ADHERENCE TO ANTIRETROVIRAL THERAPY AND ITS IMPACT ON CLINICAL AND IMMUNOLOGIC OUTCOMES

By

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DECLARATION

The research described in this dissertation was carried out at Kwame Nkrumah University of Science and Technology (KNUST) under the supervision of Rev Prof Charles Ansah and Dr. K Ohene Buabeng. I declare that this dissertation is my original work and has not otherwise been submitted in any form for any degree at any university. Where use has been made of the work of others, it is duly acknowledged in the text.

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DEDICATION

I would like to dedicate this research work to my wonderful daughter, Owusuaa Nkunim Otoo Sakum. Your coming into this world and into my life gave me enough reason to keep pressing on and never give up. I work myself out every day without feeling a pinch because of you. Thank God you came. I love you so much.

ABSTRACT

Adherence to highly active antiretroviral therapy (HAART) has been associated with achieving success in virologic suppression, CD4 cell recovery, and improved patient well-being. Most of these researches reporting on the impact of adherence to HAART on treatment outcomes are published works from resource rich setting with little or no literature from Ghana. This study was therefore conducted to assess the impact of adherence to HAART on clinical and immunologic outcomes at two nationally designated HIV treatment centers in Kumasi, Ghana.

The study was a prospective non- randomised study of HIV- infected patients at Aniwaa medical center and Bomso specialist hospital, private health facilities in the Kumasi metropolis. The patients were recruited to initiate antiretroviral therapy. A total of 86 patients were enrolled and 85 completed. Data collection lasted for 1 year 1 month. Patients were assessed for their level of adherence to HAART over a nine month period during interviews and pill counts. Patients who took ≥95% of their medication were classified as adherent whiles those who took ≤ 95% of their regimen were described as non- adherent. Data regarding clinical outcomes were collected at baseline, 3 month, 6 month and 9th month, whereas data on immunologic outcomes were collected at baseline, 6 month and 9 month respectively. The data obtained was coded, entered into SPSS version 20.0 and analyzed.

Over 90% of the participants were adherent to their therapy. Common reasons for missing medications were side effect (44.7%), forgetfulness (42.4%), being away from home (42.4%). The mean CD4 count at baseline was 235cells/uL, 6th month (394cells/uL) and 9th month (469cells/uL). Mean number of opportunistic infections and signs and symptoms was 3.34 and 4.79 at baseline, 1.56 and 2.03 at 3rd month,

1.12 and 1.16 at 6th month and 1.00 and 1.13 at 9th month. Overall physical health of patients improved from poor at baseline to good at the 9th month.

Adherence to HAART was a strong predictor of immune recovery, growth and clinical progression but adherence was seen not to be the only predictor of treatment outcomes. Baseline CD4 count was also found to predict outcomes for HIV infected patients.

The most frequently used ARV in combination therapies was Tenofovir. Majority of patients in the study were adherent. After the nine months of study, both immunologic and clinical outcomes of patients significantly improved.

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ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired immuno- deficiency syndrome
ART	Antiretroviral Therapy
ARVS	Antiretrovirals
BID	Twice Daily
CASCADE	Children's Social Case Research and Development Group
D4T	Stavudine
DdI	Didanosine
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
EDM	Electronic Drug Monitoring Device
EFV	Efavirenz
FDA	Food and Drugs Authority
FDC	Fixed Dose Combinations
FTC	Emtricitabine
GHS	Ghana Health Service
HAART	Highly Active Antiretroviral therapy
HCV	Hepatitis C virus
HIV	Human Immuno Deficiency Virus
IDSA	Infectious Disease Society of America
JAIDS	Journal of Acquired Immuno- deficiency Syndromes
JAPA	Journal of American Psychoanalytic Association
MEM	Medical Electronic Monitoring Device
MOH	Ministry of Health
NIH	National Institute of Health
NNRTIs	Non-nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleotide/ Nucleoside Reverse Transcriptase Inhibitors.
OARAC	Office of AIDS Research Advisory Council
OI	Opportunistic Infections
OPD	Out Patient Department
PEPFAR	President's Emergency Plan for AIDS Relieve
PI	Protease Inhibitors

QD	Once Daily
RNA	Ribonucleic Acid
SPSS	Statiscal Package for the Social Sciences
SSA	Sub- Saharan Africa
TDF	Tenofovir Disoproxil Fumurate
UNAIDS	United Nations Programe on HIV/AIDS
WHO	World Health Organization
ZDV	Zidovudine

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND TO THE STUDY

Globally, almost 78 million people have been infected with the Human Immuno-deficiency virus (HIV) and about 39 million people have died of HIV since it was discovered in the early 1980s (UNAIDS, 2013). The number of people living with HIV at the end of 2013 were estimated to be between 33.2 and 37.2 million (UNAIDS, 2013). According to UNAIDS, the burden of the HIV epidemic vary considerably between countries and regions with Sub-Saharan Africa being the most severely affected region and accounting for nearly 71% of the people living with HIV worldwide (UNAIDS, 2013). The HIV prevalence rate in most Sub-Saharan African countries is higher than the global average of 0.8%.

In Ghana, the UNAIDS estimates the prevalence rate of HIV to be 1.3% amongst ages 15-49 years (UNAIDS, 2013). Although HIV prevalence rate in Ghana appears to be on a downward trend from 3.6% in 2003, to 1.5% in 2010 and remaining at 1.3% in 2011 and 2012 (Ghana Aids Commission, 2014), an estimated 220 000 of the population living with HIV and 10 000 deaths per annum makes it a public health problem in Ghana (UNAIDS, 2013; Ghana Aids Commission, 2014). Amongst the interventions taken in Ghana to increase survival among infected individuals is the scaling-up of antiretroviral (ARV) treatment. The number of people living with HIV and receiving ARV treatment has increased from 0.4% in 2003 to 47.4% in 2012 (Ghana Aids Commission, 2014). ARV treatment has been associated with an improved quality of life in people living with HIV/AIDS (Liu *et al*., 2006). Significant improvement in HIV patient outcomes has been observed for those on

ARV therapy resulting from slowing down the progression of HIV to AIDS, decreased incidence of opportunistic infections and reduced morbidity and mortality (Bangsberg and Machtinger, 2005; Erah and Arute, 2008; Chi ***et al***. 2009; Kredo ***et al***. 2009; WHO, 2009; Kamau, 2010; Valerie, 2010). Other positive outcomes related to ARV treatment include decreased hospital readmissions and reduced cost (Wools - Kaloustian *et al*, 2006). Hammer *et al*. (2006) asserts that even patients who initiate ARV treatment relatively late in the course of infection show benefit from ARV treatment.

The challenge to ARV treatment is adherence (Bangsberg and Machtinger, 2005; Mini *et al*., 2012; Panel on Antiretroviral Guidelines for Adults and adolescents, 2014). Adherence which is the extent to which a patient takes a medication in the way recommended by the healthcare provider (Bangsberg and Machtinger, 2005) has been identified as a major factor associated with achieving therapeutic success of anti- retroviral therapy (Bangsberg and Machtinger, 2005; Mannheimer *et al*, 2005; Miller *et al*, 2006). Virologic suppression, improved immunologic outcomes, good clinical outcomes as well as reducing mortality and HIV/AIDS related morbidity are some of the therapeutic successes associated with adherence to ARV treatment (Muyingo *et al*, 2012, Wang H *et al*, 2009; Casado *et al*, 2002).

Adherence to Highly Active Antiretroviral therapy (HAART) which is a major determinant and predictor of HAART success or failure has become a public health concern (Erah and Arute, 2008; Bangsberg and Machtinger, 2005). Adherence to HAART has been demonstrated to be a predictor of drug resistance (Bangsberg *et al*. 2003; Oyugi *et al*. 2007), CD4 cell count recovery (Nash *et al*. 2008; Chi *et al*.2009),

viral load suppression (Nachega *et al*.2007; Bajunirwe *et al*.2009) and survival (Lima *et al*. 2008; Abaasa *et al*. 2008; Chi *et al*. 2009).

Several other studies have demonstrated a significant correlation between adherence and overall therapeutic outcomes. Low-Beer *et al*. (2000) in a prospective cohort study demonstrated that response to viral load is directly proportional to the level of adherence to HAART. A high level of adherence is correlated with greater possibility of achieving success with virologic suppression. A similar relationship between adherence and virologic response has been demonstrated by Casado *et al*. (2002). In a study of 3004 patients initiating protease inhibitor based HAART, only 52% of patients who maintained a 90% - 95% rate of adherence at six months achieved a satisfactory virologic response (Casado *et al*, 2002). Muyingo *et al*. (2012) and Wang *et al*. (2009) also reported that consistent and good adherence is associated with greater CD4 growth, recovery and reduced mortality.

Non adherence to treatment has also been described by Wang *et al* (2009) as an important predictor for losing the long term clinical and economic benefits of HAART. Non-adherence with treatment reduces the expected clinical benefits of HAART by 12% (Munakata *et al*. 2006). Interruption with treatment has been identified as a significant factor leading to a slow increase in CD4 cell counts (Yu *et al*, 2005). The prevalence of opportunistic infections has also been linked with reported incidence of missing doses and HAART interruption (Gao, 2005; Wang *et al*, 2009). Although an abundance of literature on adherence to antiretroviral therapy and its impact on patient outcomes exist, little literature could be found on the association of adherence to ART and patient outcomes to inform decision making

and policies in Ghana. It is against this background that this study sought to assess the impact of adherence to HAART on clinical and immunologic outcomes in two nationally designated HIV/AIDS treatment centers in Kumasi, Ghana.

1.2 PROBLEM STATEMENT

The main aim of the Ghanaian government scaling-up antiretroviral (ARV) treatment since 2003 is to improve the life span of people living with HIV and reduce the burden of the disease on them. To achieve this goal, it is important that HIV positive patients, who are put on ART, adhere to their medications. According to Ohene and Forson (2009), as steps are taken to scale-up ARV treatment, an assessment of those already on treatment particularly their adherence levels are needed due to the lifelong nature of ARV treatment. ARV treatment services in Ghana are provided by teaching, regional, district and private hospitals (Ohene *et al*. 2013). Almost all the research on adherence to ARV treat has been undertaken in teaching, regional and district hospitals Ghana (Ohene and Forson, 2009; Annison *et al*. 2013; Ohene *et al* 2013). However, waiting times for government hospitals have been found to be longer as a result of inefficiencies in the supervision compared to private hospitals in Ghana (Mensah *et al*. 2014). Most people therefore use private providers for their ARV treatment services, yet no research has been undertaken to determine the adherence levels of patients using private hospitals and particularly the impact of adherence on patient outcomes.

Although some studies on levels of adherence to ART have been carried out in Ghana and in the Ashanti region in particular by (Ohene and Forson, 2009; Annison *et al*. 2013), these were mostly carried out at the Komfo Anokye Teaching Hospital

(KATH) that has had long experience in dealing with ARV treatment. Also little attention has been given to the effect of adherence to ARVs on outcomes of HIV/ AIDS patients in Ghana as most of the studies have focused on factors affecting adherence. Assessing adherence levels at private medical facilities that provide ARV treatment as well as determining the impact of adherence on patient outcomes was therefore necessary. The aim of this study was to determine the impact of adherence to HAART on clinical and immunologic outcomes of HIV/AIDS patients receiving ARV treatment at two nationally designated private medical facilities.

1.3 PURPOSE OF THE STUDY

The overall objective of this study was to assess the impact of adherence to antiretroviral therapy on clinical and immunologic outcomes of HIV infected patients recruited to start HAART at two nationally designated private medical facilities in the Kumasi Metropolis.

1.4 RESEARCH QUESTIONS

- Is there an association between adherence to HAART and treatment outcomes?
- Does adherence to HAART have a significant effect on recovery of CD4 cells?
- Does adherence to HAART decrease the prevalence of opportunistic infections?
- Does adherence to HAART decrease the incidence of hospitalization?
- Does adherence to HAART influence weight in HIV – infected patients?

1.5 RESEARCH OBJECTIVES

The objective of this research was to:

- determine the current adherence rate of study participants
- assess the impact of adherence to HAART on clinical outcomes
- assess the impact of adherence to HAART on immunologic outcome

1.6 SIGNIFICANCE OF STUDY

Although an abundance of literature on adherence to ART and its impact on patient outcomes exist, very little literature could be found for HIV/AIDS patients in Ghana that is specific to the Ghanaian context and more specific to patients receiving treatment at the Aninwah medical center and Bomso specialist hospital.

It is accordingly essential to investigate the Ghanaian context (that is examine adherence levels in Ghana and how it impacts on clinical and immunological outcomes) in order to identify similarities, differences and exceptions to the existing body of knowledge. When this is done, health professionals and Government officials in Ghana can design and implement policy interventions aimed at enhancing and maximizing long term adherence to ART for successful treatment outcomes for HIV/AIDS patients.

The study will also determine practical implications of adherence to ART on the health of the HIV/AIDS patient as against what the theory says with a view to suggesting possible intervention measures to sustain or improve adherence.

The findings of this study will also be useful to other scholars conducting studies in this area and might have significant clinical benefits for people living with HIV in Ghana and more especially in Kumasi.

1.7 OPERATIONAL DEFINITION OF TERMS

Assess: To evaluate the effect of antiretroviral drugs on the clinical and immunologic outcomes of HIV infected patients.

Participants: HIV infected patients recruited from the study sites and are being used for the study.

Rate: It is the measure of adherence among HIV infected patients on antiretroviral drugs

Adherent: Adherence rate ≥ 95%

Non- adherent: Adherence rate ≤ 95%

Outcome: It is the measureable results seen in patients who adhere or did not adhere to their anti-retiroviral drugs.

Impact: The effect of antiretroviral drugs on the clinical and immunological outcomes of HIV infected patients

Antiretroviral Drugs: They are drugs approved by the FDA, USA for the management of HIV infection.

Antiretroviral therapy: Consist of a combination of at least three antiretroviral drugs.

Clinical: Actual subjective and objective outcomes observed in HIV/AIDS patients on HAART through direct physical examination of and reports giving by the patient.

Immunological: Response of the immune system to antiretroviral drugs observed through biomedical quantification of the CD4 cells

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 MEASURES OF ADHERENCE

There is no gold standard by which adherence to medication is measured. Many studies have employed a number of methods, either alone or in combination to measure adherence. The most common include: 1. various self-reporting tools such as questionnaires and visual analogue 2.Electronic drug monitoring (EDM) devices, 3. Biochemical markers, 4. Pill counts and 5.Pharmacy refill records (Nyambura, 2009). According to Gill *et al*. (2005) the hierarchy of adherence measures ranks physician and self-assessment report the least accurate, pill count intermediate and EDM the most accurate adherence measure. No single measure is however appropriate for all settings or outcomes. It has been found that the use of more than one adherence measure allows the strength of one to compensate for the weakness of the other and to more accurately capture the information needed to determine adherence levels (Vitolins *et al*. 2000). The guidelines for antiretroviral therapy in Ghana recommend that adherence be monitored using one of the following methodologies: self-reports, pill counts and pharmacy records (National HIV/AIDS/ STI Control Programme, 2008).

2.2 METHODS FOR MEASURING ADHERENCE

2.2.1 Patient self-reports

Self-report has been used by Mannheimer *et al* (2005) in assessing the adherence rate of 100 HIV infected patients and has described it as reliable. Allowing the patients to give self- account of their adherence levels is a more valid procedure, but it is also

associated with many difficulties. The benefit of this is the low cost and flexibility of design. Data is easily collected and can also help determine why patients are non-adherent. A major limitation of self- report is that they reflect only short-term or average adherence and may lead to overestimation of adherence, both in the HIV setting and non-HIV setting (Haynes *et al*. 1998). Patients could also lie to avoid condemnation from their health care provider; secondly, they may simply not know their own rate of adherence. While under-reporting of adherence is common, so is over-estimation of adherence. Thus for these reasons self-reported adherence measures have questionable validity and should usually be used with other assessment methods. Studies that compare data from self-report measures to pill counts or electronic measurements have found differences, suggesting that self-reports provide inflated estimates of adherence behaviour (Chesney, 2000).

2.2.2 Incidences of missing or forgetting to take pills (Pill counts)

Patient reports on any incidences of missing or forgetting to take their pills are almost always reliable, thus self-reports can be helpful for understanding the dynamics surrounding missed medication. Pill counts have been used widely and the return of excess pills provides concrete evidence of non-adherence. However, this requires that the patients return the pill packaging but they sometimes forget to or inadvertently discard them (Berg *et al*. 1998).

