INFLUENCE OF SELF-REPORTED HIGHLY ACTIVE ANTI RETROVIRAL THERAPY SIDE EFFECTS ON ADHERENCE AMONG PERSONS WITH HIV ATTENDING TIGONI DISTRICT HOSPITAL, KENYA

HELLEN WAMBUI KIARIE

MASTERS OF SCIENCE
(Public Health)

JOMO KENYATTA UNIVERSITY OF AGRICULTURE AND TECHNOLOGY

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Influence Of Self-Reported Highly Active Anti Retroviral Therapy Side Effects On Adherence Among Persons With HIV Attending Tigoni District Hospital, Kenya.

Hellen Wambui Kiarie

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other university.

Signature …………………………. Date………………………..

Hellen Wambui Kiarie

This thesis has been submitted for examination with our approval as University supervisors.

1. Signature …………………………. Date………………………..

   Prof. Marion Mutugi

   JKUAT, Kenya

2. Signature …………………………. Date………………………..

   Dr Peter Wanzala

   KEMRI, Kenya

DEDICATION

This thesis is dedicated to my precious girls Leona and Sienna, who give me a reason to smile every day. Thank you for making my life so much more interesting and fulfilling. I also want to thank God for his guidance in every step throughout my master's study.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ADR	Adverse Drug reaction
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti Retroviral Therapy
ARV	Anti Retro Viral drug
AZT	Zidovudine
CD4	CD4 lymphocyte
D4T	Stavudine
ddi	Didanosine
EDM	Electronic Drug monitoring
EFV	Efavirenz
HAART	Highly Active Anti Retroviral Therapy
HIV	Human Immunodeficiency virus
IDV	Indinavir
LPV/r	Lopinavir/Ritonavir
NNRTI	Non- nucleoside Reverse transcriptase inhibitors
NRTI	Nucleoside Reverse transcriptase inhibitors
NVP	Nevirapine
PI	Protease inhibitors
PLWHA	Persons Living With HIV/AIDS
SES	Social economic status
TDF	Tenofovir
VL	Viral load

ABSTRACT

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in Acquired Immunodeficiency Syndrome (AIDS)-related morbidity and mortality.

Adverse drug reactions are a commonly cited cause of poor adherence to HAART. The short-term adverse effects are potential threats to successful introduction and maintenance of HAART, while long term adverse effects can threaten sustenance of long term treatment. Although the association of side effects with adherence behavior seems intuitive, few studies have addressed this issue specifically. The objectives of this cross sectional descriptive study were to assess the level of adherence to HAART; variables predictive of sub-optimal adherence; medication side effects associated with HAART, and their association with adherence. Interviewer-administered questionnaires were used to assess adherence in the past 3 days (short term) and past one month (long term). The questionnaire also assessed the type and perceived intensity of 13 common HAART-related symptoms experienced during the last one month, and how these had affected the participant's adherence to HAART.

Data analysis was done using SPSS 17.0. Summaries were made for; HAART related side effects, regimen characteristics, patient factors and socio demographic characteristics. Short term (3 day) adherence and long term (1 month) adherence were categorized at the 95% level as adherent, (taking 95% or more of the prescribed drugs), or non-adherent (taking less than 95% of the prescribed drugs). Logistic regression was used to determine the factors significantly associated with adherence. Chi square tests were

used to assess association between adherence and number and perceived intensity of side effects.

A total of 183 patients were interviewed; 67.8% female and 32.2% male. The mean age was 39.2 years (±9.4) and 64.5% had been on treatment for over 13 months. Mean 3 day adherence was 96.4% (+/- 14.5) while mean 1 month adherence was 98.1% (+/-9.2). The most common reasons for missing medications were running out of drugs (11%) and being away from home (8.7%). During the preceding one month, 30.6% of patients had experienced at least one medication side effect. The most commonly reported side effects were; tiredness/general malaise (20.6%), rash (19.8), dizziness (17.5), nausea and vomiting (15.9%), stomach upsets (15.9%), sleepiness (15.9%) and headache 20(15.9%). Only 14.2% of patients who experienced side effects reported that they influenced their medication taking in some way. Among these, only 5.4% stopped taking their medications as a result. Side effects were neither associated with short term adherence (OR 1.98 P-value 0.13); nor long term adherence (OR 1.01 P-value 0.97). The last time a patient missed medication predicted long term adherence (OR, 1.7; P=0.03). Other patient factors and regimen characteristics were not found to predict adherence to HAART. The duration a patient had been on treatment was significantly associated with the number of side effects (Chi-square p-value 0.04); patients who had been on treatment for longer had more side effects than those who had been on treatment for a shorter period.

These results show that HAART patients in Tigoni had optimal of over 95%. Those who had a gap in taking medication during the preceding 2 weeks were more likely

to be non-adherent. General Malaise, Rash, Dizziness, Nausea and Vomiting, Stomach Upsets, Sleepiness and Headache were side effects that were commonly experienced in this setting. However, side effects did not significantly affect adherence.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Acquired immunodeficiency syndrome (AIDS), is one of the most destructive epidemics the world has ever witnessed. It claimed 3.1 million lives in 2005 of which more than half a million (570 000) were children. In 2007, 33.2 million people were estimated to be living with HIV, 2.5 million people became infected and 2.1 million died of AIDS. The Sub-Saharan Africa accounts for 68% of the global total HIV infections and AIDS deaths (WHO 2007). In Kenya, the Kenya Demographic Health Survey, 2008-09 estimated the percentage of adults aged 15-49 living with HIV/AIDS at 6%. Among women aged 15-49, prevalence was 8% while it stood at 4% among men in the same age bracket (KDHS 2008-09).

Highly active antiretroviral therapy (HAART), a combination of at least three drugs has led to substantial reductions in morbidity and mortality in HIV-1 infection. Many HAART regimens result in near-complete suppression of HIV-1 replication making HIV infection more of a chronic disease than a fatal one. HAART is now the standard-of-care therapy for patients infected with HIV. (Hogg *et al.,* 1999; Palella *et al.,* 1998). Mutugi and others found that the quality of life in patients treated with HAART over a period of 9 months improved markedly with increase in weight and reduction in number of opportunistic infections as well as decreased hospitalization and ability to return to work (Mutugi *et al.,* 2010).

Adherence to HAART is an important determinant of the outcome of therapy in the treatment of HIV/AIDS. Successful long-term treatment of HIV/AIDS requires at least 95% adherence to HAART, which practically means missing no more than 3 doses over an entire month for a twice daily regimen (Bangsberg *et al.,* 2000; Paterson *et al.,* 2000, Gross *et al.,* 2001). Failure to follow strict adherence is associated with treatment failure and resistance to ART, both of which are adverse consequences for both the patient and the general public (Moutouh *et al.,* 1996; Cinatl *et al.,* 1994; Gill *et al.,* 2005). Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of medication related side effects within the first year of therapy according to studies done in Italy, USA and in South Africa (Ammassari *et al.,* 2001, Lucas *et al.,* 1999; Malangu, 2008). Medication side effects have been reported by various studies, both in developing and developed countries to be significantly associated with less than optimal adherence (D'Arminio *et al.,* 2000).

This study sought to identify variables associated with suboptimal adherence to HAART in a rural population and in particular, to assess how self-reported medication side effects are related to HAART adherence.

Using a cross sectional descriptive study on patients who had been on treatment both in the short and long terms, this study demonstrated how side effects occurring in the preceding 1 month influenced adherence in the same period, and in the preceding 3 days.

