *J Int Assoc Physicians AIDS Care (Chic).* 2011;10(6):373–83.
227. Chang LW, Kagaayi J, Arem H, Nakigozi G, Ssempija V, Serwadda D, et al. Impact of a mHealth intervention for peer health workers on AIDS care in rural Uganda: a mixed methods evaluation of a cluster-randomized trial. *AIDS Behav.* 2011;15(8):1776–84.

228. Huang D, Sangthong R, McNeil E, Chongsuvivatwong V, Zheng W, Yang X. Effects of a Phone Call Intervention to Promote Adherence to Antiretroviral Therapy and Quality of Life of HIV/AIDS Patients in Baoshan, China: A Randomized Controlled Trial. AIDS Research and Treatment 2013.
229. Mbuagbaw L, Thabane L, Ongolo-Zogo P, Lester RT, Mills EJ, Smieja M, et al. The Cameroon Mobile Phone SMS (CAMPS) trial: a randomized trial of text messaging versus usual care for adherence to antiretroviral therapy. PLoS One 2012;7(12):e46909.
230. Da Costa TM, Barbosa BJ, Gomes e Costa DA, Sigulem D, de Fatima Marin H, Filho AC, et al. Results of a randomized controlled trial to assess the effects of a mobile SMS-based intervention on treatment adherence in HIV/AIDS-infected Brazilian women and impressions and satisfaction with respect to incoming messages. Int J Med Inform. 2012;81(4):257-69.
231. Rodrigues R, Shet A, Antony J, Sidney K, Arumugam K, Krishnamurthy S, et al. Supporting adherence to antiretroviral therapy with mobile phone reminders: results from a cohort in South India. PLoS One 2012; 7(8):e40723.
232. Shet A, De Costa A, Kumarasamy N, Rodrigues R, Rewari BB, Ashorn P, et al. Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India. BMJ. 2014;349:g5978.
233. Roux SM. Diary cards: preliminary evaluation of an intervention tool for improving adherence to antiretroviral therapy and TB preventive therapy in people living with HIV/AIDS [MPH thesis]. University of the Western Cape; 2004 [cited 2014 December 10]. Available from: http://etd.uwc.ac.za/xmlui/bitstream/handle/11394/1840/Roux_MPH_2004.pdf?sequence=1
234. Serrano C, Laporte R, Ide M, Nouhou Y, De Truchis P, Rouveix E, et al. Family nutritional support improves survival, immune restoration and adherence in HIV patients receiving ART in developing country. Asia Pacific journal of clinical nutrition 2010;19(1):68.
235. Cantrell RA, Sinkala M, Megazinni K, Lawson-Marriott S, Washington S, Chi BH, et al. A pilot study of food supplementation to improve adherence to antiretroviral therapy among food insecure adults in Lusaka, Zambia. *J Acquir Immune Defic Syndr.* 2008;49(2):190–95.
236. Ndekha M, van Oosterhout JJ, Saloojee H, Pettifor J, Manary M. Nutritional status of Malawian adults on antiretroviral therapy 1 year after supplementary feeding in the first 3 months of therapy. Trop Med Int Health. 2009;14(9):1059–63.