HIV patients are prescribed a number of antiretroviral agents and may be required to bring the container of each medication during their visit to the clinic. The disadvantage of this adherence measure is pill counting for the entire regimen can be cumbersome and time-consuming (Berg *et al*. 1998). Generally, 10% of patients

report missing at least one antiretroviral dose on any given day and 33% report missing at least one dose in the past month (Bangsberg *et al*. 2001).

2.3 ADHERENCE RATES IN SUB-SAHARAN AFRICA

There is scarcity of studies on ART adherence in resource poor settings such as Sub-Saharan Africa (SSA) (Byakika *et al*. 2005). Thus, the expected patient adherence levels commonly used are derived from studies conducted in resource-rich countries. This could be due, in part, to the fact that much of the efforts in Sub- Saharan Africa have been devoted to providing access to ART to HIV-infected patients, rather than concerted efforts to study adherence rates. The challenge to ART is changing from gaining access to maintaining adherence in order to realize the full benefits of reduced HIV- related mortality and morbidity, as well as improved quality of life (Sarna *et al*. 2005).

Weiser *et al*. (2003) in Bostwana found self- reported adherence and provider assessment adherence rates of 54% and 56% respectively. In another study done in Dakar, Senegal by Laurent *et al* (2002), the authors found that 78% of the patients were adherent while the optimal level of adherence was set at 80%. A similar adherence level (79%) was reported by Daniels (2004) in Nigeria. Anude *et al* (2013) in a study in Nigeria also reported a higher adherence rate with Tenofovir containing regimen due to its superiority, convenient dosing, low toxicity and high potency (Gallant, 2006; Pozniak, 2006).

A lower adherence level of 66% was reported in a study conducted in Uganda by Byakika *et al* (2005) while Munganzi (2004), Uganda found a relatively higher

adherence of 98%. The differences in the rate of adherence reported by Byakika *et al* and Muganzi may be due to the different methods used in measuring adherence.

In South Africa, adherence rates of 77% and 80% were respectively reported by Ferris *et al*. (2004) and Darder *et al*. (2004). A favourable adherence rate of 87% was recorded in Uganda in a study by Omes (2004). A meta-analysis of adherence studies done in sub-Saharan Africa and North America found an estimated 77% in Africa compared to 55% found in North America (Mills *et al* 2006). Contrary to expectations, adherence rates in Africa are quite favourable

2.4 FACTORS INFLUENCING ART ADHERENCE

2.4.1 Drug Factors

One of the challenges to successful ART adherence is regimen complexity. Antiretroviral therapy clearly does not easily fit into patients' lifestyles. Commonly reported regimen -related reasons for not adhering to HAART regimens include being too busy with daily activities and simply forgetting to take their pills, or being away from home and experiencing a break in the daily routine. Due to regimen complexity, patients cannot adhere adequately to their current therapy to effectively reduce HIV RNA to levels "undetectable" and to ensure control of HIV replication over the long term. Almost all of those who are on ART are on regimens of three or more ARVs *(*Grierson *et al*., 2000).

A patient's adherence to a given regimen may decline with polypharmacy, the frequency of dosing, the frequency and severity of adverse effects and the complexity of the regimen (Nakiyemba *et al*. 2005). Among the factors known to

influence ART adherence, Paterson *et al* (2000), discovered other factors such as adverse effects, inconvenient dosing frequency, pill burden, and dietary restrictions.

2.4.2 Adverse effects

Negative side-effects and concerns over the long-term effects of treatment can lead to patients deciding to stop treatment. Others quit when treatment is taken over a long period (Carter, 2004). Though most HIV-infected patients understand that their current therapy will inevitably result in adverse effects, dealing with negative effects of medications is nonetheless highly stressful (Gao *et al*. 2000). Too often, medication side effects may limit the effectiveness of HIV therapy because patients cannot continue with the regimen. Despite the development of newer antiretroviral agents, adverse effects are still very common (Gao *et al*. 2000). Although adverse-effects have been cited by some studies in developed countries as predictors of adherence, experience of adverse effects and views about medications may be complex and may vary according to the type of regimen (Murphy *et al*. 2004)

A study conducted by Weiser *et al*. (2003) in Botswana indicated that side-effects did not pose a major barrier to adherence. The study found that while 51% of respondents experienced some adverse-effects, less than 10% of the patients reported adverse-effects as a significant barrier to ARV treatment adherence. This was also noted in a study by Akam *et al*. (2004) who found only 5% of study participants citing adverse effects as a reason for skipping doses or missing medications. The side-effects were however reported in the study by Akam and colleques to disappear over time.

2.4.3 Dosing frequency and pill burden

It is well known that the degree to which adherence to a regimen interferes with daily life is an important factor contributing to non-adherence. Adherence decreases as the number of doses per day increases (Chesney *et al*. 2000). The physical aspects of a particular medication (for example taste, size or formulation) may also impact on patient's ability to adhere (Nakiyemba *et al.* 2005). Reducing the frequency of taking the medication to once or twice daily can also help to improve adherence (Masokoane, 2009). Availability of once-daily combination antiretroviral regimens represents a considerable advancement, which has been welcomed by patients (Stone *et al*. 2002). .

The development of fixed dose combinations (FDCs) has further reduced pill counts. Fixed-dose combinations offer obvious advantages. Not only can they reduce pill burden and treatment costs, but they can also improve patient satisfaction and overall adherence as well as reduce the risk of dosing errors. From a clinical viewpoint, these benefits are extremely valuable, because patients' adherence, and therefore efficacy, seem to improve with simpler regimens. (Dejesus, 2012)

Although once daily (QD) dosing was deemed the most desired dosing, actual QD regimens currently available were perceived as no more likely to improve adherence as a BID regimen consisting of one pill per dose when multiple features of HAART regimens were considered concurrently. This seems to be in large part again, because patients seem to prefer low pill count over QD dosing as the most important attribute (IDSA, 2002). Further, IDSA found that QD regimens requiring more than two pills

per day were less favorably rated than a BID regimen requiring a total of two pills per day.

2.4.4 Dietary restrictions

HAART regimens, in addition to requiring many daily doses with multiple pills, often impose very specific food requirements that must be observed in order to ensure maximum blood levels of the drugs. Dietary restrictions add to the complexity of ART regimen and often require adjustments in patient's lifestyle. Patients' meal schedules can be compromised by ARVs that need to be taken on an empty stomach. This could be particularly difficult if workmates, family or friends are uninformed of the patients HIV status (Grierson *et al*. 2000; Nakiyemba *et al*. 2005).

2.4.5 Other factors influencing adherence to ART

Several other factors unrelated to drug regimen and treatment complexities have been identified by researchers across the world. Among these factors are; cost of medications (Weiser *et al*. 2003; Byakika *et al*. 2005), cost of transportation, stigma (Hardon *et al*, 2007), poor patient- provider relationship (Kagee and Delport, 2010), language barrier (Ashton *et al*. 2003), medication stock outs (Erah and Arute, 2008), being away from home (Wang and Wu, 2007), and forgetfulness (Wang and Wu, 2007)

2.5 MONITORING ART EFFICACY IN TREATMENT ADHERENT PATIENTS

HIV RNA (viral load) and CD4 T lymphocyte cell counts are the two surrogate markers of antiretroviral treatment (ART) responses and HIV disease progression that have been used for decades to manage and monitor the progress of HIV infection. It is an established fact that virologic failure occurs first and is subsequently followed by immunologic failure, then clinical failure (Mocroft *et al*. 2013)

A patient's pre- therapy viral load level and the magnitude of viral suppression after initiation of ART provide prognostic information about the probability of disease progression. The most important goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load as a marker is to monitor the effectiveness of ART after initiation (Panel on ARV guidelines for adults and adolescents, 2011).

Measurement of CD4 cell count is particularly useful before initiation of ART. The CD4 cell count provides information on the overall immune function of HIV-infected patients. CD4 count measurement is critical in establishing thresholds for the initiation and the discontinuation of opportunistic infection prophylaxis and in assessing the urgency to initiate ART (Panel on ARV guidelines for adults and adolescents, 2011)

2.5.1 Viral Load monitoring

Viral load is the most important marker of initial and sustained response to ART and must be measured in all HIV- infected patients at entry into care, at initiation of

therapy and on regular basis thereafter (Panel on ARV guidelines for adults and adolescents, 2014)

Studies involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death (Thiebaut *et al*., 2000). Thus viral load testing is an established surrogate marker for treatment response (HIV surrogate marker collaborative group, 2000). The minimal change in viral load considered to be statistically significant is a three- fold change (equivalent to a 0.5 log 10 copies/ mL change). Optimal viral suppression is defined generally as a viral load persistently below the level of "detection" (Panel on ARV guidelines for adults and adolescents, 2011).

2.5.2 CD4 cell count monitoring

CD4 T- cells are fundamental to the development of specific immune responses to infections, particularly intracellular pathogens. As the primary target of HIV, their depletion severely limits the host response capacity. The HI virus, largely infects activated cells causing the activated T- cells directed against the virus to be at greatest risk of infection (Stebbing, 2004). The ability of the immune system to mount a specific counter response to HIV is a key factor in the subsequent disease progression (Chinen and Shearer, 2002)

The CD4 cell count is the most important laboratory indicator of immune function in HIV- infected patients. It is also the strongest predictor of subsequent disease progression and survival according to findings obtained from clinical trials and other studies (Egger *et al*. 2002). The US Department of Health and Human Services

(DHHS) ART treatment guidelines recommends treatment commencement to be based on CD4 cell count in preference to any other surrogate marker (Bartlett and Lane, 2005). The use of the CD4 cell count as a means of monitoring ART efficacy is well established (Bartlett and Lane, 2005).

2.6 EFFECT OF LATE INITIATION OF ART ON PATIENT OUTCOMES

Late initiation of ART puts an individual at a risk of developing AIDS- defining conditions which is associated with higher risk of morbidity and mortality. Many individuals who start treatment with CD4 cell counts less than 350 cell/uL never achieved counts ≥ 500 cells/uL even after 6 years on ART (Moore and Keruly, 2007). Other studies have demonstrated a gradient of increased risk of AIDS and death when ART is initiated at a lower CD4 count (Lordwick *et al*, 2010; Philips *et al*, 2007; Grabar, 2009).

Recent studies by (Granich *et al*, 2009; Le *et al*, 2013) also reported that patient who initiate ART at lower CD4 counts were less likely to have CD4 cell recovery and had lower rate of recovery than those who initiated with high CD4 counts. Lower CD4 counts are associated with increased risk of disease progression. The risk of disease progression at baseline CD4 counts of 200cells/uL generally doubles than the risk of initiating therapy at CD4 counts of 350 cells/uL(CASCADE, 2004).

Increased risk of morbidity and mortality is also associated with initiating ART at CD4 cell counts of 200 cell/ uL (Hecht *et al* 2006). In a cohort study by Nash (2008), they showed that risk of morbidity and mortality diminishes with increasing CD4 count. Lower CD4 counts are associated with greater risk of disease progression.

CD4 counts from 350 to 500 cells/mm^3 are associated with risks of ≤ 5% across all age and HIV-RNA strata, while the risk of progression to AIDS increases considerably at CD4 counts < 350 cells/mm^3. The greatest risk of disease progression occurs as CD4 counts fall below 200 cells/mm (CASCADE, 2004).

An adequate immunologic response for patients on ART is defined as an increase in CD4 cell count within the range of 50 – 100 cell/ uL in the first year of ART, with an accelerated response in the first three months of treatment. Subsequent CD4 cell increases average approximately 50- 100 cells/ uL per year until a steady state is reached (Kaufman *et al*. 2003).

Patients who initiate therapy with low CD4 count or at an older age may have a diminished increase in their counts despite virologic suppression (Moore and Keruly, 2007; Panel on ARV guidelines for adults and adolescents, 2014). Baseline CD4 count is a predictor virologic failure. Van Leth *et al*. (2005) found a statistically significant positive association between baseline CD4 count < 200 cells/uL and HIV RNA > 50 copies / ml at 48 weeks of therapy.

2.6 IMPACT OF ADHERENCE TO ART ON CLINICAL OUTCOMES

Optimal adherence is an essential factor determining plasma viral suppression and immunologic outcome for HIV infected patients (Garcia *et al*. 2006; Munakata *et al*. 2006). In patients who are adherent to their therapy, CD4 counts can raise quickly and viral loads may drop to undetectable levels within one year (Akileswaran *et al*. 2005; Fairall *et al*., 2008). Improvement in these clinical markers can lead to fewer opportunistic infections and overall reductions in AIDS-related morbidity and

mortality (Fairall *et al*., 2008). Participants who report of consistent adherence present with a low prevalence of opportunistic infections. San-Andres et al. (2003) evaluated the effect of early ART and showed that the clients who had good adherence demonstrated a low incidence of opportunistic infections (OIs). The occurrence of OIs is closely related to the virulence of the pathogens and the suppression of the immune system (Wang *et al*. 2008)

HIV/AIDS clients who maintain optimal adherence to ART can reduce the prevalence rate of OIs from 56.1% before treatment to 9.8% 3 years after starting treatment (Wang *et al*. 2008). Wang *et al*. (2008) demonstrated an association between consistent adherence and a reduced utilization of medical resources, such as a decreased number of hospitalizations, shorter hospital stays, and reduced hospitalization cost. Effective use of ART helps clients achieve the expected virologic and immunologic benefits of ART, and slows down the progression of HIV to AIDS, which in turn reduces the high medical costs associated with in-patient HIV/AIDS care. Nosyk *et al*. (2006) found that clients on ART have significantly lower odds of hospitalization compared to clients not receiving ART. Non-adherence is an important contributor to losing the long-term clinical and economic benefits of ART. Munakata *et al*. (2006) in his study reported that non-adherence with treatment reduces the expected clinical benefits of ART by 12%.

2.7 IMPACT OF ADHERENCE TO ART ON IMMUNOLOGIC OUTCOMES

After ART initiation, most patients experience improved immune activity and maintain viral suppression; however, there remain subsections of patients who have sub-optimal immunologic responses. Sub- optimal immunologic response is defined

as the failure to achieve and maintain an adequate CD4 response despite virologic suppression. In treatment-naive patients on initial ARV regimens, during the first year of ART, CD4 counts usually increase by about 150 cells/mm^3. A CD4 count plateau may occur after 4 to 6 years of ARV treatment with suppressed viremia (Garcia, 2004; Moore and Keruly, 2007).

The proportion of patients experiencing suboptimal immunologic response depends on the researcher's or clinician's definition of suboptimal response, the observation period, and the baseline CD4 count. In previous studies conducted, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/mm^3 through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/mm^3, 66% in those starting with a CD4 count 200 to 350 cells/mm^3, and 85% in those starting with a CD4 count >350 cells/mm^3 (Moore and Keruly, 2007).

In an observational clinical- based cohort study, Anude *et al*. (2013) found a robust immunologic response of more than 50 cells/mm^3 in 77.4% of patients at 12 months with a median CD4 count increase of 139cell/mm^3. Similarly, in another prospective cohort of HIV – infected infants, Tukei *et al*. (2013) found a significant increase in CD4 cells from a baseline mean percentage of 23% to 30% at month 6 and 33% at month 12 of anti-retroviral therapy. By the end of the second year of therapy, the mean CD4 cell percentage rose to 36% (Tukei *et al*. 2013)

A persistently low CD4 count while on suppressive ART is associated with a small, but substantial, risk of AIDS- and non-AIDS-related morbidity and mortality (Loufty *et al*. 2006; Moore *et al*. 2008). In a study by Baker (2008), a low CD4 count while on therapy was associated with an increased risk of AIDS-related complications.

Similarly, a low CD4 count was associated with an increased risk of non-AIDS clinical events, including cardiovascular, hepatic, and renal disease and cancer. (Monforte *et al*. 2008; Lichtenstein *et al*. 2010).

Adherence undoubtedly correlates with CD4 counts in a number of settings. In a prospective cohort study of 1095 patients enrolled in two randomized studies, participants who reported adherence rate ≥ 95% had a mean increase in CD4 cell count of 83cell/uL while those with adherence rate < 95% had mean increase of only 6 cells/uL(Paterson *et al*. 2000). In a prospective cohort study of 173 HIV- positive patients studied for 2 to 6 months using self- report as adherence measurement tool, the authors (Haubrich *et al*. 1999) found patients reporting 95-99% adherence at 6 months having CD4 count increase of 59 cell/uL from baseline while patients with < 80% adherence had a net loss of 8 cells/uL from baseline.