1.2 Problem Statement

The sustained benefits of HAART have led to far greater numbers of HIV-1-infected patients receiving at least three drugs for greater periods of time. The declining incidence of HIV-1-associated opportunistic disease has led to increased recognition of drug-related toxicity, while the severity of the HIV epidemic has led to accelerated licensing of many antiretroviral agents. The long-term safety of some of these agents is little known. Additionally, side effects to ARVs become more complex due to the need to combine three antiretroviral drugs to form an effective regimen. Each of these drugs could potentially contribute to the adverse effects a patient experiences. The fact that these patients are also likely to be taking opportunistic infections drugs, for treatment and/or prevention means that there could be additional or overlapping toxicities. For example, a patient taking Nevirapine and Cotrimoxazole may experience a rash from either of these drugs. Adverse effects negatively affect patients adherence to HAART compromising the outcome of therapy.

1.3 Justification

Although many factors have been identified as being associated with less than optimal adherence, the various self reported HAART associated symptoms affecting adherence are still not well elucidated, as few studies have addressed this issue specifically.

Given that adverse drug reactions is a commonly cited cause of poor adherence to HAART (Ammassari *et al.,* 2001), a better understanding of adverse effects, and how

they affect adherence is needed in order to maximize the effectiveness of currently available treatments.

Studying how adverse effects influence adherence in the short and long term is critical. This is because short term side effects are potential threats to successful introduction and maintenance of HAART, whilst long term toxicities threaten sustenance of HAART in the long run. Exposure to adverse effects may affect medication taking behavior in the short term and long term, depending on the magnitude of effect, hence the need to study both long term and short term effects.

The outcomes of this study elucidate the importance of self reported medication side effects on adherence in optimizing patients' therapy. Information gained from this study will help in identifying specific areas where there's need for improvement patients' management related medication side effects, and the importance of integrating pharmacovigilance concepts in clinical practice.

1.4 Study Objectives

1.4.1 General Objective

To determine the association between self-reported HAART side effects and adherence to HAART among persons with HIV attending Tigoni District Hospital.

1.4.2 Specific Objectives

i. To determine the short term and long term adherence levels for patients on HAART

ii. To determine the socio demographic characteristics of patients with short term and long term adherence.

iii. To determine the self reported HAART related side effects among patients on HAART.

iv. To determine the association between self reported HAART related side effects and adherence.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Antiretroviral Therapy

HAART drastically reduces mortality and morbidity due to HIV/AIDS (Hogg *et al.,* 1999), however, this is highly dependent on strict medication adherence. Less than 95% adherence has been associated with incomplete viral suppression, decline in number of CD4 cells, disease progression and death (Gross *et al.,* 2001) and further the public health threat of development and spread of multidrug-resistant HIV, similar to that seen with multidrug-resistant tuberculosis (Moutouh *et al.,* 1996; Cinatl *et al.,* 1994; Gill *et al.,* 2005).

Given that HAART programs can still fail if they do not adequately address factors influencing adherence, there's need to address any adherence barriers as the number of patients put on HAART continue to grow, in order to have successful programs (Moutouh *et al.,*1996).

2.2 Adherence to Antiretroviral Therapy

Globally, even though ART is the single most dramatic development yet in the treatment of HIV, many patients have been described as being inconsistent with their treatment regimens, either not taking prescribed medication, taking medications only when they felt up to it, or needing breaks (Amico *et al.,* 2006, Veinot *et al.,* 2005). ART adherence is now widely recognized as a critical health promotion behavior for HIV positive individuals on therapy (Amico *et al.,* 2006). Some studies instructions (Carrieri *et al.,*

2001; Nieuwkerk *et al.,* 2001; Schonnesson *et al.,* 2006) in resource-rich settings have documented less than 50% of patients taking all their antiretroviral medications according to instructions.

Several factors have been found to be associated with non-adherence; depression and psychiatric illness, active alcohol or drug use, and lack of social support have been found to be associated with lower adherence (Chesney *et al.,* 2000; Paterson *et al.,* 2000*).* In general, sociodemographic factors do not seem to predict adherence behavior, although some studies have found that male sex, white ethnicity, older age, higher income and higher education and literacy correlate with better adherence (Ickovics *et al.,* 2002). A patient's ability to identify medications and his/her understanding of the relationship between adherence and medication resistance also predict better adherence (Chesney *et al.,* 2000). Health literacy and HIV related knowledge are found to be associated with better adherence (Servellen *et al.,* 2005; Weiser *et al.,* 2003). Disease characteristics such as prior opportunistic infections implying an increased perceived severity of illness appear to motivate patients to adhere better (Singh *et al.,* 1996) while patient provider relationship and trust in the provider is believed to be a motivating factor for adherence (Altice *et al.,* 2001). A high pill burden and inability to integrate the treatment regime into patient's daily routine have been reported as barriers to adherence (Ickovics *et al.,* 2002).

A systematic review conducted recently identified barriers to adherence in both developed and developing countries as;- fear of disclosure, concomitant substance abuse, forgetfulness, suspicions about treatment, overly complicated regimens, number of pills

required, decreased quality of life, work and family responsibilities, falling asleep, and access to medication. .Barriers reported specifically by persons from resource-poor countries from this review were; fear of side effects, access to treatment, financial constraints and a disruption in medication availability (Mills *et al.,* 2006). Important facilitators reported by patients in developed nation settings included having a sense of self-worth, seeing positive effects of antiretrovirals, accepting their seropositivity, understanding the need for strict adherence, making use of reminder tools, and having a simple regimen . Generally however, barriers to adherence were consistent across multiple settings and countries.

In the Sub- Saharan Africa, there has been a concern about the capability of patients in resource-limited settings to adhere to ART, especially in the African context (Moutouh *et al.,* 1996). Recent reports show that HAART adherence and clinical success rates vary widely across sub-Saharan Africa programs (Moutouh *et al.,*1996).Several studies from resource-limited settings have documented high levels of adherence amongst these patients but more recent studies have shown poor adherence (Orwell *et al.,* 2003; Nachega *et al.,* 2004). A recent review highlights the need for an increased focus on adherence in the face of findings from Cote d'Ivoire, Cameroon and Botswana that documented lower adherence levels in ART programmes in Africa (Mills *et al.,* 2006). Large numbers of patients will have disease progression if adherence is suboptimal.

Several studies done in African settings have reported varying levels of adherence and its predictors as summarized in the table 2.1.

Table 2. 1   Levels of HAART adherence and its predictors from some African studies.