237. Ndekha MJ, van Oosterhout JJ, Zijlstra EE, Manary M, Saloojee H, Manary MJ. Supplementary feeding with either ready-to-use fortified spread or corn-soy blend in wasted adults starting antiretroviral therapy in Malawi: randomised, investigator blinded, controlled trial. BMJ. 2009;1309-12.
238. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: A meta-analysis. Clin Infect Dis. 2009; 48:484–88.
239. Kauf TL, Davis KL, Earnshaw SR, Davis EA. Spillover adherence effects of fixed-dose combination HIV therapy. Patient Preference and Adherence 2012;6:155-64.
240. Harries AD, Zachariah R, Lawn SD, Rosen S. Strategies to improve patient retention on antiretroviral therapy in sub-Saharan Africa. Trop Med Int Health. 2010;15:70–75.
241. Chaiyachati KH, Ogbuoji O, Price M, Suthar AB, Negussie EK, Bärnighausen T. Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. AIDS 2014;28(2):187-204.
242. Beith A, Johnson A. Interventions to Improve Adherence to Antiretroviral Therapy: A Review of the Evidence. 2006 [cited 2014 Dec 15]. Available from: http://pdf.usaid.gov/pdf_docs/Pnadg527.pdf
243. Rueda S, Park-Wyllie LY, Bayoumi AM, Tynan AM, Antoniou T, Rourke S, et al. Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. Cochrane Database Syst Rev. 2006:CD00144.
244. Skhosana NL, Struthers H, Gray GE, McIntyre JA. HIV disclosure and other factors that impact on adherence to antiretroviral therapy: the case of Soweto, South Africa. African Journal of AIDS Research 2006;5(1):17-26.
245. Biadgilign S, Deribew A, Amberbir A, Deribe K. Barriers and facilitators to antiretroviral medication adherence among HIV-infected paediatric patients in Ethiopia: A qualitative study. SAHARA J (Journal of Social Aspects of HIV/AIDS Research Alliance) 2009;6(4).
246. Kabore I, Bloem J, Etheredge G, Obiero W, Wanless S, Doykos P, et al. The Effect of Community-Based Support Services on Clinical Efficacy and Health-Related Quality of Life in HIV/AIDS Patients in Resource-Limited Settings in Sub-Saharan Africa. AIDS Patient Care STDS. 2010;24(9):581-94.
247. Kipp W, Konde-Lule J, Rubaale T, Okech-Ojony J, Alibhai A, Saunders DL. Comparing antiretroviral treatment outcomes

between a prospective community-based and hospital-based cohort of HIV patients in rural Uganda. BMC International Health and Human Rights 2011;11(2):12.
248. Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Antiretroviral Treatment for HIV in Rural Uganda: Two-Year Treatment Outcomes of a Prospective Health Centre/Community-Based and Hospital-Based Cohort. PLoS One, 2012;7(7):e40902.
249. Weidle PJ, Wamai N, Solberg P, Liechty C, Sendagala S, Were W, et al. Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda. The Lancet 2006, 368(9547):1587-94.
250. Jaffar S, Amurron B, Foster S, Birungi J, Levin J, Namara G, et al. Rates of virological failure in patients treated in a home-based versus a facility- based HIV care model in Jinja, southeast Uganda: a cluster-randomized equivalence trial. The Lancet 2009;374(9707):2080-89.
251. Abaasa A, Todd J, Ekoru K, Kalyango J, Levin J, Odeke E, Karamagi C. Good adherence to HAART and improved survival in a community HIV/AIDS treatment and care programme: the experience of The AIDS Support Organization (TASO), Kampala, Uganda. BMC Health Services Research 2008;8(1):241.
252. Mermin J, Were W, Ekwaru JP, Moore D, Downing R, Behumbiize P, et al. Mortality in HIV-infected Ugandan adults receiving antiretroviral treatment and survival of their HIV-uninfected children: a prospective cohort study. The Lancet 2008;371(9614):752–59.
253. Wools-Kaloustian KK, Sidle JE, Selke HM, Vedanthan R, Kemboi EK, Biot LJ, et al. A model for extending antiretroviral care beyond the rural health centre. Journal of the International AIDS Society 2009;12(1):22.
254. Root R, Whiteside A. A qualitative study of community home-based care and antiretroviral adherence in Swaziland. Journal of the International AIDS Society 2013;16(1).
255. Birbeck GL, Chombo E, Kvalsund M, Bradbury R, Mang'ombe C, Malama K, et al. Antiretroviral adherence in rural Zambia: the first year of treatment availability. J Trop Med Hyg. 2009;80(4):669-74.
256. Kunutsor S, Walley J, Katabira E, Muchuro S, Balidawa H, Namagala E, Ikoona E. Improving Clinic Attendance and Adherence to Antiretroviral Therapy Through a Treatment Supporter Intervention in Uganda: A Randomized Controlled Trial. AIDS and Behaviour 2011;15(8)1795-1802.
257. Mannheimer SB, Morse E, Matts JP, Andrews L, Child C, Schmetter B, Friedland GH. Sustained benefit from a long-term antiretroviral