The following are some factors known to be associated with poor CD4 cell response: CD4 count <200/mm^3 at initiation of ART, Older age, Coinfection with hepatitis C virus [HCV], HIV-2, human T-cell leukemia virus type 1 [HTLV-1], HTLV-2), type of ARVs the patient is on (e.g., zidovudine [ZDV], tenofovir disoproxil fumarate [TDF] + didanosine [ddI]), persistent immune activation, loss of regenerative ability of the immune system and Concomitant medical conditions (Huttner , 2007; Lacombe *et al*, 2005; Negredo, 2005).

2.8 DEMOGRAPHIC CHARACTERISTICS, ADHERENCE AND TREATMENT OUTCOMES

Younger age less than 30 years was significantly associated with 79% increased odds of virologic failure and 50% increased odds of immunologic failure in the Glass (2006) study. Majority of studies including one previous study conducted in Nigeria to evaluate the country's Action program demonstrated an association between adherence and improved outcomes increasing with age (Glass, 2006). Young people are more likely to be single, engaged in high risk behaviours, financial stability and maturity (Pettifor, 2009; Speizer, 2009).

HIV infected adolescents and young adults in Southern Africa who are on ART have both poorer adherence levels and poorer therapeutic outcomes than do adults. Compared with adults on ART, adolescents have lower rates of optimal virologic suppression at all-time points after initiation of ART and experience more rapid viral rebound (Nachega *et al* 2009). In the Nachega *et al* (2009) studies, 20.7% and 14.3% of adolescents achieved a 100% adherence at 6 months and 12 months respectively compared with 40.5% and 27.9% of adults achieving 100% adherence at 6months and 12months respectively. The proportion of adolescents achieving a viral suppression in the Nachega *et al* (2009) study was lower than that of adults. After six months of ART initiation, 63.0% of adolescents as against 69.3% of adults achieved viral suppression but adolescents had significantly shorter times to viral rebound than did adults.

Various studies including an extensive review of the barriers to accessing HIV treatment and treatment outcomes suggest that longer distances from treatment sites

are associated with poorer outcomes (Pettifor, 2009; Speizer, 2009; Posse, 2008). In a study by Anude *et al*. (2013), they found that compared to those living less than 50 miles away from the treatment site, those who lived 50–100 kilometers away had a 56% significantly decreased odds of virologic failure while those who lived more than 100 kilometers away had a 37% increased odds of virologic failure that was not significant. Since most Nigerians live close to more than 300 HIV treatment sites in the country, it appears that adherent patients who travel > 50 kilometers to treatment sites make the personal choice to travel such long distance and/or are probably motivated than patients who live close to the clinic. However, the more distant the patient is from the treatment site (> 100 kilometers), the more difficult it is for the patient to handle the logistics and financial difficulties of bearing the cost of transportation. Anude *et al*. (2013) confirmed that adherence levels using pharmacy refill/ records was best in patients who live 50–100 kilometers from the treatment sites.

Socio-economic status (SES) have been linked to HIV treatment outcomes (Van Oesterhaut, 2005). The most common socio-economic factors impacting on HIV treatment is the cost of HIV drugs, laboratory work-up and the commodities. Educational status, particularly post-secondary education have been associated with positive treatment outcomes in previous studies (Marc, 2007). Increased odd of immunologic failure and immunologic discordance is significantly associated with the male gender. Male gender is noted to be consistently associated with poor health seeking behaviours (Keizer, 2008; Braistein, 2008), lower baseline CD4 count levels and poor HIV treatment outcomes (Nash, 2008). This confirms the need to make many health care facilities male-friendly and encourage male peer-support systems

as well as investing in research and programs that adequately engage males and try to find ways that seek to positively influence the health-seeking behavior of men (Anude *et al*, 2013).

2.9 CLINICAL PHARMACOLOGY OF ANTIRETROVIRALS USED BY CLIENTS IN THIS STUDY

2.9.1 Introduction

Highly active antiretroviral therapy (HAART), over the past decades have transform HIV- infection into a manageable chronic disease in patients who have access to drugs and can achieve durable virologic suppression (Palella *et al*.1998). Excess mortality among patients with AIDS was reduced drastically in the HAART era, but remains approximately 5 times higher in patients with AIDS than in Non- AIDs patients (Rathbun, 2014).

2.9.2.1 Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside reverse transcriptase inhibitors (NRTIs) are a class of oral antiretroviral (ARV) drugs that are effective against HIV. Effective use of this class of ARV is found to reduce HIV viremia and improve CD4 T cell counts (Thompson *et al*. 2012). NRTIs are the first agents available for the treatment of HIV infection. Although NRTIs are less potent against HIV than the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), the NRTIs have played a central role in antiretroviral therapy and remain part of the current standard care (Shen *et al*. 2008; Panel on Antiretrovial Guidelines for Adults and Adolescents, 2011). They exhibit activity against HIV-1 and HIV-2. The NRTIs class is made up of seven agents approved for use and is currently available in the United States. They

are the adenosine- derived nucleotide reverse transcriptase inhibitor, tenofovir disoproxil fumarate (TDF); the guanosine analog, abacavir sulfate (ABC); the thymidine analogs, stavudine (d4T) and zidovudine (ZDV); cytosine analogs, emtricitabine (FTC) and Lamivudine (3TC); the inosine derivative didanosine (ddI); and Zalcitabine. The latter are no longer commercially available (Thompson *et al*. 2012).

2.9.2.2 Mechanism of action

NRTIs interrupt the HIV replication cycle by competitively inhibiting the HIV reverse transcriptase and terminating the DNA chain (Weller and Williams, 2001). Reverse trancriptase is an HIV – specific DNA polymerase that allows the viral RNA to be transcribed into a single strand and ultimately a double strand proviral DNA which is incorporated into the host- cell genome. Proviral DNA chain elongation is needed before genome incorporation can occur and is accomplished by the addition of purine and pyrimidine nucleosides to the end of the growing chain (Rathbun, 2014). NRTIs are structurally similar to the DNA nucleoside bases and become incorporated into the proviral DNA chain, leading to chain termination of the proviral DNA (Elion, 2008). Tenofovir, lamivudine and emtricitabine exhibit additional activity against hepatitis B virus and are frequently incorporated into antiretroviral regimens for patients with HIV who are coinfected with Hep B virus (Panel on ARV guidelines for adults and adolescents, 2011).

2.9.2.3 Pharmacokinetics of NRTIs

NRTIs are prodrugs and must undergo phosphorylation by intracellular kinases to exert their pharmacological activity. The oral bioavailabity of the NRTIs ranges from

25%- 93%, with tenofovir and didanosine on the lower end of the spectrum. Food does not significantly affect absorption of any of the NRTIs except didanosine, which must be taken on an empty stomach to achieve optimal absorption and maximum drug levels (Rathbun, 2014). Although plasma half- lives of NRTIs are relatively short, intracellular drug levels are the best indicator for drug activity and determinant of the dose administered for each NRTI (Piliero, 2004). Most NRTIs are renally excreted and require dose adjustments in patients with renal insufficiency; the exception to this rule is abacavir, which is given at the normal dose regardless of reduced creatinine clearance (Rathbun, 2014). NRTIs are not metabolized by the cytochrome P450 enzyme system; therefore, minimal drug-drug interactions can occur (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011).

Drug- drug interactions that have been found to be clinically significant involve didanosine. When given in combination with tenofovir, didanosine levels are higher than is expected, and lower doses must be given to avoid potentially serious adverse effects. Similar observation has been made when didanosine is combined with ribavirin in the treatment of patients with HIV and hepatitis C virus (HCV) coinfection (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011).

2.9.2.4 Resistance

Resistance to NRTIs occurs by one of the two mechanisms: (1)" impaired incorporation into the proviral DNA chain or (2) removal from the proviral DNA chain" (Clavel and Hance, 2004). Mutations normally occur gradually; with accumulation of several mutations before a clinically significant resistance develops. An exemption is the M184V mutation, which confers high-level resistance to

lamivudine and emtricitabine in a single step. Mutations that selectively weaken incorporation into the proviral DNA chain include M184V, Q151M, and K65R (Rathbun, 2014). Thymidine analog mutations (mutations associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y, T215F, K219Q, K219E) remove NRTIs from the DNA chain by confering a conformational change in the reverse transcriptase domain that allows the addition of ATP or pyrophosphate. This placement according to Elion and Witt, (2003); Clavel and Hance , (2004) causes a break in the proviral DNA and NRTI bond, enabling continued elongation of the proviral DNA strand.

2.9.2.5 Adverse effects

Negative side effects of the NRTI class include mitochondrial toxicities such as lactic acidosis, pancreatitis, hepatic steatosis, peripheral neuropathy, and lipoatrophy. Mitochondrial toxicities are due to the binding of NRTIs to human mitochondrial DNA polymerase-γ enzyme, impairing cellular respiration. In these conditions, normal aerobic metabolism shifts to an anaerobic process, resulting in the manifestations of the above (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011). Antiretroviral drugs reduces the risk of chronic kidney disease along with CD4 cell restoration and suppression of plasma viral load, despite the risk associated with initial treatment regimens that include tenofovir plus a ritonavir-boosted protease inhibitor (Kalayjian *et al*. 2012).

The binding affinity of NRTIs for mitochondrial DNA polymerase-γ is predictive of the potential for adverse-effect and varies as follows (in decreasing order of affinity): zalcitabine, didanosine, stavudine, lamivudine/emtricitabine, zidovudine, abacavir,

and tenofovir (Cote *et al*. 2002; Birkus *et al*. 2002). Individual drug-specific adverse effects include bone marrow suppression, myopathy, and headache with zidovudine and generalised hypersensitivity reaction with abacavir (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011). Abacavir and didanosine have been associated with increased risk of adverse cardiovascular events (D.A.D Study Group, 2008). Treatment with ARVs is associated with increased bone turnover and bone loss particularly from the spine and hip, with considerable number of patients losing about 6% bone density within 1 year after being on treatment (Stellbrink *et al*., 2010).

2.9.3.1 Non-nucleoside Reverse Transcriptase Inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) were introduced in 1996 with the approval of nevirapine alone. NNRTIs exhibit potent activity against HIV-1 and are part of preferred initial regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011; Shen *et al*. 2008). Efavirenz, in particular, confers the most significant inhibition of viral multiplication among the class of NNRTIs (Shen *et al*. 2008). First-generation NNRTIs approved for use are delavirdine (Rescriptor), efavirenz (Sustiva), and nevirapine (Viramune). Second-generation NNRTIs, approved for use in the United States in 2008 is etravirine (Intelence) , and rilpivirine (Edurant) approved in 2011 respectively (FDA News, 2011). All NNRTIs exhibit the same mechanism of action. First-generation NNRTIs have similar resistance patterns, whereas etravirine and rilpivirine display a more distinct resistance profile (Rimsky *et al*. 2009). Their pharmacokinetic properties and adverse-effects profile have significant differences.

2.9.3.2 Mechanism of action

HIV reverse transcriptase is a heterodimer composed of 2 subunits (p66 and p51) (Sluis- Cremer *et al*, 2004). NNRTIs bind to the p66 subunit at a hydrophobic pocket distant from the active site on the enzyme. This noncompetitive binding confers a conformational change in the enzyme that alters the active site and limits its activity (Sluis- Cremer *et al*, 2004). Etravirine differs from first-generation NNRTIs in that it is able to bind at this site despite the presence of some mutations that limit the efficacy of first-generation agents. Etravirine is a highly flexible molecule that is able to rotate within the binding site to allow multiple binding conformations (Knoll *et al*. 2008). All the four NNRTIs exhibit activity against HIV-1. In vitro studies have shown that etravirine has additional activity against HIV-2 (Vingerhoets *et al*. 2005).

2.9.3.3 Resistance

Mutations within the reverse transcriptase gene domain alter the ability of the NNRTIs to bind to the enzyme. First-generation NNRTIs have a low genetic barrier to resistance, whereas a single mutation in the binding site can limit the ability of the drug to bind. This significantly diminish their activity (Soriano and de Mendoza, 2002). First-generation NNRTIs resistance has been associated with mutations at multiple points; however, the presence of either a K103N or Y181C mutation is significantly enough to cause clinical failure of delavirdine, efavirenz, and nevirapine (Soriano and de Mendoza, 2002).

Associated mutations include the following (Soriano V & de Mendoza, 2002):

- Delavirdine - A98G, L100I, K101E, K103N, K103T, V179D, Y181C, Y188L, M230L, P236L, Y318F

- Efavirenz - L100I, K101E, K103N, V108I, V179D, Y181C, Y188L, G190S, M230L
- Nevirapine - A98G, L100I, K101E, K103N, V106A, V106I, V108I, Y181C, Y191I, Y188C, Y188H, G190A, P225H, M230L, P236L, Y318W

Etravirine, unlike other currently available NNRTIS has a higher genetic barrier to resistance. A single point mutation at positions 103 or 181 is not sufficient to cause clinical failure of etravirine (Seminari *et al*. 2008).Reports from clinical trials have identified 17 resistance mutations which is associated with decreased response to etravirine: V90I, A98G, L100I, K101E, K101H, K101P, V106I, E138A, V179D, V179F, V179T, Y181C, Y181I, Y181V, G190A, G190S, and M230L (Vingerhoets *et al*. 2008). Vingerhoets *et al*. (2008) have found that different mutations affect viral susceptibility to etravirine to varying degrees. Every etravirine resistance-associated mutation was given a relative weight. Virologic response was found to be a function of the number and the weight of resistance mutations. With a 0-2 cummulative score, a response rate of 74% was reported. With a 2.5-3.5 score or 4 or more, response rates of 52% and 38% were reported respectively. Etravirine mutation weighting scheme is as follows (Vingerhoets *et al*. 2008):

- 3 - Y181I, Y181V
- 2.5 - L100I, K101P, Y181C, M230L
- 1.5 - V106I, E138A, V179F, G190S
- 1 - V90I, A98G, K101E, K101H, V179D, V179T, G190A

2.9.3.4 Pharmacokinetics

Concerning pharmacokinetic properties, NNRTIs display considerable inter-individual variability. All NNRTIs currently available utilize the cytochrome P450 system for metabolism and exert varying induction and inhibition effects on specific iso-enzymes (eg, CYP3A4, CYP2C9). All NNRTIs have a significant potential for drug-drug interactions (Knoll *et al* 2008; Ma *et al* 2005). Delavirdine primarily uses CYP 3A4 isoenzyme for metabolism. Nevirapine is metabolized mainly by CYP 3A4 but some secondary metabolism is achieved with CYP 2B6. Efavirenz is primarily metabolized through 2B6 with some secondary metabolism through 3A4. Etravirine is a substrate of CYP 3A4, 2C9, and 2C19. With the exception of Nevirapine, all NNRTIs are highly bound to plasma proteins (98-99%), primarily to albumin and alpha$_1$ acid glycoprotein. The plasma half-lives of the NNRTIs are fairly prolonged, ranging from 25-55 hours, except for delavirdine, which has a relatively short half-life (2-11 h) (Knoll *et al*. 2008; Ma *et al*. 2005).

2.9.3.5 Adverse effects

Nevirapine related skin rash, which is the most common adverse effect associated with the NNRTIs (Panel on Antiretroviral Guidelines for Adults and adolescents, 2011), usually develops within the first few weeks of initiating therapy and resolves with continued treatment (Knoll *et al*. 2008; Warnke *et al*. 2007). All NNRTIs, with the exception of etravirine have the ability to cause some degree of hepatotoxicity (Knoll *et al*. 2008). Delavirdine likewise efavirenz can increase transaminase levels, while nevirapine is found to cause severe toxicity, including hepatic necrosis in patients with CD4 counts that exceed 250 cells/μL (Rivero *et al*. 2007; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011). Efavirenz is exceptional

among NNRTIs, causing CNS effects such as insomnia, vivid dreams, dizziness, confusion, and hallucinations (Rathbun, 2014). Tolerance to efavirenz-related CNS adverse effects develops after several weeks of being on therapy. Bedtime administration and taking the drug on an empty stomach can minimize the severity of adverse effects. CNS effects is likely to persist in a small number of patients and may require discontinuation of the drug (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011). Gutiérrez-Valencia *et al*. (2009) in their study found that gradual upward titration of efavirenz over 2 weeks reduce neuropsychiatric symptoms and insomnia. In a randomized, double-blind, controlled trial of 114 patients, Gutiérrez-Valencia *et al*. (2009) again found that patients who received a full dose of 600 mg daily from day 1 had a higher incidence and severity of dizziness (66% vs 32.8%), hangover (45.8% vs 20.7%), lack of concentration (22.9% vs 8.9%), and hallucinations (6.1% vs 0%) during the first week, compared with patients who had gradual efavirenz titration to 600 mg daily by day 14. During week 2, the incidence of the above-mentioned adverse effects was similar in each group; however, the severity of adverse effect was greater in the full-dose group. Virologic and immunologic response to efavirenz was similar in both groups (Gutiérrez-Valencia *et al*. 2009).