Country	Reference	Study summary	Level of adherence	Predictors of adherence
Cote d'Ivoire	Eholie *et al.,* 2004	Cross sectional	40% with > 90% ADH	None available
Botswana	Weiser *et al.,* 2003	qualitative and quantitative research methods	54% with>95% by self-report, 56% with>95% by provider assessment	financial constraints (most significant), stigma, travel/migration, Side effects.
Cameroon	Akam *et al.,* 2004	Prospective longitudinal	Mean ADH 68% (ADH Declined over time)	pill burden, finance, side effects, forgetting, difficulty in fitting drug schedule with daily activities, Stigma, level of conviction on efficacy
South Africa	Orrell *et al.,* 2003	Prospective monitoring	Mean ADH 93.5%	pill burden, not speaking English
South Africa	Aspeling *et al.,* 2008	Descriptive case study	N/A	HIV education, adequate treatment preparation, supportive patient provider relationship
Ethiopia	Alemayehu *et al.,* 2008	prospective study-self reports	Mean ADH 94.3%	Social support, Not being depressed, memory aids.
Senegal	Laniece *et al.,* 2003	cross sectional analysis and prospective observational	Mean ADH 91%	cost of treatment, pill burden
Uganda	J Byakika-Tusiime *et al.,* 2005	cross-sectional study-self reports	68% with>95% ADH	inability to pay for ART
Kenya-Kericho	Njeru, 2006	cross-sectional study-self reports FGD	Mean ADH 98.8%	Forgetting, financial constraints , improved health ,away from home, side effects
Kenya- Nyeri PGH	Mutugi *et al.,*2010	prospective study and self reports	Mean ADH 62%	Cost of treatment, adverse side effects

Key: - ADH-adherence**, VL-** Viral load**, SES-**social economic status**. FGD-**Focus Group Discussions

A cross-sectional study in Botswana used questionnaires and interviews on patients receiving ARV treatment and their health care providers to elicit principal

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barriers to adherence.109 patients and 60 health care providers were interviewed over a 6 month period.54% of patients were adherent by self-report, while 56% were adherent by provider assessment. Observed agreement between patients and providers was 68%. Principal barriers to adherence included financial constraints (44%), stigma (15%), travel/migration (10%), and side effects (9%) (Weiser et *al.,*2003).

Orrell and others in South Africa used prospective monitoring to determine adherence of 289 indigent African patients infected with HIV initiating antiretroviral therapy, and to identify predictors of suboptimal adherence ($< 95\%$) and virologic failure (> 400 HIV RNA copies/ml). Adherence was determined over 48 weeks by counting tablet-returns. Mean adherence of the cohort was 93.5%. Independent predictors of suboptimal adherence were three times daily dosing, speaking English and age. Socio-economic status, sex and HIV stage did not predict adherence. Independent predictors of virologic failure included baseline viral load and three times daily dosing, incomplete adherence, age and dual nucleoside therapy (Orrell *et al*., 2003).

Another study in South Africa used a descriptive approach and found the factors associated with adherence to HAART to be; lack of HIV education facilitating reversion to traditional customs, adequate treatment preparation, comprehensive HIV education and supportive patient-provider relationship (Aspeling *et al.,* 2008).

In a prospective study undertaken in Ethiopia on a total of 400 HIV infected persons, an interviewer-administered structured questionnaire was used to collect data at first month and third month follow up visits. Self-reported adherence in the study area was 94.3%.Factors that predicted good adherence at baseline were; social support and

not being depressed At the follow up visit, social support and the use of memory aids were found to be independent predictors of adherence. The most important reasons reported for skipping doses in this study were simply forgetting, feeling sick or ill, being busy and running out of medication in more than 75% of the cases (Alemayehu *et al.,* 2008).

In Senegal, a prospective observational cohort on 158 patients participating in an ARV access programme had their adherence estimated each month over a 2 month period, using patients' self reports. The mean adherence during the 24-month study period was 91%. Patients reported to have taken the entire monthly dose during 69% of the months covered by the study period. Mean adherence was 90% during the first year and 92% in the second. Mean adherence remained above 80%, (ranging from 83 to 95% according to the month). The main barriers to adherence were making a contribution to the cost of their treatment. Adherence was better with Efavirenz regimens than with Indinavir regimens. Among the patients who were receiving their treatment free of charge, mean adherence was 89% with IDV and 97% with EFZ. Notably, IDV containing regimen is more complicated in terms of pill burden and frequency of dosing and is associated with more side effects than an EFZ based regimen (Laniece *et al.,* 2003).

In the Uganda study, 304 HIV-infected persons on ART were recruited into the cross-sectional study from three treatment centers in Kampala,Uganda. Adherence was assessed using self reports, where structured patient interviews assessed the missed doses over the last three days and dichotomized at 95% adherence. Reasons for non-

adherence were assessed with both structured patient interviews and unstructured qualitative interviews. ART-associated side-effects were collected by asking the patients if and how they were bothered by any of their medications. Sixty-eight percent of patients reported greater than 95% adherence. Shortage of drugs due to lack of money was the most common reason for non-adherence. Other reasons for non-adherence among those who had missed at least one dose of their medications included forgetfulness, drug inaccessibility, adverse effects of the drug, travelling away from home, unclear instructions by the health provider, being too busy, regimen being too complex, fear of wasting drug and presence of other disease conditions (Byakika *et al.,* 2005).

In a study carried out in Kenya at Kericho (a rural District hospital), structured interviews were used on 398 patients, 24 were surveyed using focus group discussions and 5 care givers were interviewed as key informants.

The mean adherence was 98.8% and 95.7% of patients reported taking 100% of the prescribed dose while 4.3% reported missing at least one dose. Most patients reported more than one reason for missing. The factors found to be associated with adherence were forgetting, financial constraints, improved health, being away from home and side effects. Barriers reported by patients were side effects, long distance to clinic/financial constraints, long waiting time, being depressed failure to disclose/stigma, high pill burden and inadequate psychological support (Njeru, 2006).

From these studies, it is clear that adherence varies in sub-Saharan Africa and very few studies report 95% adherence or more. Certain factors are associated with

adherence. Side effects were cited as an important barrier to adherence in most of these studies.(J Byakika-Tusiime *et al.,* 2005; Akam *et al.,* 2004; Njeru, 2006; Weiser *et al.,* 2003; Laniece *et al.,* 2003), signifying their importance as a barrier to adherence. In the Kericho study in Kenya, it was the most significant barrier to adherence at 76% (Njeru, 2006). Generally, most of these studies utilized self reports as the main measure of adherence, with only a few studies comparing multiple surrogate measures of adherence (Njeru, 2006; Weiser et *al.,* 2003). This use of self reports poses methodological limitations as these have been shown to overestimate adherence. Nevertheless, structured self reports have been shown to correlate well with objective measures of adherence and viral loads in both developed and developing country settings (Bangsberg *et al.,* 2000).

2.3 Predictors of adherence

Studies (Weiser *et al.,* 2003; Orrell *et al*., 2003; Aspeling *et al.,* 2008; Alemayehu *et al.,* 2008; Laniece *et al.,* 2003; J Byakika-Tusiime *et al*., 2005; Njeru, 2006) report varying factors in various settings as being associated with adherence.

2.3.1 Support

One of the identified predictors of adherence is support systems, programs with sufficient support systems for the patients on care reported better adherence. These include those nested in research studies, or those which are well supported- mostly by donors- to provide care for HIV patients. These programs provide free high quality clinical care and most have extra benefits for patients like community health workers,

better infrastructure and some provide extra motivation like food and soap. These are mostly absent in regular public clinics in resource limited settings. Notably, programs with no external support, - Cote d'Ivoire, Cameroon and Uganda reported poorer adherence than those with external support –Kenyan and Senegalese studies. Patients enrolled in studies are likely to benefit from the structural supports provided by the study while those in externally supported programmes are likely to get better care in terms counseling, treatment and other ART related services than a regular government run programme (Gill *et al*., 2005).

2.3.2 Time on ART

Another predictor of adherence has been identified as the time a person has been on ART. Studies show significant association between duration on ART and adherence behavior. Adherence has been reported to decline over time in most studies (Alemayehu *et al.,* 2008; Akam *et al.,* 2004; J Byakika-Tusiime *et al.,* 2005). In the Senegalese study, stated adherence during the last 3 days of each 1-month period of the survey tended to be slightly poorer than the corresponding 30-day estimate (89% versus 91%) during the 24-month study period, creating the need to assess both short and long term adherence,(Laniece *et al.,* 2003).