adherence intervention: results of a large randomized clinical trial, J Aquir Immune Defic Syndr. 2006;43:41-47.
258. Chang LW, Kagaayi J, Nakigozi G, Ssempijja V, Packer AH, Serwadda D, et al. Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial. PloS one 2010;5(6):e10923.
259. Zuyderduin JR, Ehlers VJ, van der Wal DM. The impact of a buddy system on the self-care behaviours of women living with HIV/AIDS in Botswana. Health SA Gesondheid 2008;13(4):4–15
260. Mugusi F, Mugusi S, Bakari M, Hejdemann B, Josiah R, Janabi M, et al. Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience. Trop Med Int Health. 2009;14(10):1226–1232.
261. Tenthani L, Haas A, Tweya H, Jahn A, van Oosterhout J, Chimbwandira F, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('Option B+') in Malawi. AIDS. 2014;28(4):589–98.
262. Shaffer N, Abrams EJ, Becquet R. Option B+ for prevention of mother-tochild transmission of HIV in resource-constrained settings: great promise but some early caution. AIDS. 2014;28(4):599–601.
263. Ahmed S, Kim MH, Abrams EJ. Risks and benefits of lifelong antiretroviral treatment for pregnant and breastfeeding women: a review of the evidence for the Option B+ approach. Curr Opin HIV AIDS 2013; 8:474–489. 85.
264. Agbo-Paul A. PLWHA Sell ARV Drugs In Benue Black Market. Leadership [Internet]. 2014 Jan 18 [cited 2015 Jan 20]. Available from: http://leadership.ng/news/338774/plwha-sell-arv-drugs-in-benue-black-market.
265. Oladapo O. Activism creates real hope of change for Nigerian people living with HIV [Internet]. GNP+. 2013 Dec 10 [cited 2015 Jan 20]. Available from: http://www.gnpplus.net/activism-creates-hope/.
266. Onwujekwe O, Dike N, Chukwuka C, Uzochukwu B, Onyedum C, Onoka C, Ichoku H. Examining catastrophic costs and benefit incidence of subsidized antiretroviral treatment (ART) programme in south-east Nigeria. Health Policy 2009;90(2):223-229.
267. Okonkwo P, Sagay AS, Agaba PA, Yohanna S, Agbaji OO, Imade GE, et al. Treatment Outcomes in a Decentralized Antiretroviral Therapy Program: A Comparison of Two Levels of Care in North Central Nigeria. AIDS research and treatment 2014;560623.
268. Obembe TA, Osungbade KO, Olumide EA, Ibrahim CM, Fawole OI. Staffing situation of primary health care facilities in Federal Capital

Territory, Nigeria: implication for attraction and retention policies. Am J Soc Mgmt. Sci. 2014;5(2):84-90.
269. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. PLoS medicine 2013;10(9):e1001511.
270. Psaros C, Haberer JE, Katabira E, Ronald A, Tumwesigye E, Campbell JD, et al. An Intervention to Support HIV Preexposure Prophylaxis Adherence in HIV-Serodiscordant Couples in Uganda. JAIDS Journal of Acquired Immune Deficiency Syndromes 2014;66(5):522-29.
271. Sendagala S. Factors affecting the adherence to antiretroviral therapy by HIV-positive patients treated in a community based HIV/AIDS care programme in rural Uganda: a case of Tororo district [MPH thesis]. University of South Africa 2010. [cited 2014 October 11] Available from: http://uir.unisa.ac.za/bitstream/handle/10500/5356/Sondagala_s.pdf?sequence=1
272. Nieuwkerk PT, Oort FJ. Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis. Journal of Acquired Immune Deficiency Syndrome 2005;38(4):445-48.
273. Oyugi JH, Byakika-Tusiime J, Charlebois ED, Kityo C, Mugerwa R, Mugyenyi P, Bangsberg DR. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. J. Acq. Immun. Def. Synd. 2004;36(5):1100–02.
274. Kouanfack C, Laurent C, Peytavin G, Ciaffi L, Ngolle M, Nkene YM, et al. Adherence to antiretroviral therapy assessed by drug level monitoring and self-reports in Cameroon. J. Acq. Immun. Def. Synd. 2008;48(2):216–19.
275. Bangsberg DR, Hecht FM, Charlebois ED, Chesney M, Moss A. Comparing objective measures of adherence to HIV antiretroviral therapy: electronic monitors and unannounced pill counts. AIDS and Behaviour 2001;5(3):275-81.
276. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J. Acq. Immun. Def. Synd. 2006;43(1):78–84.
277. Rougemont M, Stoll B, Elia N, Ngang P. Antiretroviral treatment adherence and its determinants in Sub-Saharan Africa: A prospective study at Yaoundé central hospital, Cameroon. AIDS