2.9.4.1 Protease Inhibitors

HIV protease inhibitors (PIs) were first introduced in 1995 and still form an integral part of the treatment of HIV infection (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011). Eight agents have been approved for use, as follows: Atazanavir (Reyataz), Darunavir (Prezista), Fosamprenavir (Lexiva), Indinavir (Crixivan), Lopinavir/ritonavir (Kaletra), Nelfinavir (Viracept), Saquinavir (Invirase)

and Tipranavir (Aptivus). Although all protease inhibitors exhibit the same mechanism of action, they have significant differences in their pharmacokinetics, efficacy, and adverse effects profiles (Rathbun, 2014).

2.9.4.2 Mechanism of action

HIV protease is a 99-amino-acid, aspartic acid protein and its function is to ensure maturation of virus particles late in the viral life cycle. Cleavage of individual proteins from the *gag* and *gag -pol* polypeptide precursors into functional subunits by HIV protease occurs systematically for viral capsid formation during or shortly after viral budding from an infected cell (Rathbun, 2014). HIV protease inhibitors act as competitive inhibitors that directly bind to the HIV protease enzyme and prevent subsequent cleaving of the polypeptides. Protease inhibitors exhibit activity against clinical isolates of both HIV-1 and HIV-2 (Flexner, 1998).

2.9.4.3 Resistance

Resistance to the HIV protease enzyme results from mutations ocurring inside and outside the active protease domain (Kim and Baxter, 2008). Resistance typically occurs through the development of one or more major viral mutations, which confer conformational changes to the protease binding site, followed by secondary compensatory mutations that improve enzymatic activity and, in a number of cases, viral fitness (Kim and Baxter, 2008). Resistance to the first-generation protease inhibitors (indinavir, ritonavir, nelfinavir, saquinavir) occurs with the development of one or more of the following primary point mutations (Kim and Baxter, 2008):

- G48V, L90M (saquinavir)
- M46I, V82A/L/F, I84V (indinavir)

- V82A/L/F, I84V (ritonavir)
- D30N, L90M (nelfinavir)
- I50L, I84V, N88S (atazanavir)
- I50V, I84V (fosamprenavir)

Multiple mutations are typically essential and must occur in order to cause high-level resistance to ritonavir-boosted protease inhibitors. The boosted protease inhibitors exhibit a higher genetic threshold for resistance than unboosted protease inhibitors (Hirsch *et al*. 2008). Cross-resistance to other protease inhibitors may develop as the number of mutations increases (Rathbun, 2014). The second-generation protease inhibitors; lopinavir/ritonavir, darunavir, and tipranavir may retain some activity in the presence of resistance to the first-generation agents. Ritonavir boosted Lopinavir requires the accumulation of 7 or more mutations in order to become clinically ineffective. Typical of darunavir and tipranavir, they retain activity against lopinavir/ritonavir and first-generation protease inhibitor–resistant strains of the virus (Kim and Baxter, 2008). Eleven resistance mutations have been identified for darunavir; accumulation of 3 or more of these mutations can cause virologic failure. Tipranavir also requires accumulation of multiple non- overlapping mutations before high-level resistance can develop (Kim and Baxter, 2008). In a review of 2725 HIV isolates for protease inhibitor susceptibility, Rhee *et al*. (2010) found that certain mutations could result in increased vulnerability to a particular drug, and that some effects on resistance had been underestimated. In conclusion Rhee *et al*. (2010) asserted that cross-resistance between the various protease inhibitors now and in the future may be missed without systematic analysis of the effects of specific mutations.

2.9.4.4 Pharmacokinetics

Protease inhibitors exhibit considerable inter-patient and intra-patient variability in their pharmacokinetic profile (King *et al*., 2004). Significant first-pass metabolism by cytochrome P450 (CYP) 3A4 and 3A5 and intestinal efflux by p-glycoprotein have been observed with the protease inhibitors (King *et al*., 2004). With the exception of indinavir, protease inhibitors are extensively bound to plasma protein (97-99%), primarily to albumin and alpha- 1 acid glycoprotein. There is limited distribution of the PIs into the CNS. Protease inhibitors have relatively short plasma half-lives compared to NRTIS and NNRTIs. Their half- lives range from 1.5-2 hours for indinavir and 7 hours for atazanavir (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011).

Metabolism through CYP3A4 results in significant drug-drug interactions with other medications cleared through this pathway. Interactions with medications cleared through other CYP450 isoenzymes and phase II pathways (eg, glucuronidation) could also occur, depending on the individual protease inhibitor (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011). Low-dose ritonavir (100-200 mg) is frequently co-administered with other protease inhibitors with the aim of blocking intestinal and hepatic CYP 3A4 metabolism. Addition of low-dose ritonavir improves pharmacokinetic variability, resulting in more consistent serum concentrations throughout the dosing interval and improved treatment response (King *et al*., 2004).

2.9.4.5 Adverse effects

Common adverse effects associated with protease inhibitors include gastrointestinal effects such as diarrhea, nausea, vomiting and metabolic complications such as dyslipidemia, insulin resistance, lipodystrophy. (Rathbun,2014). Metabolic complications are common in patients on protease inhibitors and represent an important consideration in choosing antiretroviral therapy. Up to 70% of patients receiving protease inhibitor therapy develop dyslipidemia and normally requires administration of lipid-lowering drugs (Kottler, 2008). Drug interactions can exclude the use of some lipid-lowering agents. Lifestyle and individual pharmacogenetics are important contributing factors to the type and severity of lipid abnormalities (Kottler, 2008).

In 1997, the US FDA authorized that all protease inhibitors going into the market included labeling regarding the potential for hyperglycemia and diabetes mellitus with therapy; however, the different protease inhibitors have significantly different propensities for affecting glucose metabolism. Indinavir has the greatest potential for altering glucose metabolism. Modest effects have been observed with nelfinavir, lopinavir/ritonavir, fosamprenavir, and tipranavir. Atazanavir (boosted or unboosted), darunavir, and saquinavir appear to have limited effect on insulin sensitivity and glucose homeostasis (Tebas, 2008). Alteration in fat distribution (fat redistribution) occurs in 40-50% of patients receiving protease inhibitors in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Common manifestations of altered fat distribution include fat accumulation or fat loss (sunken cheeks, wasted buttocks and extremities). Both abnormalities may develop in the same patient, but they are considered independent entities (Grinspoon and Carr,

2005). Accumulation of fat has been predominatinately associated with protease inhibitor therapy; however, more recent data demonstrate that it occurs with both protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI)–based regimens (Rathbun, 2014). Various management strategies have been explored with varied results. Change of protease inhibitor–based therapy to a protease inhibitor–sparing regimen does not produce significant improvement and is not recommended (Wohl and Brown, 2008).

Occurrence of adverse effects with the individual protease inhibitors need to be considered when selecting therapy for patients with other comorbidities. Asymptomatic hyperbilirubinemia is common in patients who are on atazanavir and indinavir but does not require discontinuation of therapy in the absence of concomitant elevation in levels of liver transaminases. Nephrolithiasis occurs with indinavir and, occasionally with, atazanavir (Panel on antiretroviral guidelines for adults and adolescents, 2011). Cardiac conduction abnormalities (atrioventricular block and bundle branch block) occur in 5% of patients receiving atazanavir. The same has been reported with other protease inhibitors (ritonavir, lopinavir/ritonavir, nelfinavir) (U. S Food and Drugs advisory committee, 2013). Tipranavir may increase levels of liver transaminases and must be avoided in patients with hepatitis B or hepatitis C coinfection. Intracranial bleeding events have also been identified with the use of tipranavir therapy (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011).

2.10 REASONS FOR CHANGE/ SWITCH IN THERAPY

Once antiretroviral therapy is initiated, patients are expected to remain on it for an indefinite period. Medication switches are especially problematic in resource- poor settings where treatment options are limited (Njuguna *et al*., 2013). A switch in antiretroviral therapy is often necessitated by both acute and chronic toxicities, treatment failure, poor adherence, desire for pregnancy, and drug interactions or comorbidity. The approach to patients requiring ART regimen switch will differ depending on a number of issues including the reason for change, previous ART experienced and the available treatment options (Wilkin *et al*. 2006)

The most important cause predicting the need for ART switching is drug toxicity (Hart *et al*. 2007; Cesar *et al*., 2010; Njuguna *et al*., 2013) with significant heterogeneity in the distribution of adverse events. These ART-related toxicities are typically not life threatening but can negatively affect quality of life and the patients' willingness to adhere to their regimen. Efavirenz -related gastrointestinal disturbances such as diarrhea, nausea and vomiting are the most frequently cited side effect leading to change in an initial ART regimen (Wilkin *et al*. 2006). Most of the toxicities resulting in treatment modifications or change occurred in the first three months of being on therapy in the Wilkin *et al*., (2006) study. Peripheral neuropathy according to reports by Beharu and Nasir (2013) was the most common reason for regimen modification resulting from Stavudine based regimen. Patients with more advanced disease at the time of initiating therapy necessitated higher rates of regimen discontinuation due to adverse effects. A study conducted in Peru reported anemia as a main reason for discontinuation of treatment (68%), and associated this finding with the use of standard 600 mg ZDV in low-weight patients (Bangsberg *et al*. 2006)

while Beharu and Nasir in Ethiopia reported of skin rash and anemia as the second and third most common reason for changes in ART regimen respectively. Rash was mainly due to the NVP-containing regimen and anemia was due to the AZT-containing regimen.

Clinical drug toxicity which occurred in patients starting Nevirapine (NVP) based regimen and Efavirenz based regimen was the most predictable reason for changing an initial ARV regimen followed by Stavudine and Zidovudine combined therapy (Wilkin *et al*., 2006). Tenofovir (TDF) containing regimen was the best tolerated with fewer reported events of adverse reactions and therefore had the lowest potential for drug substitutions due to adverse events (Njugunal *et al*., 2013; Wilkin *et al*., 2006). Efavirenz-based regimens according to reports by Beharu and Nasir (2013) had the lowest hazard for change relatively. However, increased risk for change of Efavirenz-based regimens was marked during pregnancy or when planning pregnancy

Comorbidities in patients with advanced disease and concurrent treatments for opportunistic diseases could pave the way for drug-drug interactions with a consequent increase in the risk of toxicities and decrease tolerance to ART (Cesar *et al*. 2010). Comorbidity was the other reason for changes in ART. Planning pregnancy or being pregnant was the third major reason responsible for modifying antiretroviral regimen (Beharu and Nasir, 2013; Cesar *et al*., 2010). Mediation switches during pregnancy may be due to the possible teratogenic effect of EFV, Efavirenz is avoided during the first trimester of pregnancy. In a study by Beharu and Nasir (2013), patients were more likely to change their therapy shortly after HAART

initiation, due to adverse effects, rather than treatment failure. Treatment failure was cited as the reason for change in 2.6% of the patients in the Beharu and Nasir (2013) study. However, studies by Kiguba, (2007) and Mess *et al*. (2010) cited higher treatment failure as the reason for a change in regimen. In a study in Cote d'Ivoire by Mess *et al*.,(2010), treatment failure was observed in 12.4% of the patients while according to a study by (Kumara, 2006) in India, treatment failure accounted for 14% of the reasons for modifying therapy. Rate of drug substitution due to treatment failure was similar for patients exposed to TDF, ZDV, d4T based regimen (Beharu and Nasir, 2013)

Cost of ARV treatment was one of the reasons cited for discontinuation and modification of ARV drugs according to the study conducted in India (64%) (Mess *et al*., 2010) and Uganda (23%) (Kiguba, 2007). However, cost was not a reason for modification of ARV drugs in Beharu and Nasir (2013) study, due to the provision free ARV drugs.

Increasing age is a known risk factor for adverse drug reactions. Female sex and age above 40years have been associated with increased risk of drug substitution (Beharu and Nasir, 2013). The female sex has been identified as a strong predictor of drug substitutions in several studies (Chi *et al*. 2010; Brennan *et al*. 2013).

2.11 CONCLUSION

Antiretroviral therapy over the past decades has proven to be beneficial and its benefits arguably far outweighs its risk (Siegfred, Uthman and Rutherford, 2010).

Effective use of antiretroviral drugs has been associated with improving and prolonging the lives of people infected with the HI virus significantly.

Despite remarkable progress in the management of HIV infection noted in the past years, significant challenges to therapy such as Adherence, ARV tolerability issues and emergence of drug- resistant strains of HIV still exist (Stanic and Schneider, 2005). Policies and interventions should be directed at eliminating the barriers to adherence as much as possible as well as maximizing ART adherence.

CHAPTER 3

MATERIALS AND METHODS

3.1 STUDY AREAS

The study was conducted at the HIV/AIDS treatment centers at Bomso specialist hospital and Aninwah Medical Center. These private medical facilities were chosen for the context of this research work because;

1. They both use the prevailing national guidelines issued by the National AIDS/STI control programme for the management of HIV- infected patients.
2. Patients have not been privileged to benefit from any similar research which will gear authorities towards the development and implementation of a robust policy intervention to help improve sustainable adherence behaviours.

3.1.1 Aninwah Medical Center

Aninwah Medical Center was established in 1996 to help cater for the growing sick population in the community and the surrounding villages. It is located at Emena, a suburb of Kumasi in the Ashanti region.

The hospital established its HIV treatment center in October 2007 with a mission to help the Ghana AIDS commission reach out to people living with HIV/AIDS in the Kumasi metropolis and to ensure easy access to ART. The center started with a patient population of approximately 30 and now has a population of over 600 attendants. The center has a staff capacity of eight of which four are nurses, one medical practioner, one pharmacist and two counselors from the Ghana Health

Service (GHS). The nurses however double as counselors. The center opens on Wednesday at 8am and closes at 5pm. On clinic day, activities such as voluntary counseling and testing of HIV, prevention of mother- child- transmission, treatment of HIV/AIDS are done. Patients who need nutritional counseling are referred to the nutritionist based in the hospital.

3.1.2 Bomso specialist hospital

The Bomso specialist hospital was established in 1980 as a specialist clinic to cater for cases on out- patient bases. The facility has now been upgraded into a specialist hospital with a total bed capacity of sixty and an OPD attendance rate of approximately seventy patients daily. It is located at Bomso a suburb of Kumasi and under the Kumasi metropolitan assembly.

The HIV treatment center was established in 2006 with a mission to help the Ghana AIDS commission to reach out to the growing HIV/AIDS infected population in the Kumasi Metropolis. The center started operating with few patients of about 20 and is now rendering services to over 1200 patients with 70% of the current patient population being females and 30% being males. Service rendered at the center includes serving of antiretroviral drugs, adherence counseling, and medical consultations, voluntary testing of HIV/AIDS, nutritional counseling and routine laboratory checkups. The center can boast of a staff capacity of seven with three being counselors, one medical practioner, one pharmacist and two qualified and trained nurses. Adherence counseling is however done by the pharmacist who has been trained to render such services to patients.

The center gets its supply of drugs from the procurement unit, Regional Health Directorate, Kumasi. However the center experiences frequent medication stock-outs. The center opens from Mondays to Fridays from 8am to 3pm. Medical consultations are however done on Wednesdays and Fridays.

3.2 STUDY DESIGN

This was a prospective non- randomized study designed to determine whether a 9 month adherence to highly active antiretroviral therapy will improve clinical and immunologic outcomes of HIV- infected patients receiving treatment at the Aninwah Medical Center and Bomso Specialist Hospital.

3.3 STUDY POPULATION, AND SAMPLING

A population of 86 HIV- Infected patients between the ages of 18 and 70 years was recruited through the HIV/AIDS clinics at Aninwah Medical Center and Bomso Specialist Hospital using a purposive sampling technique as described by Patton, (1990). Patients were eligible for the study if they have a CD4 T cell count ranging from 100 - 350 cells/uL, and gave informed consent. Patients were excluded from the study if they have a history of WHO stage IV AIDS defining condition, pregnancy. Other exclusion criteria included a hemoglobin level less than 8g/dL, elevated liver enzymes above the normal upper limit, serum urea and creatinine levels above the normal upper limit and a body weight less than 30kg.