2.3.3 Financial support

A third predictor is related to finances. Various studies have reported considerable associations between financial constraints and non-adherence (J Byakika-Tusiime *et al.,*

2005, Njeru, 2006, Akam *et al.,* 2004, Weiser *et al.,* 2003), however some studies have shown that social economic status does not predict adherence (Orrell *et al.*2003). In his study on how financial contribution affected patient retention in Mbagathi district hospital, Zachariaha and others observed that payment for ART in a routine district hospital programme setting is associated with a significantly higher rate of loss to follow-up than when medication was offered free of charge. (Zachariaha *et al.,* 2008).

2.3.4 Psychosocial support

Fairly consistent associations have been found between certain psychosocial factors and adherence behavior. In this regard, depression/psychiatric morbidity have been found to be closely associated with adherence (Njeru, 2006; Alemayehu *et al.,* 2008; Chesney MA., 2000; Bruno *et al.,* 2002). Active drug or alcohol use is a second psychosocial factor that has been reported as an adherence predictor (Stirratt *et al.,* 2006).A third factor is serostatus disclosure (Njeru, 2006; Bruno *et al.,* 2002; Stirratt *et al.,* 2006).Lack of social support has also been reported to predict adherence behavior(Alemayehu *et al.,* 2008).

2.3.5 Antiretroviral side effects

Yet another predictor of adherence relates to ARV side effects. In a Brazil study, adherence to treatment regimens was reduced for patients who reported adverse effects (Silveira *et al.,* 2000). In Italy, a cross-sectional multicenter study was carried out among 358 persons on antiretrovirals. Variables predictive of nonadherence to HAART and

self-reported symptoms or medication side effects related to adherence were assessed over a one year period. A self-administered questionnaire was used to assess nonadherence in the last 3 days as well as the type and perceived intensity of 24 common HIV- and HAART-related symptoms experienced during the last 4 weeks. 22% of participants reported nonadherence. Frequency of moderate/severe symptoms or medication side effects in nonadherent participants ranged from 3.6% to 30%. Symptoms and side effects found to be significantly associated with nonadherence were; nausea, anxiety, confusion, vision problems, anorexia, insomnia, taste perversion, and abnormal fat distribution. Nonadherent persons had a higher mean overall symptom score (12.3 versus 8.1; $p < .001$) and mean medication side effect score (2.9 versus 1.9; $p < .001$) when compared with adherent participants (Ammassari *et al.,* 2001).

A study in Pretoria, South Africa assessed the significance of side effects to adherence and found that 94% of the 180 respondents reported at least one side effect and the mean number of self-reported side effects was 2.6. The mean number of doses missed during the last seven days prior to the interview was 2.7, ranging from 0 to 18. Barriers to self-reported adherence (=> 95%) included having used non-prescribed medicines (to relieve symptoms) (15.6%), having suffered from headaches (28.6%) and reported symptoms such as insomnia (27.3%) and abdominal pain (20.8%) (Malangu O.A., 2008).

Various studies have shown that adherence is reduced in presence of adverse effects, and studies done in various African settings have identified side effects as an important barrier to adherence. (Weiser *et al.,* 2003; Akam *et al.,* 2004; Njeru, 2006). In

Kenya, the study in Kericho District hospital identified the fear of side effects as the most important barrier to adherence at 76% (Njeru, 2006).

Some studies however report that patients who have experienced AIDS-related symptoms perceived as serious are usually more adherent than patients who never had symptoms, or who consider their symptoms unimportant (Gao *et al.,* 2000; Steele *et al.,* 2001).

2.4 Adherence Assessment

Medication adherence is difficult to measure accurately in absence of directly observed therapy (DOTS). It can only be estimated using proxy methods which include; pill counts, self-reports, pharmacy refill records, drug level monitoring and electronic monitoring devices among others.

Pill counts are a quantitative means of measuring adherence and are often used in combination with self reports in research. They are also popular due to ease of use and being inexpensive. However, they can be affected by pill dumping leading to overestimation of adherence (Liu *et al.,* 2001). Electronic Drug monitoring (EDM) is another quantitative method of measuring adherence which involves use of an electronic pill box that registers each opening of the bottle. It is more predictive of viral suppression than pill counts and self reports.EDM offers the benefits of being objective and effective for long durations as well as measuring timing of doses. It is however expensive and complicated to provider and patient in addition to being intrusive on the patient. It is also vulnerable to pill dumping which can underestimate adherence if

patient removes more than one dose at a time (Choo *et al.,* 1999). Monitoring drug levels is an accurate and objective approach to assessing adherence. Unfortunately, it is expensive, requires skilled personnel and is very invasive, making it unsuitable for developing countries. It can under or overestimate adherence depending on patients' metabolism, genetic makeup and other co- prescribed drugs (Arnsten *et al.,* 2001)..

Monitoring pharmacy refill records is a cheap and easy way of assessing adherence which uses routine data. It is objective but inaccurate if data is not well kept. Although it can overestimate adherence, it has been found to correlate well with adherence (Liu *et al.,* 2001).These adherence assessment methods have their pros and cons as summarized in the table 3 below (Arnsten *et al.,* 2001).

The relationship between these different methods of assessing adherence has been found to vary between studies. Most studies in this area have been in developed countries. Among studies in Africa, Oyugi and others (2004) measured adherence via self-report, pill count, visual analogue score, and EDM, and found adherence levels at 24 weeks of 85, 86, 88, and 82%, respectively, implying a high degree of agreement between the various measures. However, these rates only applied to the 46% (32/70) of the participants who completed a 24 weeks follow up period. Ng'eno, on the other hand compared adherence of 188 children on HAART by caregivers self report and pharmacy pill counts and found a significant difference between adherence rates by the two methods. Adherence by pill counts was 61% while that by self report was 87% (Ng'eno, 2008). Omes and others also found high levels of discord between two forms of self-report; questionnaire and visual analogue scale (Omes *et al.*, 2004). In Botswana, 71% of

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patients who self-reported as adherent were believed to be adherent by their health care providers (Weiser *et al.,* 2003). However, none of these studies reported correlation with undetectable viral loads.

Liu and colleagues found that while EDM underestimates adherence, pill count and patient self-report both tended to overestimate adherence(Liu *et al.,* 2001).This was consistent with findings by Arnsten and others who reported mean HAART adherence rates of 79% by self-report and only 53% by EDM (Arnsten *et al.,* 2001). Bangsberg and colleagues however found that structured patient report of adherence was closely related to unannounced pill count (Bangsberg *et al.,* 2000). Balfour and others on the other hand advocated for the use of EDM to assess correct timing of doses as the best measure (Balfour *et al.,* 2001). Overall, these studies imply that adherence can reliably be measured by patient self-report as well as other methods. The context of resource-limited settings limits the choice of adherence measurement methods: plasma drug assays and EDM are beyond reach for most of these settings and illiteracy prohibits the use of self-rating questionnaires.

The accuracy of patient self-report can be optimized by appreciating the complexity of adherence, having someone other than the primary care provider collect these data, and by performing repeated measures. Validity of measurement can be ensured by asking the some key questions on adherence severally, in different forms to ensure respondents are consistent, enhance recall and correct any misunderstood responses.