Res. Ther. 2009;6(21):6405-6.
278. Inciardi JF, Leeds AL. Assessing the utility of a community pharmacy refill records as a measure of adherence and viral load response in patients infected with human immunodeficiency virus. Pharmacotherapy 2005;25(6):790-96.
279. Ross-Degnan D, Pierre-Jacques M, Zhang F, Tadeg H, Gitau L, Ntaganira J, et al. Measuring adherence to antiretroviral treatment in resource poor settings: the clinical validity of key indicators. BMC Health Serv. Res. 2010;10(1):42.
280. Low-Beer S, Yip B, O'Shaughnessy MV, Hoggs RS, Montaner JSG. Adherence to triple therapy and viral load response. Journal of Acquired Immune Deficiency Syndrome 2000; 23(4):360-61.
281. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. Journal of Clinical Epidemiology 2004; 57(10):1107-10.
282. Arnsten JH, Demas PA, Farzadegan H, Grant RW, Gourevitch MN, Chang CJ, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. Clinical Infectious Diseases 2001;33(8):1417-23.
283. McNabb JJ, Nicolau DP, Stoner JA, Ross J. Patterns of adherence to antiretroviral medications: the value of electronic monitoring. AIDS 2003;17(12):1763-67.
284. Bova CA, Fennie KP, Knafl GJ, Dieckhaus KD, Watrous E, Williams B. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. AIDS and Behaviour 2005;9(1):103-10.
285. Liechty CA, Alexander CS, Harrigan R, Guzman JD, Charlebois ED, Moss AR, Bangsberg DR. Are untimed antiretroviral drug levels useful predictors of adherence behaviour? AIDS 2004;18(1):127-29.
286. San Lio MM, Carbini R, Germano P, Guidotti G, Mancinelli S, Magid NA, et al. Evaluation of adherence to highly active antiretroviral therapy with use of pills counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique. Clin. Infect. Dis. 2008;46(10):1609–16.

ANNEX 1.

Basic Indicators (2012 & 2013)	
Under-5 mortality rate (per 1000 live births), 2012	124
Infant mortality rate (under 1, per 1000 live births), 2013	72.97
Neonatal mortality rate (per 1000 live births), 2013	46
Annual number of births (thousands), 2013	31828
Annual number of under-5 deaths (thousands), 2013	861
Maternal Mortality Ratio (per 100,000 live births), 2013	560
Total fertility rate (per woman), 2012	6
Life expectancy at birth (years), 2012	54
Crude birth rate (per 1000 population), 2012	41.5
Crude death rate (per 1000 population), 2012	12.3

Table 2. Nigerian Health Indicators. Source: GARPR report [2] & WHO [24]

ANNEX 2.