3.3.1 Justification for the inclusion of patients with CD4 cell counts < 350 cells/ uL in the study

Baseline CD4 cell counts required for initiation of therapy in resource limited settings according to the WHO treatment guideline is 350cells/uL (WHO, 2009). This protocol may not be fully or strictly adhered to in resource poor settings like Ghana due to delayed detection of HIV cases. Most patients who are recruited to start treatment usually come with baseline CD4 cell count < or equal to 100 cells/uL when symptomatic signs and symptoms have developed (CASCADE, 2004). A similar observation is made by Cohen *et al*. (2009). According to Cohen *et al*. (2009), in sub- Saharan Africa many HIV- infected patients only access health care when advanced symptomatic disease has developed. This delay in the view of Cohen and co is further compounded by health system delays.

The median CD4 cell count among those enrolling in ART programs at the research setting was often < or equal to 100 cells/uL though programs have been well established for several years. This according to CASCADE (2004) and WHO (2009) is a programmatic challenge common to all sub- Saharan countries.

The above necessitated the researcher's decision to select clients with baseline CD4 cell count ranging from 100- 350 cells/uL as entry requirement into this study as against the WHO protocol.

3.3.2 Sample size justification

The estimated minimum sample size for the study was calculated to be 47 based on estimated HIV prevalence rate of 3.2% in Ashanti region as at 2012 (Ghana Aids

Commission, 2013). With an expected difference of 5% between the sample and the general population and a type1 error of (α) 0.05, the sample size was determined using the cochran's formular:

$$n = \frac{z^2 (1 - p) p}{d^2}$$

Where n = minimum sample size; Z = standard normal variance (1.96) to obtain a power of 95% confidence interval and a type 1 error probability of 5%; Absolute standard error d = 0.05; P= prevalence rate (3.2%); 1- P = The proportion of the population without HIV infection. Based on the formular above, the sample size was supposed to be 47. The figure was projected to 100. However, due to the number who satisfied the inclusion criteria and gave consent, the projected number was reduced to 86

3.4 ADHERNCE MEASUREMENT

Individual patient adherence rate was measured using self-reports and pill counts at the clinic premises. Self-report has been used by Mannheimer *et al* (2005) in assessing the adherence rate of 100 HIV infected patients and has described it as reliable. Structured questionnaires were administered to patients to give self-account of their adherence behaviour by responding to a number of questions. Patient self-reporting procedure as previously described by Weiser *et al* (2003) and Erah and Arute (2008) was followed. With this method, patients were made to answer questions about their adherence behavior over the previous day, week and the previous month sequentially in an attempt to reduce recall bias. Common reasons for missing doses as described in other literature (Wang *et al*., 2008; Wang and Wu, 2007; Erah and Arute, 2008) were listed

in the questionnaire. Patients were asked to check all reasons and choose as many as they want.

The questionnaire was also used to gather other information such as basic drug information and side effects experienced. Questions were drafted in such way that it eliminates elements of judgment and allow for free responses (Fairman and Motheral, 2000). Based on the number of doses/pills missed in a month, percentage adherence was calculated using this formular;

$$\text{Rate} = 100\% - \frac{\text{No. of pills missed in a day}}{\text{Total No. of pills to be taken in a day} \times 30} \times 100$$

In order to validate information provided by patients, they were asked to come along with their pills at each visit. Number of pills left for that particular month was counted to confirm the number of pills missed as reported by patients.

Patients were described as 100% adherent if they took all prescribed doses in a month, sub-optimally adherent if they missed 5% of all prescribed doses in a month and non-adherent if they missed more than 5% of all prescribed doses in a month. Patients were classified this way based on reports by Bangsberg and Machintinger, (2005) that in order to achieve durable viral suppression and clinical success, patients will require a near perfect adherence rates of $\geq 95\%$.

3.5 PROCEDURE

Patients who satisfied the inclusion criteria were made to start first line combined antiretroviral therapy as recommended by the Ministry of Health in line with WHO protocols. Before drugs were given to patients, adherence counseling was done. Patients were monitored for adherence every month throughout the 9 months period. Mean adherence rate for each patient was calculated using this formular;

Mean adherence = % adherence for 1st month + 2nd Month + 3rd month +…../ number of months

Immunologic outcomes were assessed by laboratory quantification of CD4 cell counts. CD4 T cell count was done at baseline, 6th month and the 9th month. The difference in CD4 counts from baseline through to the 9th month was assessed and analyzed.

Clinical outcomes were assessed by the presence of opportunistic infections, prevailing signs and symptoms, frequency of hospitalization and overall physical health. According to Mannheimer *et al*. (2005), Clinical outcomes of ART could be measured indirectly by following weight, symptoms, and the ability to return to performing the activities of daily life. Clinical assessment was done by an independent medical practioner. Patients were then rated as good, averagely well or poor based on the above indices. Results of clinical outcomes were assessed and analyzed.

3.6 DATA COLLECTION

Data collection lasted for a period of one year, one month. A face to face interview was conducted while using the structured questionnaire. Information regarding patients' socio demographic characteristics, clinical features at baseline, adherence

behavior and clinical outcomes was obtained as the study progressed. Data were collected at baseline, 3rd month, 6th month and 9th month with the same instruments.

All interviews were conducted at clinic visit and were done in a secluded area of the treatment site which was out of earshot of clinic staff and other patients. Medical records of patients were reviewed to obtain data about laboratory results, CD4 cell counts, and presenting complaints. Patients' records were also reviewed at baseline and the successive months for the number of HIV/AIDS- related hospitalization and opportunistic infections.

3.7 EXPECTED OUTCOMES

The medical records of each patient were reviewed at the end of the 6th month and 9th month for the latest laboratory results of CD4 counts. Medical records of individual patients were reviewed at 3rd month, 6th month and 9th month successively for the determination of any of the clinical indices.

The expected outcome of this study was;

- Evidence of improved immune function, CD4 cell growth and recovery as shown by an increase in cell counts greater than the baseline – 100- 350cells/ ul (before initiation of therapy)
- Evidence of reduced opportunistic infections, sign and symptoms as verbalized by the patient and confirmed by the researcher through a review of patient's current medical records.
- Evidence of reduced incidence of hospitalisation as shown by patient's medical records.
- Evidence of increased body weight and improved physical health.

3.8 STATISTICAL ANALYSIS

The data entry and analysis were performed using IBM statistical package for social science (SPSS) version 20. Descriptive statistics such as frequencies, and percentages were used to summarize patients' socio-demographic characteristics. Chi-square test was used to compare association between adherence rate and patient outcomes. All results were confirmed at 5% level of significance. P value less than 0.05 was considered statistically significant difference. ANNOVA was used to compare the differences in mean.

3.9 ETHICAL CONSIDERATION

Institutional approval was sought before the commencement of this study and approval of the participant was through the consent form. The participants were fully informed of the purpose, procedures, risks, and benefits of participating in this study. Each participant was assured that their responses would be kept confidential. A code was assigned for each subject and personal identifying information was not allowed to appear in the questionnaire. All data was locked and were accessed only by the researcher. Participants with poor adherence and inaccurate medication knowledge were allowed to receive immediate counseling and advice from the researcher.

CHAPTER 4

RESULTS

Eighty six (86) patients enrolled for this study. Eighty five completed the study. One (1) was excluded from the study in the 6th month due to a confirmed pregnancy.

4.1 Sociodemographic characteristics

Out of the 86 patients studied, 31.4% were between the ages of 36-45 and 4.7% were between 66- 75 years. About 68% were females and 30.2% were males. Sixty – seven percent of the population had completed JHS & SHS (Table 1). Only 2 (1.2%) had completed A-level. About 63% were self-employed, 19% were civil servants and 16% were unemployed (Table 1). Close to 42%were married, 35% singles, 16% divorced and 7% were widowed. Eighty- five percent (84.9%) were Christians and 15.1% were muslims **(Table 4.1).**

Table 4. 1 Socio-demographics of studied patients

Variable	N=86	Percentage (%)
Age group		
18-25	8	9.3
26-35	24	27.9
36-45	27	31.4
46-55	13	15.1
56-65	10	11.6
66-75	4	4.7
Gender		
Male	26	30.2
Female	59	68.6
Highest level of Education		
Basic	4	4.7
JHS	29	33.7
SHS	29	33.7
O-Level	2	2.3
A-Level	1	1.2
Tertiary	7	8.1
Not educated	14	16.3
Employment Status		
Self Employed	54	62.8
Unemployed	14	16.3
Civil Servant	16	18.6
Student	2	2.3
Marital Status		
Married	36	41.9
Single	30	34.9
Divorced	6	7.0
Widowed	14	16.3
Religion		
Christian	73	84.9
Muslim	13	15.1

*4.2 DISTRIBUTION OF ARVS USED BY PATIENTS OVER THE NINE **MONTHS***

PERIOD

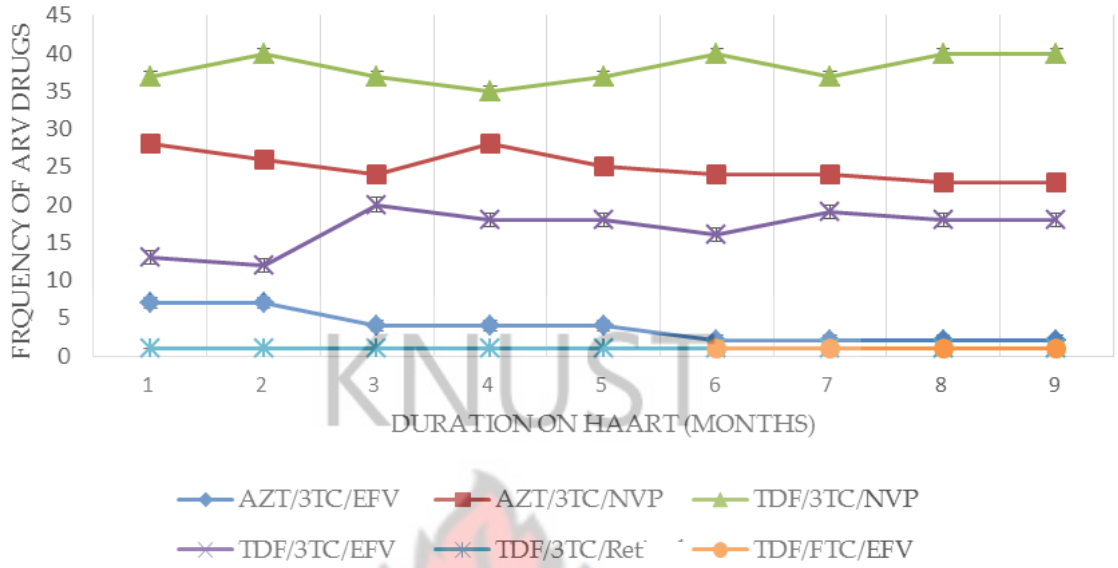

Figure 4. 1 Distribution of antiretroviral combination therapy
AZT/3TC/EFV - zidovudine/ lamivudine/ efivarenz; AZT/3TC/NVP - zidovudine/ lamivudine/ nevirapine; TDF/3TC/NVP - tenofovir/ lamivudine/ nevirapine; TDF/3TC/EFV - tenofovir/ lamivudine/ efavirenz; TDF/3TC/Ret - tenofovir/ lamivudine/ ritonavir boosted Lopinavir; TDF/FTC/EFV- tenofovir/ emitricitabin/ efavirenz

The most frequently used ARV drug was TDF/3TC/NVP (refer legend, fig 4.1), followed by AZT/3TC/NVP, TDF/3TC/EFV, AZT/3TC/EFV, TDF/3TC/Ret and TDF/FTC/EFV **(Figure 4.1).** The fluctuations in the graph are indication of frequency of drug switches among patients with reasons for drug switches being mainly side effects and drug shortages. Side effects that resulted in medication switches were skin rashes, nausea/vomiting. Changes in medication occur in the 2nd month through to the 7th month. There was no association between type of ARV combination and outcomes (p> 0.05).

4.3 ADHERENCE RATES OF THE PARTICIPANTS

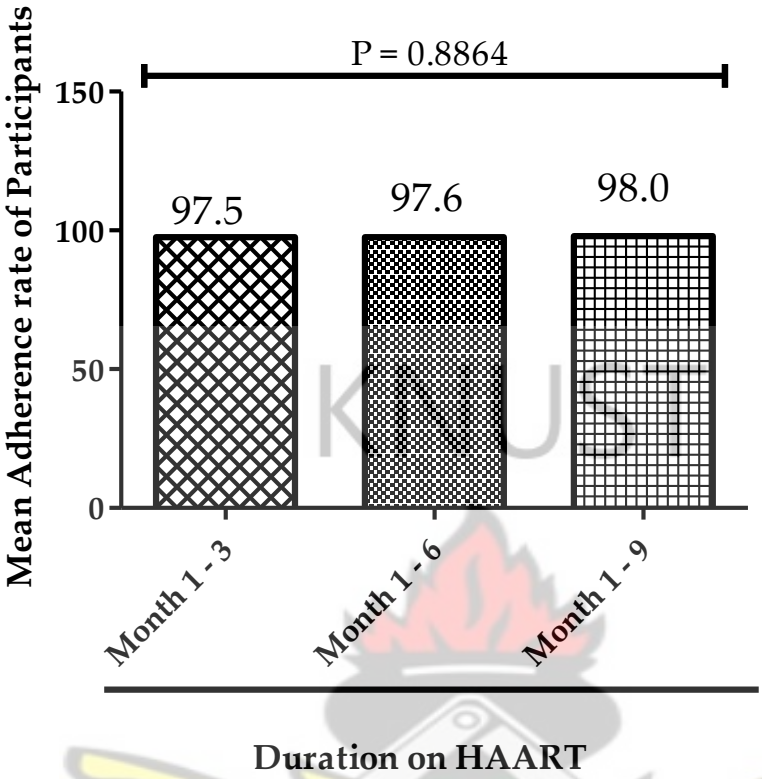

Figure 4. 2 Mean rate of adherence

The mean rate of adherence increased with increasing duration on HAART. Mean adherence rate was 97.5 % at 3rd month, 97.6 at 6th month and 98.0% at 9thmonth.

(Figure 4.2)

4.4 OVERALL RATE OF ADHERENCE

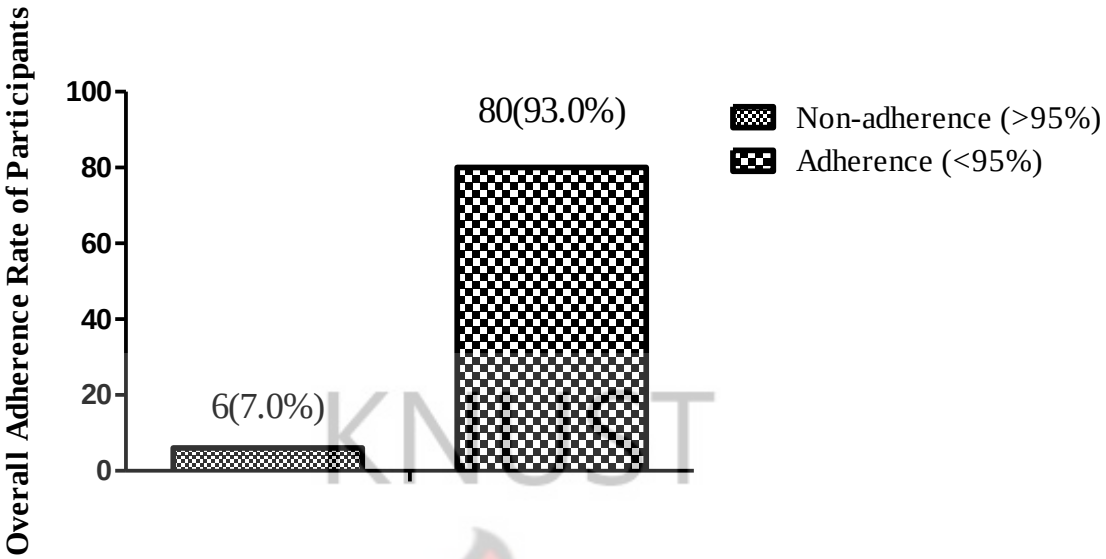

Figure 4.3 Overall Rate of adherence of participants.

Majority (93%) of the participants were adherent and 7 % were not adherent.