Given that barriers to adherence are diverse and complex and evolve over time, monitoring of medication taking behaviors is complicated and needs further investigation especially in developing countries hence appropriate study methods are needed.

2.5 Adverse drug effects

While use of HAART has led to a significant reduction in AIDS-related morbidity and mortality (Hogg *et al.,* 1999), up to 25% of patients discontinue their initial HAART regimen because of toxic effects and other HIV related symptoms within the first 8 months of therapy. With the sustained major declines in opportunistic complications, more drugs are being used on more patients for longer periods and large numbers of patients are now on HAART in developing nations and more continue to be initiated every day. (Lucas *et al.,*1999; D'Arminio *et al.*, 2000). Medication side effects are frequent in HIV-positive patients treated with HAART (Max *et al.,* 2000; Evans 2008), and the effect of these side effects on adherence remain largely unknown. Short term side effects are potential threats to successful introduction and maintenance of HAART whilst the long term toxicities threaten sustanance of HAART in the long run (Blake and Renslow 2000).

Antiretroviral toxicity may well be the major hindrance for long term maintenance of this treatment (Carr and Cooper, 2000). The adverse effects of antiretroviral therapy cause substantial morbidity, compromise adherence, which can lead to drug resistance and cause relatively significant mortality.

Table 2.2 below summarizes the side effects associated with the antiretroviral drugs

currently being used in Kenyan programs (Valentina et al., 2004).

Table 2.2   Antiretroviral drug and common adverse effects

Drug	Common side effects
Nucleoside Reverse transcriptase inhibitors(NRTIs)	
Stavudine (D4T)	Peripheral neuropathy, diarrhea, pancreatitis, lactic acidosis, dyslipidemia (lipodystrophy).
Zidovudine (AZT)	Anemia, neutropenia, fatigue, malaise, nausea, vomiting, rash, myalgia, myopathy, hyperpigmentation of skin and nails, leucopenia, elevation of liver enzyme levels, lactic acid elevation.
Lamivudine (3TC)	Headache, dry mouth, neutropenia (rare).
Didanosine (ddi)	Pancreatitis, nausea, diarrhea, peripheral neuropathy, GI intolerance, gout.
Tenofovir (TDF)	Flatulence, nausea, diarrhea, abdominal discomfort, asthenia, acute renal insufficiency, fanconi syndrome, chronic renal insufficiency, reduction of bone mineral density.
Abacavir (ABC)	Hypersensitivity reactions (fever, myalgia, malaise, nausea, vomiting) anorexia, rash, headache, nausea, vomiting, diarrhea.
Emtricitabine	Headache, nausea, insomnia, hyperpigmentation of palms and soles (occurs most frequently in dark-skinned people.
Non- nucleoside Reverse transcriptase inhibitors (NNRTIs)	
Nevirapine (NVP)	Elevations in liver enzyme levels, hepatitis, liver failure, rash.
Efavirenz (EFV)	Elevations in liver enzymes, hyperlipidemia, abnormal dreams, drowsiness,
	dizziness, confusion.
Protease inhibitors (PIs)	
Ritonavir	Nausea, vomiting, diarrhea, abdominal pain, elevations in liver enzyme levels, fatigue, peripheral numbness, taste perversion, hyperuricemia
Indinavir	Nephrolithiasis, flank pain, elevations in liver enzyme levels,, alopecia, dry skin, ingrown nails, insomnia, taste perversion , hyperbilirubinemia
Lopinavir/ Ritonavir (LPV/r)	GI upset

Although only a few studies have been done specifically on adverse drug reactions (ADRs) associated with HAART, especially in the sub-Saharan Africa, it is

clear from the available studies that ADRs are associated with impaired quality of life and level of functioning and may result in patients being non adherent to medications.

In a Cross-sectional study involving 2,765 HIV-positive adults on ARV therapies in four U.S. cities, computerized assessment of self-reported adverse effects, coping self-efficacy, and adherence were performed. Respondents with less than 90% adherence reported greater numbers and severity of adverse effects. Nausea, skin problems, vomiting, and memory adverse effects were independently related to less than 90% adherence over the prior three days. Coping moderated the relationship between nausea and adherence such that individuals who reported lower coping self-efficacy and experienced nausea were at increased risk for nonadherence, regardless of the length of time on the current ARV regimen. Specific adverse effects (skin problems, memory problems, vomiting, and nausea) were more likely than others to be associated with missing ARV medications (Mallory *et al.,* 2005).

In a Brazil study, the relationship between characteristics of HIV antiretroviral regimens and treatment adherence was studied in adolescent and adult patients on antiretroviral therapy. The use of antiretrovirals during the previous 48 hours was investigated by a self-report. Adherence was reduced for patients who reported adverse effects (Silveira *et al.,* 2000).

In Italy, a cross-sectional multicenter study was carried out among 358 persons on antiretrovirals. Variables predictive of nonadherence to HAART and self-reported symptoms or medication side effects related to adherence were assessed over a one year period. A self-administered questionnaire was used to assess nonadherence in the last 3

days as well as the type and perceived intensity of 24 common HIV- and HAART-related symptoms experienced during the last 4 weeks. 22% of participants reported nonadherence. Frequency of moderate/severe symptoms or medication side effects in nonadherent participants ranged from 3.6% to 30%. Symptoms and side effects found to be significantly associated with nonadherence were; nausea, anxiety, confusion, vision problems, anorexia, insomnia, taste perversion, and abnormal fat distribution. Nonadherent persons had a higher mean overall symptom score; 12.3 as compared to 8.1 for adherent persons ($p < .001$). The mean medication side effect score for nonadherent persons was 2.9 compared to 1.9 for adherent participants (p< .001) (Ammassari *et al.,* 2001).

A study in Pretoria, South Africa assessed the significance of side effects to adherence and found that 94% of the 180 respondents reported at least one side effect and the mean number of self-reported side effects was 2.6. The mean number of doses missed during the last seven days prior to the interview was 2.7, ranging from 0 to 18. Barriers to self-reported adherence (=> 95%) included having used non-prescribed medicines (to relieve symptoms) (15.6%), having suffered from headaches (28.6%) and reported symptoms such as insomnia (27.3%) and abdominal pain (20.8%) (Malangu 2008).

In Kenya, a study in Kericho District hospital identified the fear of side effects as the most important barrier to adherence at 76% (Njeru, 2006).

In a retrospective study to investigate the frequency, characteristics and factors associated with adverse effects in Kenyatta National hospital, 350 patients were used.