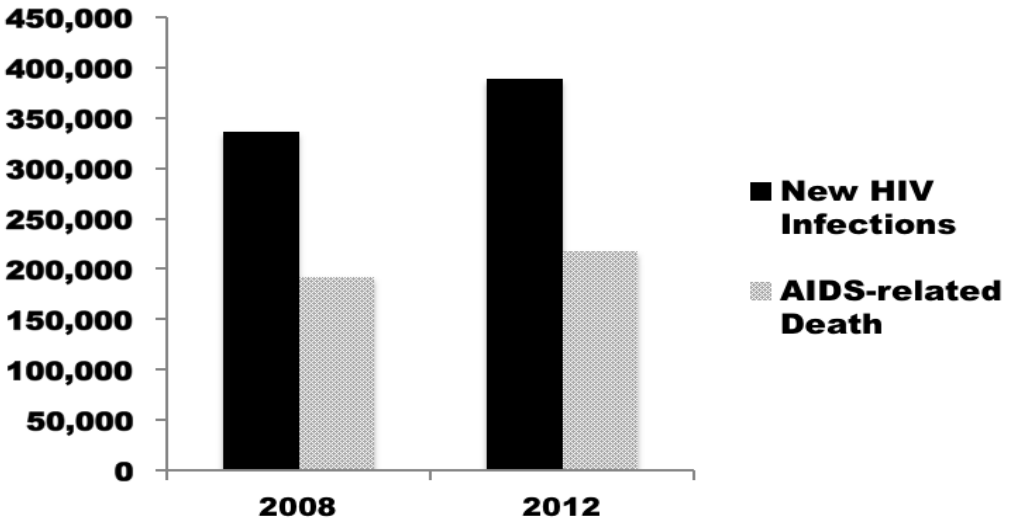

Figure 5. New HIV Infections and AIDS-related Death between 2008-2012. Source: GARPR Report [29]

ANNEX 3.

Summary of ART Adherence Studies done in Nigeria (2004-2014)

Author, Year & Reference	Geopolitical Zone	Study Design and Methodology	Number of Study Participants	Assessment Method	Adherence rate %	Additional notes/Comments
Okoronkwo et al. [75]	South East	Cross-sectional Study	221	Self-report and pill counting	14.9%	Based on 30-day recall. Validated questionnaire (ARTNa-SDCQ) used.
Uzochukwu et al. [76]	South East	Cross-sectional Study	174	Self-report	24.7%	Based on 30-day (one-month) recall. 75.3% (non-adherence rate)
Onyeonoro et al. [77]	South East	Cross-sectional Study	282	Self-report	86%	Based on 7-day (one-week) recall
Ukwe et al. [78]	South East	Prospective study (with structured questionnaire)	299	Self-report	86.1%	Based 3, 5 and 7-day (one week) recall (assessed at baseline, 4, 8 and 12 weeks).
Igwegbe et al. [79]	South East	Cross-sectional Study	368	Self-report	78.3%	Based on 30-day (one-month) recall. Study was conducted among pregnant women
Ekwunife et al. [80]	South East	Cohort study	212	Self-report	89.4% (non-CAM users) 82.5% (CAM users)	Based on MMA scale. Significant reduction in CAM users (p=0.01)
Nwankwo et al. [81]	South East	Cross-sectional study	318	Self-report	**68%***	Only 13.2% never missed a dose. While, about 72% missed medication doses more than twice a month.
Nwauche et al. [82]	South South	Cross-sectional Study	187	Self-report	49.2%	Threshold for measurement not provided in study
Oku et al. [83]	South South	Cross-sectional Study	393	Self-report	50.4%	Based on 7-day (one-week) recall
Oku et al. [84]	South South	Cross-sectional Study	411	Self-report	59.9%	Based on 7-day (one-week) recall
Oku et al. [85]	South South	Cross-sectional Study	282	Self-report	59.6%	Based on 7-day (one-week) recall. Study participants were only non-pregnant women.
Erah and Arute [86]	South South	Prospective study (with structured questionnaire)	102	Self report and pill counting	58.1%	Based on 1, 7 (one-week) and 30-day (one-month) recall. Non-adherence was defined as a 2-week treatment gap
Agu et al. [87]	South South	Retrospective assessment/analysis	196	Self-report	73.8%	69 study participants still on treatment were selected for follow-up adherence assessment
Asekomeh et al. [88]	South South	Cross-sectional study	187	Self-report	72.7%	Based on 30-day (one-month) recall. GHQ-12 used to assess depressive symptoms
Afolabi et al. [89]	South-West	Cross-sectional study, FGD and ethnographic data (2 treatment centres)	120	Self-report	44%	Based on 7-day (one-week) recall. Ethnographic data revealed higher adherence among respondents in Ilesha receiving free ART drugs and support (psychosocial counselling) services compared to Ile-Ife where this was not available.
Afolabi et al. [90]	South-West	Cross-sectional Study	379	Self-report	95.5%	Perceived Social Support Family Scale and Family APGAR Scales were used to determine family dynamics and social support for PLHIV
Olowookere et al. [91]	South-West	Cross-sectional Study	318	Self-report and pharmacy refills	62.9%	Based on 7-day (one-week) recall