4.5 REASONS FOR MISSING DOSES OVER THE NINE MONTHS PERIOD

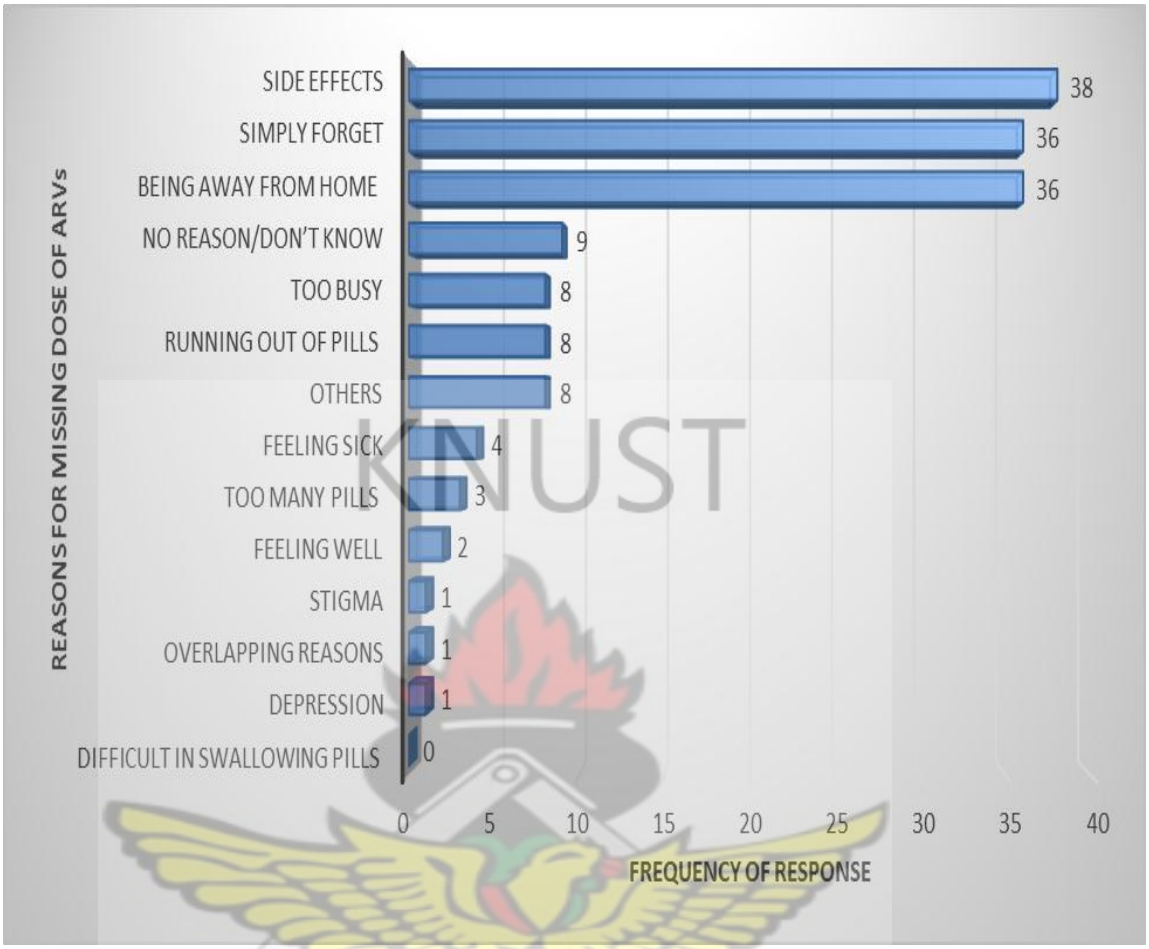

Figure 4. 4 Reasons for missing doses

Common reasons for missing doses were side effects , forgetfulness, being away from home , running out of pills, being busy, feeling sick, and too many pills in that order **(Figure 4.4)**. Common side effects experienced by participants were change in urine colour, skin rashes, nausea with vomiting and abdominal discomfort.

4.6 NUMBER OF OPPORTUNISTIC INFECTIONS

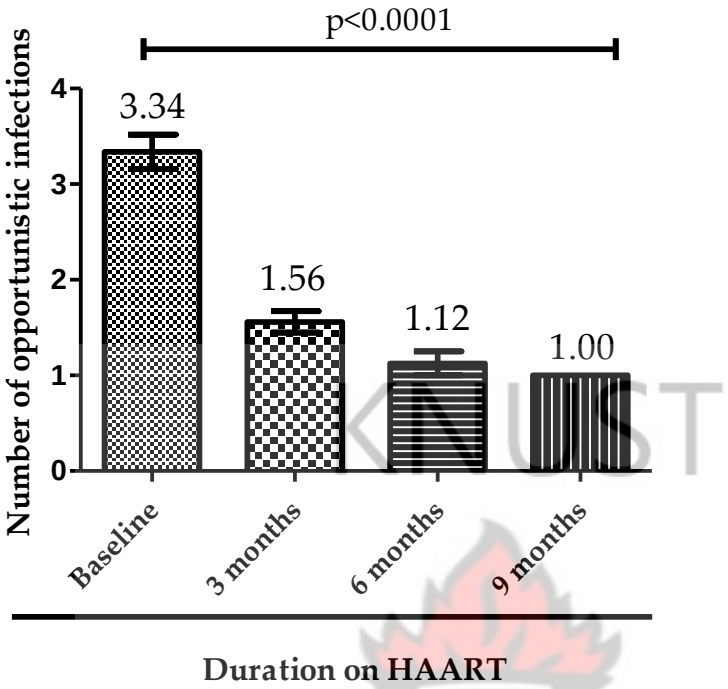

Figure 4. 5 Mean number of opportunistic infection over the nine months period on HAART

The mean number of opportunistic infections decreased with increasing duration on HAART. There was a significant difference in number of opportunistic infections over the nine month period ($p<0.0001$) **(Figure 4.5).**

The prevalence rate of opportunistic infections at baseline was 82.5%, 58.15 at 3rd month, 9.4% and 8.2% at 6th and 9th month respectively. Overall prevalence rate was 24.8%.

4.7NUMBER OF SIGNS AND SYMPTOMS

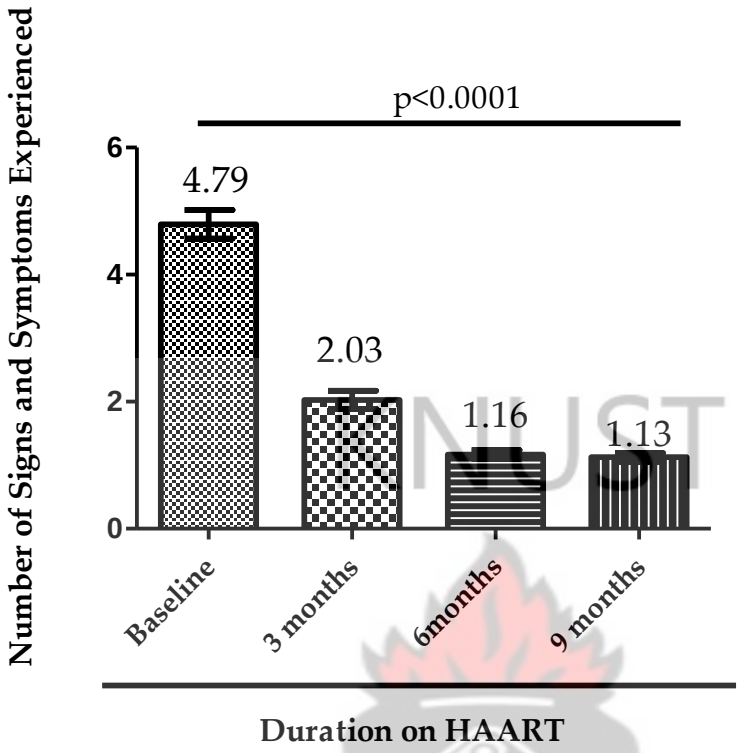

Figure 4. 6 Mean number of signs and symptoms experienced by patients over the nine months period on HAART

The average number of signs and symptoms was high at baseline but reduced from month three, through month six to month nine. The difference in average number of signs and symptoms experienced across the studied period was significant (p<0.0001) **(Figure 4.6).**

4.8 INCIDENCE OF HOSPITALISATION

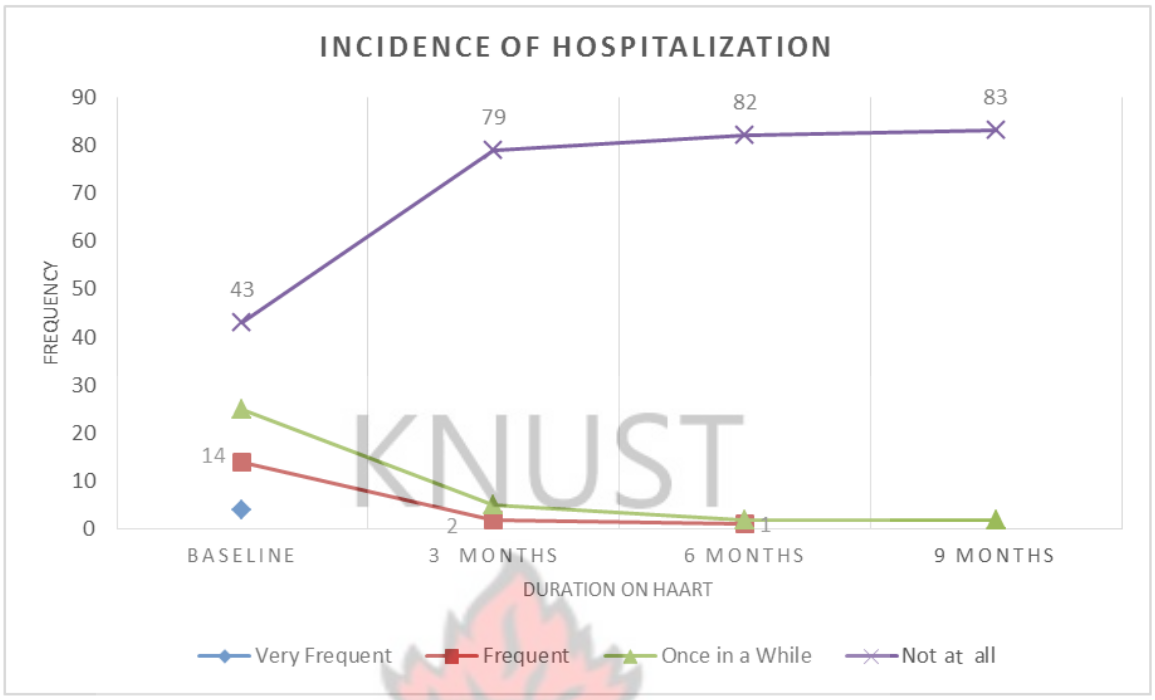

Figure 4. 7 Incidence of Hospitalization

Fourteen (14) of the patients were frequently hospitalized at baseline but was reduced to 2 patient and 1 at third and sixth month respectively. The frequency of patients who had no history of hospitalisation was 43 at baseline, 79 at third month, 82 at sixth month and 83 at ninth month **(Figure 4.7).**

4.9 OVERALL PHYSICAL HEALTH OF PATIENTS

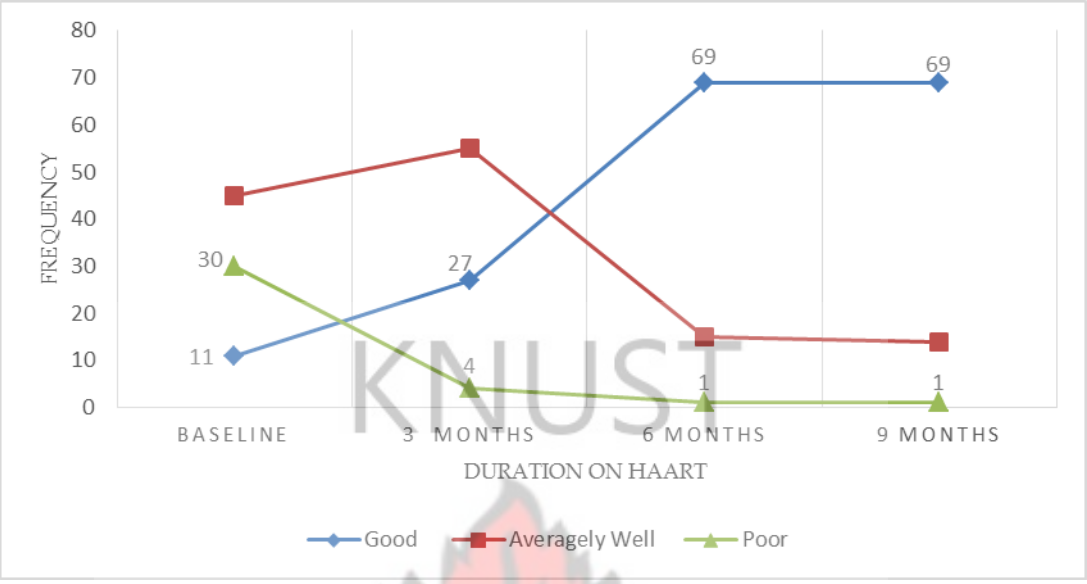

Figure 4. 8 Overall physical health

At baseline 30 of the patients had a poor physical health. The number reduced to 4 patients at the third month and 1 at both sixth and ninth month. The number of patients who had "good" physical health were 11 and 27 at baseline and third month respectively but was 69 at both sixth and ninth month. The number of patients with"good" physical health increased with increasing duration on HAART **(Figure 4.8).**

4.10 MEAN WEIGHT OF PATIENTS

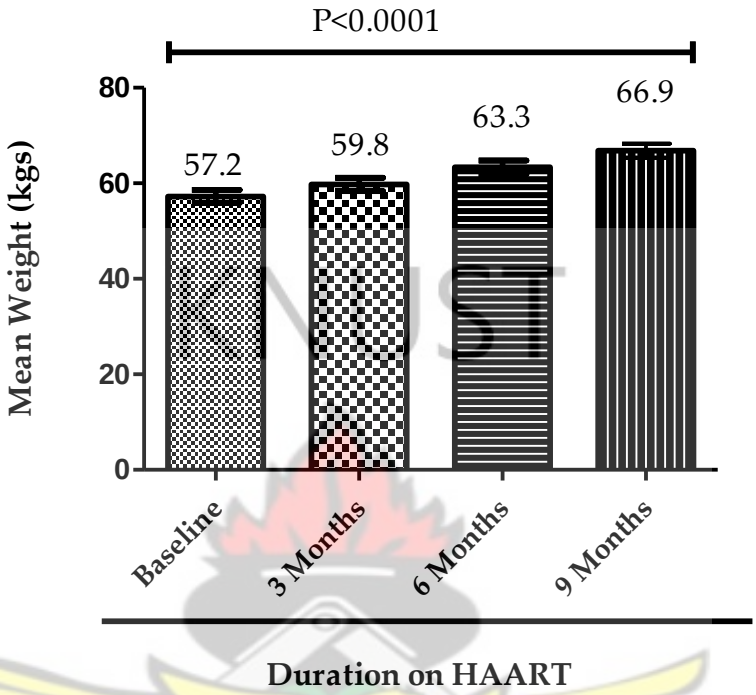

Figure 4. 9 Mean weight of studied patients stratified by the duration on HAART.

The average weight was 57.2kg at baseline, 59.8kg at the third month, 63.3kg at the sixth month and 66.9kg at the nine month (Fig 4.9). The mean weight was significantly increasing with increasing duration on HAART. The difference in mean across the studied durations on HAART was significant (p<0.0001) **(Figure 4.9).**

4.11 IMMUNOLOGIC OUTCOME

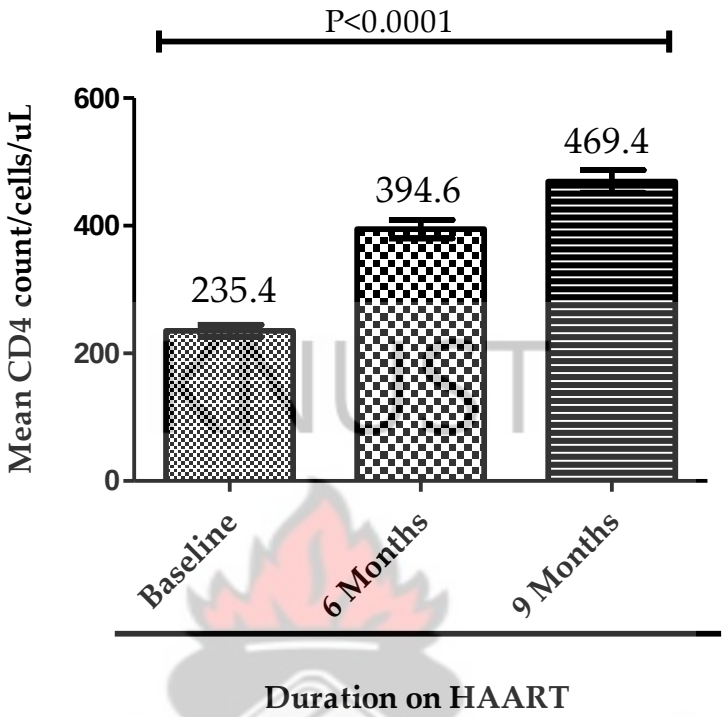

Figure 4. 10 Mean CD4 count of studied patients stratified by the duration on HAART.