The median age was 40years, 42.6% were male, 52.3% were married, 18% had co-morbidities, and the median number of months on treatment was 32, (range12 – 56). 92% were on stavudine based regimens while 7% were on Zidovudine based regimens and only 1% on Didanosine based regimen (Evans, 2008).The prevalence of adverse drug effects (ADR) was 49% in this cohort - with some patients reporting more than one ADR - and it generally increased with time. The most common ADR was peripheral neuropathy (48.6%), lipid abnormalities accounted for 28.9%. ADR was the most common reason for change of regimen accounting for 59% of all regimen changes. Time to develop ADR ranged from 2 months for rashes to 29 months for lipid abnormalities. With intervention, rashes were reported to last the shortest duration, (median 3 months) while lipid abnormalities lasted the longest (6 months). The most commonly reported risk factors for ADRs were; being on HAART for more than 32 months and being an a stavudine or didanosine based regimen.(Evans, 2008)

Mutugi and others conducted a study in Nyeri Provincial general Hospital, Kenya, to investigate the success and challenges of antiretroviral therapy among patients on HAART. The success of treatment was monitored by viral load, CD4 cell count and weight. Challenges of ART were assessed by administering a questionnaire. The mean adherence rate was 62%. Cost, forgetfulness and side effects were reported as contributors to poor adherence; Side effects perceived by patients to be associated with ART were chest pains, coughing, headache, diarrhea and malaise (Mutugi *et al* 2010).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study area

The study was conducted at Tigoni District Hospital, a public heath institution located within Kiambu District in Kenya. The hospital is within a short distance (40kms) from Nairobi, Kenyan's Capital City, but its clientele is largely a rural population. The hospital serves a large number of HIV/ AIDS patients attended at the Comprehensive Care Clinic. The clinic was started as part of a 5 clinic collaborative project implemented by University of Nairobi to provide HIV/AIDS treatment and care in 2005. This included provision and scale up of ART services, Opportunistic infections treatment & care and laboratory work up for patients, all at no cost. The University however pulled out in 2009 and the clinic now runs as most comprehensive care clinics in public hospitals. It is a standalone clinic where patients are seen from a room next to the hospital theatre (previous recovery room) due to lack of space. Patients then collect their medication from the hospital pharmacy. Staff working at the clinic consisted of medical officers, clinical officers, nurses and pharmaceutical staff working in the hospital.

3.2 Study design

This was a hospital based cross sectional descriptive study conducted between October and December 2010, among the attendees of the CCC that is at Tigoni District hospital.

3.3 Study population

The study population consisted of patients actively receiving ART, and participants were sampled from those attending the ART clinic. About 500 patients were actively on ART at the clinic between October and December 2010. Majority of patients were on the first line regimens recommended by the Ministry of Health (MOH, 2004).These regimens were dispensed both as fixed dose combinations or individual drugs consisting of 2 NRTIs and an NNRTI. Patients on second line regimens were given 2 NRTIs and a PI. Most continuing patients at the clinic routinely got two and three months' doses of their medication. New patients were given two weeks or a one month dose.

3.3.1 Inclusion Criteria

The following HIV positive patients attending Tigoni comprehensive care clinic were included in the study;

   a. On HAART, for at least 14 days and attending the ART clinic on recruitment day.

   b. Over the age of 18 years.

   c. Willing and able to provide informed consent to participate.

3.3.2 Exclusion Criteria

The following HIV positive patients attending Tigoni comprehensive care clinic were excluded from the study;

   a. Very sick patients requiring emergency care.

b. Concomitant physical illness unrelated to side effects.

c. Unwilling or unable to give informed consent

3.4 Sampling

3.4.1 Sample size determination

The sample size was calculated using adherence of 87% from a self reported study done at Kenyatta National hospital, Kenya (Ng'eno, 2008). This site was similar in support structure to Tigoni Hospital for it was locally supported without support from development partners, The sample size was based on Cochran's formula (1963) to estimate the level of adherence with a 5% precision level:-

$$n = Z^2 \, p \, (1\text{-}p) \, / \, d^2$$

Thus;

$$n = 1.96^2 * 0.87(1\text{-}0.87)/ \, 0.05^2$$

$$n = 173$$

Where:-

Z=Z critical value for alpha (At p-value of 0.05, Z=1.96)

P = estimated proportion of PLWHA on ART with adherence level at 95% or more (here 87%) using the self reports.

d = the degree of precision (5%), is the maximum error we would expect to make at 95% confidence interval.

3.4.2 Sampling technique

Systematic sampling was used to select participants into the study from patients receiving HAART, as they waited to collect their medicines at the pharmacy. Every third patient who met the study's inclusion criteria and who was willing to participate was selected for the study until the required sample size was achieved. The sample size was attained within 3 months-October to December 2010.

3.5 Study instruments

Structured Questionnaires (appendix 1), adopted and modified from NIAID ADULT AIDS CLINICAL TRIALS GROUP (NIAID) were used in this study. These have been developed specifically for assessment of adherence to HAART and have been field tested. (NIAID Adult Aids Clinical Trials Group)

The questionnaire was piloted on 10 patients to make sure questions were not ambiguous and to eliminate questions that did not yield usable data. The research assistants who assisted to collect the data were trained before data collection.

3.6 Data collection procedure

An interviewer-administered questionnaire (Annex 2) collected information on socio-demographic characteristics, regimen characteristics and HIV-related history including time since diagnosis and ART Therapy and counseling. Information on adherence during the previous 3 days and one month was collected by asking the number of pills missed in these respective periods. Possible reasons for missing or discontinuing drugs were

investigated. The questionnaire had open ended questions regarding presence and types of medication side effects and how these had affected the participant and their adherence to HAART. In addition, further questions on side effects were asked by recording the type and perceived intensity (Not at all, mild, moderate, or severe) of 13 common HAART related symptoms experienced during the last 4 weeks. These were Nausea & vomiting, general malaise/tiredness; headache, dizziness, diarrhea, rash, nightmares, insomnia, peripheral neuropathy, hypersensitivity reactions, lactic acidosis (nausea/vomiting + abdominal pain + difficulty breathing +severe weakening of muscles in the legs and arms) and fat distribution disturbances (lipodystrophy). This allowed recording of single or multiple side effects. Patients were asked how the side effects experienced had affected them (Not at all, mildly, averagely and severely), and if they had stopped taking their medication as result of the side effects.

3.7 Data entry and analysis

Data was double entered using Epi-info 3.3.2 to check for entry errors. Analysis was done using SPSS Statistics 17.0. Averages, means, ranges and percentages were used to summarize symptoms (HAART related), regimens, and sociodemographic characteristics. A summary for items most likely to represent HAART-related symptoms (i.e., nausea & vomiting, dizziness, rash, stomach upsets, nightmares, feeling sleepy, tiredness, diarrhea, abnormal fat distribution, peripheral neuropathy, hypersensitivity reactions) were done and percentages calculated according to how many times a

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symptom was reported. Cross tabulation was done to assess any association between the number and perceived intensity of side effects to Adherence and duration on treatment. For this study, patient reported 3 day (short term) adherence was computed as the actual number of pills taken over the preceding 3 days divided by the number prescribed over the same duration, expressed as a percentage. One month (long term) adherence was computed as the actual number of pills taken over the preceding one month divided by the number prescribed over the same duration, expressed as a percentage

$$\underline{\text{Number of doses taken}} \quad \text{X 100}$$

Number of doses prescribed

Adherence was dichotomized at 95%, where =>95% was considered adherent and below this non adherent. Associations between the independent variables and dependent variables were analyzed using logistic regression. Univariate analysis, using individual factors followed by multivariate analysis using all those factors considered significant explored associations between self reported HAART-related symptoms, patient factors and characteristics of the antiretroviral regimens with short and long term adherence.