Olowookere et al. [92]	South-West	Cross-sectional Study	318	Self-report and pharmacy pick-up data	62.9%	Based on 7-day (one-week) recall. Study focused on the association of adherence with knowledge and attitudes about HIV/AIDS, ART, and experience of stigma.
Ogundahunsi et al. [93]	South-West	Cross-sectional Study	53	Self-report	79.2%	Based on 7-day (one-week) recall
Daniel et al. [94]	South-West	Prospective cohort study	100	Self-report	46%	Based on patient monthly follow-up (i.e. those who miss monthly clinic appointment). Follow up done by community health extension workers (CHEW).
Ekama et al. [95]	South-West	Cross-sectional Study	170	Self-report	80.6%	Based on 3-day recall. Study conducted among pregnant women
Adewuya et al. [96]	South-West	Cross-sectional Study	182	Self-report	26.9%	Based on Morisky Medication Adherence (MMA) questionnaire (classifying into low, medium and high)
Sekoni et al. [97]	South-West	Cross-sectional Study	200	Self-report	89.4%	Based on 7-day (one-week) recall, FGD and questionnaire administered to assess domains of stigma
Kasumu and Balogun [98]	South-West	Cross-sectional Study	361	Self-report	78.4%	
Idigbe et al. [99]	South-West	Prospective observational cohort study	50	Self-report	>85%	Based on periods between clinic appointments. Recall was matched with biological markers (CD4 count, viral load monitoring, BMI, prevalence/frequency of opportunistic infections).
Agu et al [100]	North-West	Longitudinal study	297	Pill counting	83.4%**	Mean percentage of adherence was used and matched with CD4 response. Study done over 24 months.
Olisah et al. [101]	North-West	Cross-sectional Study	310	Self-report	73%	Poor adherence was significantly higher in participants with depressive disorder (63.6% vs. 21.1% in control group, $p<0.05$). CES-D and SCAN was used to screen and confirm depression
Habib et al. [102]	North-West	Longitudinal Study	243	Self-report	FT: 95.8% NFT: 98%	Based on recall before and after the Muslim Ramadan fasting period (including customary practices). No significant change in adherence levels before and during fasting. FT: 80% overall. NFT: 88% overall. Relationship between factors and ART adherence not assessed.
Habib et al. [103]	North-West	Cross-sectional Study	58	Self-report	NA	Higher poor adherence and ART failure among Hajj pilgrims compared to non-Hajj pilgrims
Iliyasu et al. [104]	North-West	Cross-sectional study	263	Self-report	54% (>80% adherent) 23.2% (100% adherent)	Based on 7-day (one-week) recall
Pennap et al. [105]	North-Central	Cross-sectional Study	250	Self-report	62.8%	Based on 7-day (one-week) recall
Bello et al. [106]	North-Central	Cross-sectional Study	213	Self-report and pill counting	SR: 73.2% PC: 70.9%	Based on 30-day (one-week) recall
Shittu et al. [107]	North-Central	Cross-sectional Study	170	Self-report	81%	CAGE, ISMI and PHQ-9 were used to elicit mental health problems in PLHIV
Falang et al. [108]	North-Central	Cross-sectional Study	461	Self-report	87.9%	Questionnaire administered

Salami et al. [109]	North-Central	Cross-sectional Study	253	Self-report	70.8%	Based on 30-day (one-month) recall
Shaahu et al. [110]	North-Central	Cross-sectional Study	428	Self-report	62.6%	Based on duration from onset of treatment to time of study on individual patient basis
Agu et al. [111]	FCT/North Central	Cross-sectional Study	118	Self-report and medication refill visit	79.1%**	Mean percentage of adherence was used
Farley et al. [112]	FCT/North Central	Cross-sectional Study	399	Pharmacy-refill record	89.6% (>95% PRR)	Elevated CES-D was associated with poor adherence. No association between AUDIT scores and pharmacy refill rate.
Mohammed and Sarki [113]	FCT/North Central	Cross-sectional Study	110	Self-report	≥95%	Based on 30-day (one-month) recall. Study on compliance to dosage and timing
Charurat et al. [58]	NA	Retrospective analysis	4529	Pharmacy refill record	74.2% (less than 95%)	5 large ART programs (tertiary level)

***Studies conducted between 2004-2014
****Study population ranged from men and women, women, pregnant women and depressed PLHIV
*****Age group (mean) of study participants in majority of the studies identified was below 50 years.