The CD4 count levels was low at baseline (235.4 cells/uL) but increased to (394.6 cells/uL) and (469.4cells/uL) ($p<0.0001$) at sixth and ninth month respectively. The mean increase in CD4 cell count from baseline to sixth month was 159 cells/uL and 74.8cells/uL from sixth month to the ninth month **(Figure 4.10)**

4.12 ASSOCIATION BETWEEN ADHERENCE RATE AND CD4 COUNT

Table 4. 2 Association between CD4 count and % rate of adherence

	Adherence rate (%)			Chi-Square	P-Value
	<95%	≥95%	Total		
CD4 counts	N (%)	N (%)	N (%)		
At 6 month					
150 -250ul	3(25)	9(75)	**12 (100)**	6.441	0.183
251- 350 ul	2(8.0)	23(92.0)	**25(100)**		
351-450ul	0(0)	19(100)	**19(100)**		
451 - 550ul	1(7.1)	13(92.9)	**14(100)**		
551 - 650ul	0(0)	11(100)	**11(100.0)**		
651 - 750ul	0(0)	2(100)	**2(100)**		
751 -850ul	_	_	_		
851 - 950ul	_	_	_		
At 9 month				6.59	0.304
150 -250ul	1(16.7)	5(83.3)	**6(100)**		
251- 350 ul	3(20)	12(80)	**15(100)**		
351-450ul	0(0)	15(100)	**15(100)**		
451 - 550ul	2(8.3)	22(91.7)	**24(100)**		
551 - 650ul	0(0)	12(100)	**12(100)**		
651 - 750ul	0(0)	9(100)	**9(100)**		
751 -850ul	0(0)	1(100)	**1(100)**		
851 - 950ul	0(0)	1(100)	**1(100)**		

Values are presented as frequency with percentages in parenthesis.

There was no statistically significant association between CD4 count and the rate of adherence ($p>0.05$). The proportion of patients with >95% adherence who increased their CD4 count beyond 350 cells/ uL were comparably higher (70.5%) than those with <95% adherence**.**

4.13 ASSOCIATION BETWEEN ADHERENCE RATE AND RATE OF OIs

Table 4. 3 Association between Rate of Opportunistic Infection and % rate of adherence

	Adherence Rate %				
	<95%	≥95%	**Total**	Chi-square value	P-value
Rate of Opportunistic Infection	N (%)	N (%)	**N (%)**		
At 3 Month					
Too many	1(100)	0 (0)	**1(100)**		
Few	1(5.3)	18(94.7)	**19(100)**		
Very few	2(6.7)	28(93.3)	**30(100)**	0.316	0.69
None	2(5.6)	34(94.4)	**36(100)**		
At 6 Month					
Too many	0(0)	0(0)	**0(0)**		
Few	1(100)	0(0)	**1(100)**		
Very few	2(28.6)	5(71.4)	**7(100)**	0.835	0.605
None	3(3.9)	73(96.1)	**76(100)**		
At 9 Month					
Too many	0(0)	0(0)	**0(0)**		
Few	1(100)	0(0)	**0(100)**		
Very few	2(28.6)	5(71.4)	**7(100)**	0.779	0.247
None	3(3.8)	75(96.2)	**78(100)**		

Values are presented as frequency with percentages in parenthesis.

There was no statistically significant association between rate of opportunistic infections and the rate of adherence (p>0.05). The proportion of adherent patients with fewer or no opportunistic infections was comparably higher than the non-adherents (< 95%) **(Table 4.3).**

There was no statistically significant association between adherence levels and other clinical indices (sign and symptoms, incidence of hospitalisation, weight, overall physical health) (P > 0.05). The proportion of adherent patient with improved clinical indices was comparably higher than the non- adherent patients

4.14 ASSOCIATION BETWEEN BASELINE CD4 COUNT AND RATE OF OIs

Table 4.4 Association between Baseline CD4 count and rate of opportunistic infections

Baseline CD4 count	Rate of opportunistic infections					Total
	Too many	Many	Few	Very few	None	
CD4 count						
100-150ul	12 (66.7%)	5 (27.8%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	18 (100.0%)
151-200ul	7 (41.2%)	2 (11.8%)	6 (35.3%)	0 (0.0%)	2 (11.8%)	17 (100.0%)
201-250ul	3 (20.0%)	6 (40.0%)	4 (26.7%)	2 (13.3%)	0 (0.0%)	15 (100.0%)
251-300ul	0 (0.0%)	2 (33.3%)	3 (50.0%)	0 (0.0%)	1 (16.7%)	6 (100.0%)
301-350ul	2 (7.1%)	4 (14.3%)	4 (14.3%)	7 (25.0%)	11 (39.3%)	28 (100.0%)
Total	**24 (28.6%)**	**19 (22.6%)**	**18 (21.4%)**	**9 (10.7%)**	**14 (16.7%)**	**84 (100.0%)**

Chi-square value=59.09; p=0.0001

There was association between baseline CD4 count and rate of opportunistic infections ($p < 0.05$). Lower baseline CD4 count < 200cells/uL was associated with increased rate of opportunistic infections while CD4 count > 250 cells/uL was associated with fewer opportunistic infections **(Table 4.5).**

4.15 ASSOCIATION BETWEEN BASELINE CD4 COUNT AND INCIDENCE OF HOSPITALISATION

Table 4. 5 Association between baseline CD4 count and Incidence of hospitalization

		Incidence of hospitalization				Total
		very frequent	frequent	once in a while	not at all	
	Baseline CD4 cell count					
	100-150ul	0(0.0%)	9(50.0%)	7(38.9%)	2(11.1%)	18(100.0%)
	151-200ul	1 (5.9%)	2 (11.8%)	7(41.2%)	7(41.2%)	17(100.0%)
	201-250ul	3(20.0%)	1(6.7%)	5(33.3%)	6(40.0%)	15(100.0%)
	251-300ul	0(0.0%)	0(0.0%)	1(16.7%)	5(83.3%)	6(100.0%)
	301-350ul	0(0.0%)	1(3.6%)	5(17.9%)	22(78.6%)	28(100.0%)
Total		**4(4.8%)**	**13(15.5%)**	**25(29.8%)**	**42(50.0%)**	**84(100.0%)**

Chi-square value=42.99; p<0.0001

There was association between baseline CD4 count and incidence of hospitalisation ($p < 0.05$). Lower baseline CD4 count $\leq$ 200cells/uL was associated with increased incidence of hospitalization than CD4 count > 250 cells/uL **(Table 4.6).**

4.16 ASSOCIATION OF BASELINE CD4 COUNT AND NUMBER OF SIGNS AND SYMPTOMS

Table 4. 6 Association between baseline CD4 count and Rate of presentation of signs and symptoms

	Rate of presentation of signs and symptoms					Total
	Too many	Many	few	very few	none	
Baseline CD4 count						
100-150ul	17(94.4%)	1(5.6%)	0(0.0%)	0(0.0%)	0(0.0%)	18(100.0%)
151-200ul	11(64.7%)	3(17.6%)	3(17.6%)	0(0.0%)	0(0.0%)	17(100.0%)
201-250ul	9(60.0%)	4(26.7%)	2(13.3%)	0(0.0%)	0(0.0%)	15(100.0%)
251-300ul	2(33.3%)	3(50.0%)	0(0.0%)	1(16.7%)	0(0.0%)	6(100.0%)
301-350ul	7(25.0%)	2(7.1%)	13(46.4%)	1(3.6%)	5(17.9%)	28(100.0%)
Total	46(54.8%)	13(15.5%)	18(21.4%)	2(2.4%)	5(6.0%)	84(100.0%)

Chi-square value=49.25; p<0.0001

There was statistically significant association between baseline CD4 count and number of signs and symptoms ($p < 0.05$). Lower baseline CD4 count ≤ 200cells/uL was associated with presentation of numerous signs and symptoms than CD4 count > 250 cells/uL **(Table 4.7).**

CHAPTER 5

5.0 DISCUSSION

5.1 ARVS USED BY PARTICIPANTS IN THE STUDY

Almost all the participants in the study were on the standard first-line antiretroviral regimen (2NRTI+1NNRTI) as proposed by WHO. All the participants were managed on the three combinations as found in other study reports in Africa (Potchoo, 2010; Ohene and Forson, 2009). There was no significant association between type of ART combination and patient outcomes; however, majority of the adherent participants had better outcomes (both immunological and clinical).

Majority of the participants were on Tenofovir (TDF) based combination. This may be due to its efficacy, convenient dosing, low toxicity profile and high potency (Gallant, 2006; Pozniak, 2006). Tenofovir had the least toxicity profile with fewer reported events of. It was well tolerated by patients and had the least likelihood for drug substitutions due to side effects. This is consistent with reports by Wilkin *et al* (2006) and Njugunal *et al* (2013).

Zidovudine, Lamivudine and nevirapine based regimen were taken by patients with no regards to food. Food has no significant effect on their absorption and bioavailability except for Tenofovir which was to be taken with a high fat diet to achieve maximum drug concentration levels (Rathbun, 2014). Dietary restrictions of Tenofovir could not impact on patients' adherence as suggested by Nakiyemba *et al* (2005) nor its absorption since most Ghanaian dishes contain moderate amounts of fat (Ela, 2012).

Zidovudine and Nevirapine had to be taken twice daily due to its relatively short half- life (Piliero, 2004). However the dosing frequency of these drugs did not impact on patients' adherence. This is consistent with findings of Arnsten *et al* (2001).

Medication switches due to side effects was observed with patients on Nevirapine and Efavirenz based regimen. Nevirapine - related toxicity resulted in treatment modifications or change in regimen in the first two – three months of being on therapy. The median side effect reported with the Nevirapine based regimen was skin rashes. This is consistent with studies conducted by Wilkin *et al*. (2006) and Beharu and Nasir (2013). Nevirapine related skin rashes necessitated change in regimen mostly in women who were more concern about their body image. Women have a three- fold risk for nevirapine- related skin rashes than men (Allan *et al*. 2003). One reason for this is that women generally have increased body fat and therefore increased volume of distribution for highly lipophilic drugs (Craft, 2003; Whitley and Lindsey, 2009)

Gastrointestinal disturbances such as mild- severe abdominal pains, nausea, diarrhea and vomiting were the most frequently cited adverse reaction by patients on Efavirenz based regimen. Toxicities with efavirenz based regimen was the second most common reason for medication change in patients and occurred in the first three months. This is in line with study reports by Wilkin *et al* (2006) in their study of medication switches in HIV- infected patients. Efavirenz - related CNS adverse effects such as dizziness, drowsiness and nightmares as cited by patients in the study may not have impacted on their adherence since Efavirenz was taken at bedtime. This is similar to findings reported in a study by Obirikorang *et al* (2013). Bedtime

administration of Efavirenz and avoidance of food at the time of administration can minimize the intensity of CNS adverse effects (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011)

Almost all the patients cited change in urine colour as a side effect. This confirms study reports by Geretti *et al*. (2006), WHO (2001) and Izzedine *et al*. (2001) which state that excretion of NRTIs, NNRTIs are mainly through the urine except for Efavirenz which is eliminated mainly through the feces (Burton *et al*., 2006). However, break down of red blood cells resulting from HIV infection could have accounted for the change in urine colour.

Contrary to reports citing drug toxicities as the most probable indication for medication switches (Hart *et al*., 2007; Cesar *et al*., 2010; Njuguna *et al*., 2013), it was shown in this study that drug shortages was the most predictable cause for medication switches. Drug shortages resulted in the highest number of pills missed over a month as patients had to wait until they were put on the available drug. Important observation made in this study was the fact that patients were switched on other ARV drugs without satisfying the WHO recommended conditions as described in other studies (Mess *et al*, 2008; Reynolds et al, 2009). This may have contributed to the low CD4 counts (<350) observed in a fifth of the participants in the study. Medication switches presents the patient with newer challenges such as having to cope with and adhered to a new drug (Praveen, 2011). Without regulated access to ART, rapid emergence of drug- resistant viral strains and treatment failure is a potential threat to treatment success and could curtail future treatment options leading to transmission of drug resistant strains of HIV (Harries *et al*., 2001;

Praveen, 2011). Interventions and policy implementation should be directed at ensuring sustainable supply of ARVs to all HIV centers across Ghana.

Frequent medication switches observed in this study was mainly due to drug shortages. This may have contributed to failure of a portion of the population to achieve CD4 counts > 350 cells/uL despite being adherent. Medication switches are known to cause rapid emergency of drug resistant viral strains and diminished activity of ARVs significantly (Soriano & de Mendoza, 2002; Praveen, 2011; Harries *et al*, 2001).

Given that a single point mutation is sufficient to cause resistance and clinical failure with Nevirapine and Efavirenz (Soriano and de Mendoza, 2002), it was necessary to have checked for drug resistance in patients who experienced medication switches. However, this could not be done due to unavailability of equipments and reagents. Future study is recommended to investigate the association between medication switches and drug resistance. Etravirine relatively has a higher genetic barrier to resistance. A single point mutation with etravirine is insufficient to cause clinical failure of the drug (Seminari *et al*., 2008). Etravirine should be considered a drug of choice for patients switching to second line antiretroviral therapy in Ghana as suggested by other study reports in Africa (Madruga, 2007; Kakuda, 2010).

5.2 ADHERNCE TO ANTIRETROVIRAL THERAPY

Antiretroviral therapy has transformed HIV infection into a manageable chronic condition. However, successful treatment; sustained viral suppression, sustained clinical progression, recovery of CD4 count require high levels of adherence to

prescribed regimens (Li *et al*., 2010). It was observed that ART adherence was a challenge to some patients, but majority of the participants (over 90%) were fully adherent.

Unlike studies conducted in Sub-Saharan Africa (Mukhtar-Yola *et al*., 2006 in Nigeria reported 80% adherence; Daniel *et al*., 2004 in Nigeria, 79%; Darder *et al*., 2004 in South Africa, 80%; Omes, 2004 in Uganda, 87%), this study showed a relatively higher adherence rate of ≥ 95% with majority of the study participants. Adherence rate found in this study was however consistent with studies in China and Uganda by Munganzi (2004) and Wang and Wu (2007) who reported adherence rate of 95% and 98% respectively with majority of study participants. This study is also consistent with adherence rate (>95%) reported by Abaasa *et al*. (2008). The differences in methods of adherence measure used may have accounted for the differences in adherence rate.

On the whole, the level of adherence increased with time and became relatively stable from the 3rd – 7th month. It should however be noted that adherence is not static. During the study period, adherence improved in some participants and became worse in others. Medication adherence is a continuous and sustained process and ART is a lifelong treatment. It is therefore necessary to assess clients' adherent behavior periodically to understand fully the characteristics of ART adherence (Tesoriero *et al*., 2003).

5.3 REASONS FOR MISSING DOSES OF MEDICATIONS

The reasons for missing doses as reported by participants moved from being specific to "don't know" as they progressed on treatment. Side effects, being away from home, simply forgetting, and running out of pills due to medication stock outs were some of the reasons for missing doses in the study, which are similar to reasons reported in other studies (Chesney, 2000; Garcia *et al*., 2006; Wang *et al*., 2009; Wang and Wu, 2007). Ten percent of the participants however missed doses within the 8th and 9th month without having any reason. This may be due to treatment fatigue as reported by Van Dyke, (2008) in his study of HIV/AIDS care and counseling in South Africa. Adherence counseling should therefore not be a one-time occurrence. Re-counseling on regular bases is extremely important (Van Dyke, 2008). People receiving ART need to integrate taking medication into their daily routines, have individualized medication plans, and adopt strategies such as carrying a pillbox when going out, using medication reminders, and providing continuous support and thus reducing the likelihood of missing doses and improving their level of adherence (Jones *et al*., 2001).

5.4 CLINICAL IMPLICATIONS OF ADHERENCE

The utmost goal of treatment with antiretroviral therapy is to prevent the development of HIV- related morbidity and mortality. It was shown that, adherence to antiretroviral therapy was associated with improved clinical outcomes. This is consistent with studies conducted in China by Wang *et al*. (2009) and Gao *et al*. (2000). These studies showed a strong association between adherence and clinical outcomes.

A portion of the population who were described as non-adherent (adherence rate < 95%) had some improvement in clinical outcomes and increase in CD4 counts. The result of this study is in line with other study reports (Panel on ART guidelines for Adults and Adolescents, 2011; AIDSTRUTH Research Group, 2010). Despite this, the goal when taking ART should always be to maximize adherence to near perfect levels.