3.8 Theoretical framework
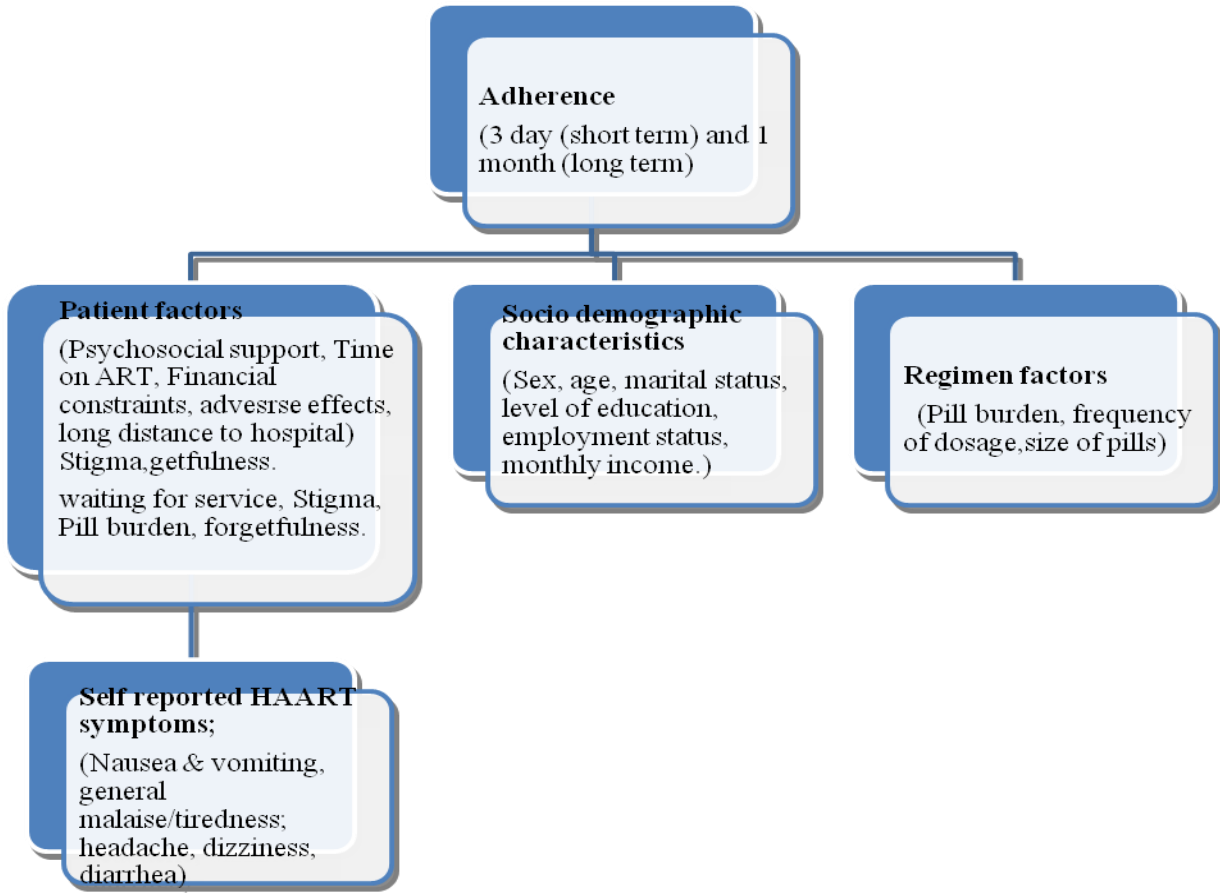
Figure 3.1 Theoretical framework

3.9 Ethical considerations

This study was approved by the KEMRI Scientific Committee and the KEMRI National Ethical Review Committee before implementation. The details and importance of the study was explained to the recruited patients. Selected participants were invited into a private room where the interviewer explained the study particulars, details of the consent document (appendix 2) including the fact that participation was voluntary. They were

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further informed that the decision not to take part in the study would not affect their future treatment and care in the hospital. Participants were additionally informed that there would be no direct benefits to them but information provided would help improve management of their condition particularly in regards to side effects and compliance to HAART regimens. Those who did not feel comfortable participating in the study were not forced or coerced and they were not questioned further. Those who chose to participate had the right to withdraw from the study at any time without needing any explanation. Information was obtained from patients in a manner that did not disrespect cultural and social beliefs, or make them uncomfortable.

All willing patients were asked to sign an informed consent form.

CHAPTER FOUR

4.0 RESULTS

A total of 183 patients were recruited into the study. This was slightly higher than the minimum sample size calculated of 173.

4.1 Demographics

This section describes the socio-demographic characteristics of patients recruited into the study.

4.1.1 Socio-demographic profile

Out of the 183 patients who were interviewed, 69% were female and 31% were male. Age ranged from 18 to 75 years mean age being 39.2 ($\pm$9.4) years. Majority of participants (72%) were aged between 26 to 45 years while 24.5% were between 46 and 75 years. Only a small proportion,(3.3%) were aged between 18 and 25 years (Fig. 4.1).
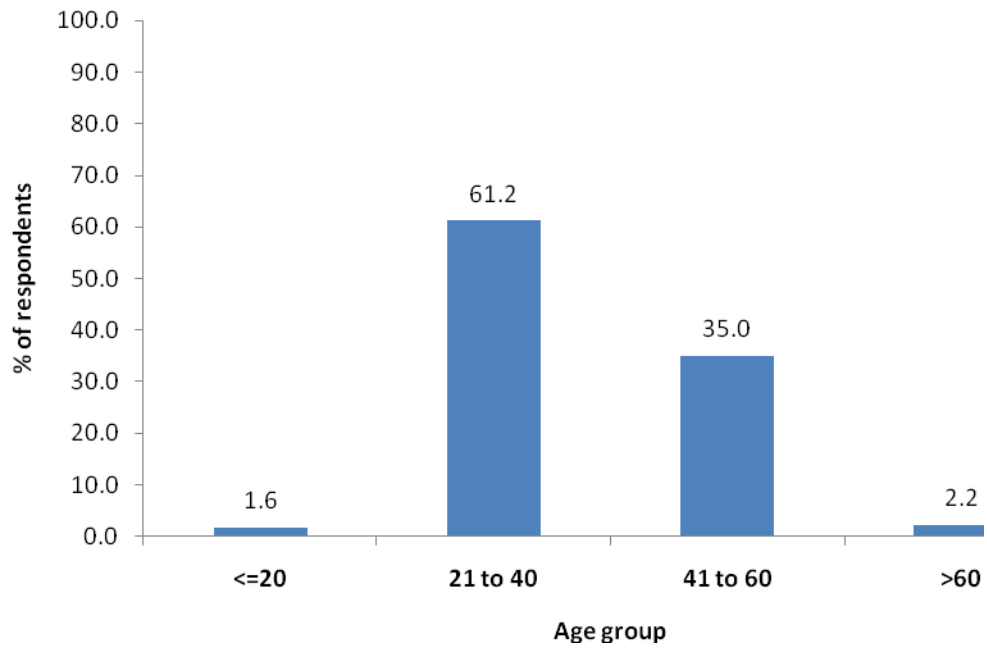
Figure 4.1 Distribution of respondents by age group