ABBREVIATIONS

*: Adherence rate queried
**: Mean percentage of adherence
ARTNa-SDCQ: ART non-adherence and socio-demographic characteristics questionnaire
CAM: Complimentary and Alternative Medicine
CG: Control group
FT: Fasting
IG: Intervention group
ISMI: Internalized Stigma of Mental Illness Scale
MMA: Morisky Medication Adherence
NFT: Non-fasting
PC: Pill count
PHQ-9: Patient Health Questionnaire
PRR: Pharmacy refill record
SCAN: Schedule for Clinical Assessment in Neuropsychiatry
SR: Self report

ANNEX 4.

Summary of ART Adherence Intervention Studies done in Nigeria

Reference	Geopolitical Zone	Study Design and Methodology	Number of Study Participants	Length of Study (Months)	Adherence Assessment Method	Intervention	Adherence rate %	Additional notes/Comments
Holstad et al. [192]	South-West	Quasi-Experimental (Pilot study)	60	6	Self-report	Motivational Interviewing	MI: 93% HPP: 77.8%	1. AGAS: 93% in MI group versus 77.8% for HPP group (MW Z =−3.581, p<0.001). 2. Single item adherence question: 93% (MI group) reported not missing medications versus 40% in HPP group (χ^2=15.777, df=1, p < .0001). 3. ACTG Reasons for Missing Medications score: 40.8 in MI group vs. 35.2 in HPP group) (MW Z = -3.072, p=0.002). 4. Significantly higher mean HIVKQ-18 knowledge scores in MI group: 83.7% correct vs. 74.7% (Z = −2.394, p = 0.017).
Taiwo et al. [193]	North-Central	RCT	499	12	Self-report	Treatment supporter and DOT/DAART	24 weeks TPA: 88.7% SOC: 72.1% (OR 3.06, p<0.01) 48 weeks TPA: 80.2% SOC: 67.3% (OR 1.95, p<0.01)	LTFU: 10%
Idoko et al. [194]	North-Central	Cohort Study, Direct Observational Study	175	12	Family and/or community members	DOT, TWOT, WOT	Undetectable Plasma Viral load (48 weeks): DOT: 91% TWOT: 88% WOT: 84% SAT: 79%	Based on outcomes of 4 groups observed over 1 year (DOT, TWOT, WOT and SAT)
Ukwe et al. [73]	South-East	Prospective study (with structured questionnaire)	299	3	Self-report	Pillboxes (Reminder)	86.1%	Use of pillboxes as adherence aid was significantly associated with increased adherence (r=0.22, p<0.001).
Busari et al [195]	NA	RCT	620	8	NA	10 structured education modules	Mean adherence rate IG: 99% CG: 88% (p<0.001)	CD4 cell count: 238 cell/mm^3 (IG) versus 141 cell/mm^3 (CG), p<0.001. Hospitalization rate lower in IG compared to CG

Busari et al [196]	NA	RCT	420	8	NA	10 structured education modules	Mean adherence rate IG: 99% CG: 88% (p<0.001)	Lower mortality (p=0.008) and rate of hospitalization in IG versus CG
Maduka and Tobin-West [13]	South-South*	RCT	104	4	Self-report	Monthly counselling and twice-weekly SMS	76.9% (IG) 55.8% (CG)	
Udo et al. [197]	South-East	NA	150	NA	NA	Treatment supporters (family and peers)	NA	Increase in study participants adhering to ART on time (80%) from 43% (baseline)

ABBREVIATIONS

*Based on authors' research institution

AGAS: Antiretroviral General Adherence Scale

CG: Control Group

HIVKQ-18: HIV Knowledge Questionnaire

HPP: Health Promotion Program

IG: Intervention Group

MI: Motivational Interviewing

NA: Not available

SOC: Standard of Care

TPA: Treatment Partner-assisted therapy (intervention)

ANNEX 5.