5.4.1 Rate of opportunistic infections

HIV/AIDS-related OIs were still a concern for clients receiving ART because many participants had CD4 counts less than 200 cells/µl in this study. The overall prevalence rate of adherence was 24.7%. This is in agreement with the prevalence rate of 20% and 22.4% documented by Corey *et al*. (2007) and Iroezindu *et al*. (2013) in Peru and Nigeria respectively. It was also comparable with that reported in China and Senegal by Gao *et al*. (2000) and De Baudrap *et al*. (2010) respectively. The prevalence rate reported in this study was however relatively lower than that (47.6%) reported in Taiwan by Sun *et al*. (2006).

The prevalence of opportunistic infections (OIs) before the commencement of therapy was 82%. The high pre-therapy rate of OIs reported in this study was consistent with that reported by Sun *et al*. (2006). The pre- therapy burden of OIs was however not stated in other similar studies.

Both the number and rates of opportunistic infections reduced progressively with increasing duration on HAART. Adherence to HAART was found to be significantly associated with the prevalence of opportunistic infections. This is consistent with

studies in China, Nigeria and Europe .In a study in China, Wang *et al*. (2009) found participants with consistent adherence to have lower rates of opportunistic infections. San-Andres *et al*. (2003) evaluated the effect of early ART and found that the clients who adhered better demonstrated a low prevalence of OIs. Iroezindu *et al*. (2013) studied HIV infected patients on antiretroviral therapy for a duration of 3 years and found more than 60% decline in the number of HIV- related opportunistic infections. Patients achieving adherence rates of ≥ 95% had their number of HIV related OIs reduced from being many at baseline to none by the 9th month. Nonetheless baseline CD4 cell count had a strong association with prevalence of OIs (P = 0.0001). This is similar to findings reported in other studies by Wang *et al*. (2009) and Kaplan *et al*. (2001). Patients with baseline CD4 count < 200 cells/uL had to battle with OIs throughout the studied period despite being adherent. Preventive treatment and periodic checking for OIs are essential for the participants to prevent and control AIDS-related OIs in a timely manner. There is the need to investigate other clinical and non- clinical risk factors for the occurrence of OIs in order to identify the determining factors of OIs. Intervention programs could also be re-strategized to either enhance or eliminate these factors before the commencement of ARTs.

5.4.2 Rate / incidence of hospitalization

The study showed a decreased frequency of hospitalization with increased duration on HAART and adherence. Effective use of ART helps clients achieve the expected virological and immunological benefits of ART, slows down the progression of HIV/AIDS, which in turn reduces the incidence of hospitalization (Wang *et al*., 2009). Positive outcomes of adherence to ART including decreased hospital

readmissions and reduced cost have also been described in some studies (Nosyk *et al*., 2006; Munakata *et al*., 2006).

Similar to previous reports by Fielden *et al*. (2008) and Juday *et al*. (2011), this study found that patients who were adherent to any of the HAART regimen were less likely to be hospitalized. Increased risk of hospitalization was associated with inadequate adherence (<95%) as reported by Cohen *et al*. (2012). Cohen *et al*. (2012) found partial or incomplete adherence to be associated with an additional statistically significant risk of hospitalization. Juday *et al*. (2011) also found reduced rates of hospitalisation among patients with highest levels of adherence irrespective of their combination therapy. Though this study could not detect a statistically significant association between the type of ARV combination and outcomes, the study similarly found patients with adherence levels >95% to have better outcomes and therefore decreased rate of hospitalization. The findings of this study support suggestions that facilitating greater adherence to ART at any stage of illness may result in reducing hospitalization risk.

5.4.3 Adherence to ART and weight gain

An increase in weight gain was associated with effective use of HAART in the study. A steep increase in mean weight was observed over the six months period of therapy. This is consistent with findings reported in other studies by Madec *et al*. (2009), Ross- Degnan *et al*. (2011) and Tang *et al*. (2011).

The pattern of weight gain shown in this study is consistent with that reported in previous studies (Madec *et al*. 2009; Tang *et al*. 2011). The highest rate of weight gain occurred in the first six months after ART initiation. Similar to reports by Madec *et al*. (2009), patients in this study continued to gain weight after the six months with a mean increase of 1.2 kg per month up to the 9th month. Tang *et al*. (2011) on the other hand found weight of patients to remain stable after the first six months of therapy.

The level of weight gain observed in this study for the initial six months (6.6 kg) is comparably higher than average weight observed in reports from other populations. In 488 patients starting ART in four African countries (Ethiopia, Kenya, Rwanda, and Uganda), an average weight gain of 3.9 kg over 6 months was recorded (Madec *et al*. 2009). In India, investigators reported an average weight gain of 2.8 kg over 6 months in 190 patients starting ART (Saghayam *et al*. 2004). The quantum of mean weight gain observed in this study may be attributable to factors such as haematinics given to patients alongside their ARTs, adequate nutrition, counseling and reassurance.

In 185 Nigerian patients followed up for two years, the average weight of the group increased from 52 kg pre-ART to 59 kg post-ART(difference of 7 kg) (Olawuni *et al*, 2008). In comparison, the mean weight in this study increased from 57.2 kg pre-ART to 66.9 kg after 9 months of being on ART (difference of 9 kg). This study suggest that other significant predictors of weight changes such as malnutrition, alcohol and tobacco abuse, co- morbidities (Tang *et al*., 2011) should be investigated in further studies to determine the mechanism through which they

influence weight. Further studies are also needed to understand whether weight gain by any means is associated with improved outcomes of ART.

The study had some limitations. The study was conducted at only two sites in the country and the findings may not be generalizable to other clinical settings. There is no gold standard for measuring adherence and the measurement of adherence used in this study was based on patients' self- reports and pill counts which may be subject to social desirability and recall biases. There may also be over- estimation of adherence. However, several studies have demonstrated a good correlation between patient self- reported adherence and virologic outcomes (Wood *et al*., 2008; Liu *et al*., 2001). Drug resistance testing was not done due to unavailability of equipments and reagents. Patients who would have otherwise required modifications in treatment due to resistance were not captured.

5.5 IMMUNOLOGICAL IMPLICATIONS OF ADHERENCE

The study found that ART adherence is significantly associated with ($P < 0.0001$) immunologic recovery in HIV-infected clients, and good adherence contributes to greater growth of CD4 cell counts. A Chinese clinical study conducted between 2003 and 2006 reported that only 5% of patients receiving antiretroviral drugs showed drug resistance and adherence played key roles in the recovery of immunity (Yang *et al*., 2006). Mannheimer *et al*. (2002) also found that participants who reported 100% adherence at all study visits were more likely to achieve better virological and immunological outcomes after 12 months of treatment. Yu *et al*. (2005) reported that missing doses and interrupting ART were significant factors that lead to a slow increase of CD4 counts.

The study found participants with adherence rate ≥ 95% to increase in their CD4 count from baseline through to month 6 and 9 with mean increase of 159 cells/uL at 6th month and 74.8 cells/uL at month 9. In a prospective cohort study of 1,095 patients enrolled in 2 randomized multicenter trials of initial and salvage ART, Mannheimer *et al*. (2002) found participants who reported adherence levels of 100%, 80-99%, and 0-79% to have CD4 cell count increases of 179, 159, and 53 cells/µL, respectively, from baseline to month 12. This supports the need to promote and encourage consistently high levels of adherence to achieve a good immunological outcome and slow the development of drug resistance.

About 20% of the population who achieved a ≥ 95% adherence still had CD4 counts below 350 cells/uL even after 9 months of being on therapy. This confirms reports that adherence alone is not a determining factor to CD4 recovery and increases (Carter, 2004; Kullkarni, 2011).

Baseline CD4 count is a significantly associated with CD4 cell recovery and growth. Lower baseline CD4 count is associated with slow increase in CD4 count (Carter, 2004; Kulkarni, 2011; Mckinnon *et al*., 2010). Participants who initiated therapy at CD4 counts below 200 cells/ uL were less likely to achieve CD4 counts beyond 500cells/uL as participants who initiated therapy at counts ≥ 350 cell/uL. This is consistent with findings of (Carter, 2004; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2014; Goicoechea *et al*., 2006). Predictors of immunologic response to ART are multi-factorial (Gazzola *et al*., 2009). This calls for further investigations to better understand the influences of ART response to immune reconstitution and to develop alternative therapeutic strategies.

Furthermore, given that, many HIV- infected patients only access health care when advanced symptomatic disease has developed in developing countries (CASCADE, 2004; Cohen *et al*. 2009), the results of this study supports the need to further promote voluntary HIV testing and counseling in order to facilitate early detection and initiation of ART in order to maximize the clinical and immunologic benefits to the patient.

CHAPTER 6

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

The most frequently used ARV was Tenofovir combined with other ARVs as HAART. Majority (93%) of the participants were adherent to their medication. Though rapid HIV scale up has been successful in Ghana, challenges with drug shortages still exist.

With patients showing greater commitment to adhere to antiretroviral regimen in spite of the difficulties that come with long- term therapies like HAART, it is essential for the government of Ghana and its agencies responsible for HIV/AIDS prevention, control and care, to implement policies that would ensure the continuous and sustainable supply of ARV drugs across the country.

Adequate adherence to HAART lead to reduced number of opportunistic infections, reduced incidence of hospitalization, and improved patients' weight gain. Immunologic outcomes also improved significantly. Efforts should therefore be intensified to maximize adherence and eliminate the factors that influences adherence negatively such as medication side effects.

Lower baseline CD4 counts was also found to be significantly associated with outcomes for patients on long term antiretroviral therapy.

6.2 RECOMMENDATIONS

6.2.1 Promoting adherence to ART and reducing incidence of missing doses.

- The Government through the Ministry of Health should implement policies and strategies that will ensure continuous and sustainable supply of ARVs at all treatment centers across Ghana.
- HIV infected patients on ART should integrate taking their medications into their daily routines, have individualized medication plans and adopt strategies such as carrying their pills with them when going out and using reminders in order to reduce the likelihood of missing doses

6.2.2Promoting early detection and initiation of ART

- The MOH should intensify education on the need for voluntary counseling and testing through the media, churches, mosque, durbars etc. to help detect and initiate ART treatment early among the population to reduce mortality, HIV transmission and increase the life expectancy of people living with HIV/AIDS.

6.2.3 Resistance testing

- The Ghana AIDS Commission should make provision for laboratory testing for drug resistance for patients who fail to significantly increase their CD4 count after 6months of therapy.
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6.2.4 Switching medications

- Prior to medication switches, patient must satisfy the WHO recommended conditions.

RECOMMENDATIONS FOR FUTRE STUDIES

Further studies is recommended to;

- Determine the impact of frequent medication switches on drug resistance, viral load, immune recovery and clinical outcomes of HIV/AIDS patients.
- Investigate clinical and non- clinical risk factors of opportunistic infections.

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APPENDICES

APPENDIX

INFORMED CONSENT

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY

FACULTY OF PHARMACEUTICAL SCIENCES

DEPARTMENT OF CLINICAL AND SOCIAL PHARMACY

MPHIL CLINICAL PHARMACOLOGY

RESEARCH TOPIC: ADHERENCE TO ANTI-RETROVIRAL THERAPY, IMPACT ON CLINICAL AND IMMUNOLOGIC OUTCOMES

I ……..

hereby consent to give my maximum cooperation/ participation by sincerely giving responses to a set of questions posed to me. I have adequately been briefed/ informed of what the research study is all about. The purpose and significance of the study has been made clearly to me.

I understand the study involves no risks or harm and that outcome of the study will be beneficial to me. I have been reassured that all information obtained from me in the course of this study will be confidential and used for the purpose of this research only. I have also been assured my name and true identity will not be disclosed or published in any article/journal.

SIGNED…….

DATE…….

RESEARCH QUESTIONAIRE ONE

Assessment of patients' adherence behavior

Dear respondent,

The researcher acknowledges that taking pills everyday may be challenging. I am going to ask you about the problems you have had taking your pills over the past

month/s. Please feel comfortable to tell me about the pills you may have missed or taken of late. I am doing this work to gather information to help you and other colleagues on anti-retrovirals to make it easier for you to take your medication.

Demographic Data

1. Age (Yrs) : 18-25[] 26-35[] 36- 45[] 46-55 [] 56- 65[]
2. Sex: M [] F []
3. Weight (Kg): 45- 55 [] 56- 65[] 66-75 [] 76-85[] 86- 95 [] 96- 105 [] 106- 115[]
4. Height (cm) 140-149[] 150- 159[] 160- 169[] 170- 179[] 180- 189[] 190- 199 [] 100-109 [] 110-119 [] 120-129 []
5. Educational level: Primary [] JHS [] SHS [] O- Level [] A-Level [] Tertiary [] No formal education []
6. Employment status: self- employed [] unemployed [] civil servant [] student []
7. Marital status: married [] single [] Divorced [] Widowed []

Drug information

1. Which of the ARVs do you take? ……
2. If drug was changed state reason for change of drug

   ……

3. How many pills do you take in a day? Two b. three c. four d. five e. six others specify…….
4. How many times in a day do you take your pills?
   a. Once b. two times c. three times d. four times
5. Do you have special instructions for any of the pills?
   a. Diet restrictions

b. Take drug on empty stomach

c. Extra fluid requirement.

d. No special requirement.

e. Take drug some minutes after eating

6. What adverse drug effects do you experience? (You can tick more than one)

   a. Diarrhea b. abdominal discomfort c. Nausea with vomiting

   d. Nausea without vomiting e. epigastric pain f. loss of appetite g. Body weakness h. severe anaemia i. Dizziness

   others specify……

Adherence Rate.

1. How many pills have you missed

   a. In the previous day…….

   b. The day before yesterday……

   c. 3 days ago……

   d. In the past 7 days…….

   e. Over the past one month……..

Reasons for missing doses

(In this column, please help the researcher know the reason why you could not take your pills. You can tick as many as you want)

a. Simply forgetting

b. Being away from home

c. Too busy

d. Side effects

e. Feeling sick

f. Depression

g. Running out of pills

h. Difficulty swallowing pills

i. Too many pills

j. Stigma

k. Feeling well

RESEARCH QUESTIONAIRE TWO

Assessment of Patients clinical data at baseline (prior to treatment) and subsequent months after being on treatment.

Dear respondent,

This questionnaire assesses and compares your quality of life precisely physical health prior to starting treatment and after starting ART. Please be sincere in responding to a number of questions below as this will help you, the researcher and the hospital authorities to know the impact the drugs are having on your physical health. Thank you

Background information

1. Age;
2. Gender
3. Educational level
4. Employmeny status
5. Marital status ;
6. Religion;

Data on physical health

7. How would you rate your prevailing opportunistic infections now?
    a. Too many
    b. Few
    c. Very few
    d. None
8. Which of the opportunistic infections below are you experiencing now? (pls you can choose more than one).

a. Persistent Oral candidiasis
b. Persistent generalized lymphadenopathy
c. Herpes Zoster
d. Respiratory tract infections(sinusitis, bronchitis , otitis media , pharyngitis)
e. Pulmonary tuberculosis
f. Severe bacteria infections (pneumonia, meningitis, PID)
g. Kaposi sarcoma
h. Encephalopathy
i. Popular pruritic eruptions
j. Others specify……

9. How would you rate your incidence of hospitalization prior to treatment and after treatment?
   a. Very Frequent
   b. Frequent
   c. Once in a while
   d. Not at all
10. Which of the conditions below led to your hospitalization (you can choose more than one)
    a. Diarrhoea and vomiting
    b. Anemia
    c. Abdominal discomfort
    d. General malaise
    e. Anxiety / depression
    f. Malaria

g. Productive / unproductive cough

h. Fever

i. Others specify…….

11. What was your duration of stay on the ward?

a. One day

b. Two days

c. Three days

d. Four days

e. Five days

f. Six days

g. One week

h. Others specify ……..

12. How would you rate your presentation of signs and symptoms?

a. Too many

b. Many

c. Few

d. Very few

e. None

13. Which of the sign and symptoms below are u experiencing ? (you can choose more than one)

a. Diarrhea and vomiting

b. Losing weight

c. Loss of appetite

d. Chronic cough

e. Skin rash/ itching

f. Fever/chills

g. Jaundice

h. STIs

i. Abnormal menses

j. Oral thrush

k. Persistent headaches

l. Others specify ……

14. How would you rate your ability to perform self care activities of daily living.

a. Very able

b. Able

c. Not able

15. Do you require any assistance to be able to perform self care activities?

a. Yes

b. No

16. How would you rate your overall physical health based on the above indices?

a. Good

b. Averagely well

c. Poor