ART Adherence Assessment/Measurement Methods: literature review

1. Self-report

In ART-related clinical and research settings, the self-report method is the most commonly used adherence measurement approach [271]. It is easy to use, inexpensive and has minimal time consumption. Furthermore, in care settings, the flexibility of this approach allows for the discussions on reasons for missing/skipping doses and has a potential for offering solutions to non-adherence [271]. Research evidence shows that self-report measures correlate with HIV viral load [67,272], actual medication intake [273-274] and other more objective measures of adherence such as EDM [67,273]. Overestimation of adherence by patients as a result of "desirability bias" remains a major limitation to this approach [11,271]. Other documented limitations include recall bias as self-report methods may only effectively reflect short-term adherence, and the use of non-standardized questions [271].

2. Pill counts

This approach measures adherence based on calculations of the percentage of prescribed and dispensed ART drugs during hospital visit/appointments and the number of pills counted at the next appointment [185,271]. This is done during hospital appointments or unannounced visits at the patients home [43,185]. Limitations to this approach include overestimation of adherence, as patients may influence assessment by dumping or throwing pills away [271]. In addition, this approach does not give information on the other aspects of adherence such as medication consumption timing and/or dose skipping [67]. Reports from studies have shown that efforts to minimize the risk of pill dumping such as unannounced pill counts have been shown to predict viral load better than other approaches [271,275]. Nevertheless, this comes with added limitations such as lack of trust between healthcare provider and clients in clinical care settings [67].

3. Pharmacy refill records

This approach has been reported to be useful in resource-limited settings [276-277]. Adherence levels are calculated by comparing the actual refill dates with expected refill dates [278]. Ross-Degnan et al. [279] in a study carried out in resource-limited settings reported that pharmacy refill records correlated with CD4 count and weight gain in HIV-positive patients. Other

studies have also demonstrated that pharmacy refills records significantly correlate with viral load in PLHIV [280-281]. This approach assumes that patients who receive their pharmacy refills are adherent to prescribed treatment regimen and does not measure actual medication intake [11,271].

4. Electronic drug monitoring (EDM)

The EDM approach has been used in measuring medication adherence in HIV and other chronic diseases [271]. EDM approach utilizes devices like the medication event monitoring system (MEMS), which has a microprocessor that takes record of the date and time of each pill container/bottle opening as a presumptive dose taken by patient [11,271]. Potential benefits include the ease and ability to monitor detailed patterns of adherence and medication use like dosing interval adherence [282]. Limitations that have been reported include: underestimation of adherence from "pocket dosing effect" which can be explained as the act of the patient removing more than the required pill dose to use at another time [67,271]. In addition, there can be overestimation of adherence as a result of patients opening the pill container without using or removing pills- "curiosity opening" [67,271,283-284].

5. Therapeutic drug monitoring (TDM)

The TDM approach is an established therapeutic intervention used in measuring medication adherence. This approach involves the measurement of drug levels in the patients' blood. Some studies have demonstrated that low plasma ART drug levels is associated with virologic failure and non-adherence (via self-report) among PLHIV [274,285]. TDM is expensive and not feasible in clinical care settings especially in resource-limited settings [11,274]. Other limitations include the fact that most ART drugs have 'short-life span' and is only reflective of adherence over a short-term (about 24 hours) with patients administering drugs in order to influence test results [11,67,185]. Furthermore, other factors that may influence TDM results include drug-drug interactions and diet [67,185,271].

6. Biological Markers Monitoring

Biological markers such as CD4 count and viral load have been used over time as indicators of ART therapeutic success and outcome [11]. Low viral load and high/increases in CD4 counts are proxies for good adherence [11]. Studies have shown that CD4 count correlates with self-report, pharmacy refill records and weight gain and viral load correlates with pill count and

good clinical outcomes in PLHIV [279,286]. However, some PLHIV on ART may still have persistent high viral load [11]. Availability and high cost of this approach in resource-limited settings is a major limitation [11].

7. Provider estimation Methods

The provider estimation method approach involves the HIV care provider assessing ART adherence via factors such as: clinic attendance, economic and sociodemographic factors. This approach is marred by overestimation of adherence as the above-mentioned factors have been reported to be ineffective in measuring ART adherence [11,279].