Concerning education level, participants who had completed college or university were 2.7% while a similar proportion had incomplete college or university education. Twelve percent had incomplete secondary education while 15.8% had completed secondary education. Participants who had complete primary education were 36.6%, incomplete primary education 25.7% and 3.8% had no education at all (Fig. 4.2).
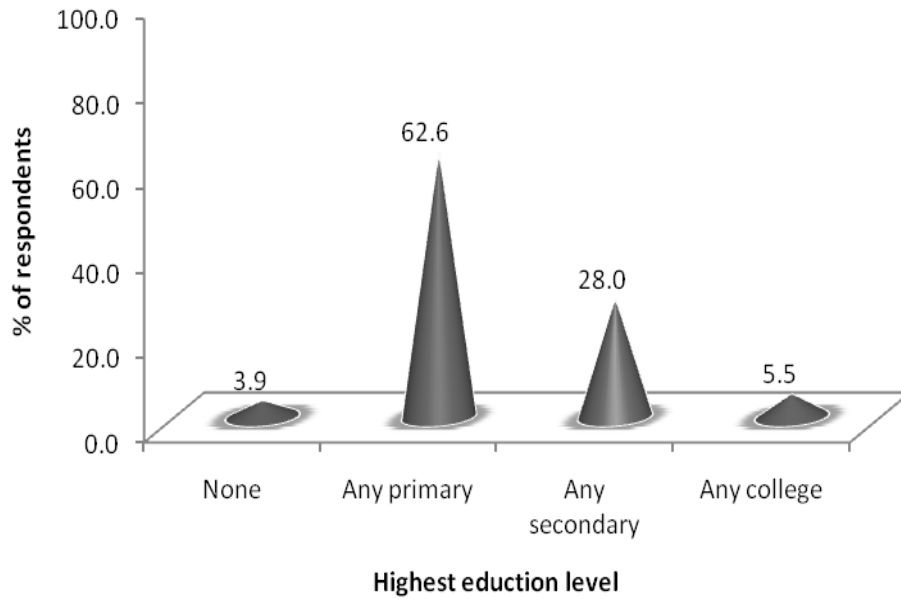
Figure 4.2 Highest education level achieved by respondents

Regarding occupation, 47.8% of participants were self employed, 19.2% were in formal employment and 15.4% were in informal (casual) employment. Housewives and unemployed consisted of 29.1% (Fig. 4.3).
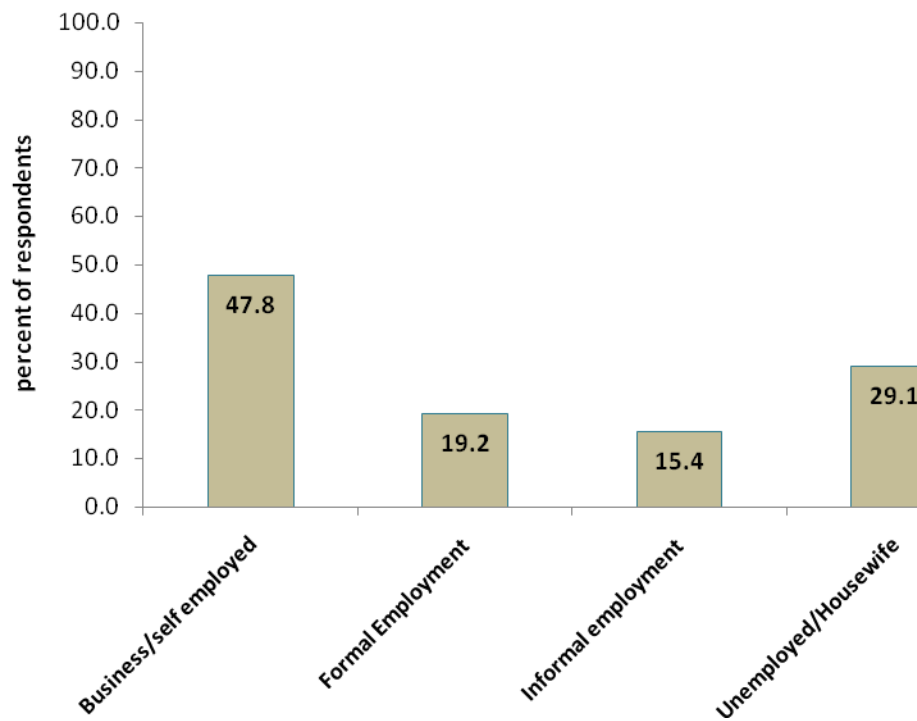
Figure 4.3 Participants' occupation distribution in percentage

Marital status consisted of 19% divorced/separated participants, 51% married/cohabiting, 15% single and 15%.widowed (Fig. 4.4).
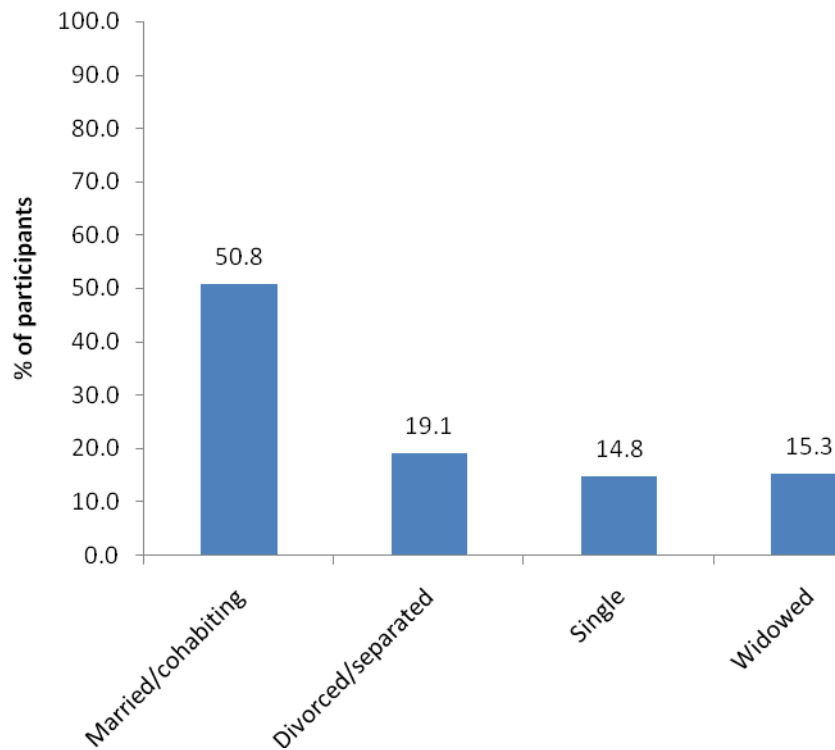
Figure 4 .4 Participants' Marital status distribution by percentage

All patients were on a triple therapy out of which 22% were using a fixed dose combination. Ninety nine and a half percent of participants were on the first line regimen based on 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a non nucleoside reverse transcriptase inhibitor (NNRTI), while one patient was using a protease inhibitor in place of an NNRTI. The most prescribed regimen was 3TC/AZT/NVP (30.6%). The combinations 3TC/D4T/NVP and 3TC/TDF/NVP were also commonly prescribed 22% and 20% respectively (Table 4.1).

Table 4.1   Regimen characteristics of participants

Regimen	n	%
Lamivudine/Zidovudine/Lopinavir/retrovir	1	0.5
Tenofovir/Zidovudine/Nevirapine	2	1.1
Lamivudine/Stavudine/Eavirenz	5	2.7
Lamivudine/Zidovudine/Eavirenz	11	6
Lamivudine/Stavudine/Nevirapine	12	6.6
Lamivudine/Tenofovir/Eavirenz	19	10.4
Lamivudine/Tenofovir/Nevirapine	37	20.2
Lamivudine/Stavudine/Nevirapine-Fixed dose combination	40	21.9
Lamivudine/Zidovudine/Nevirapine	56	30.6
Total	183	100

4.1.2 Diagnosis and Treatment history

The mean duration of treatment was 32.1(+/-32.8) months; 43.2% of participants had been on treatment for over 2 years (24 months) while 17% had been on treatment for up to 6 months. Majority of patients (64.5%) had been on treatment for over 1 year (Fig. 4.5).
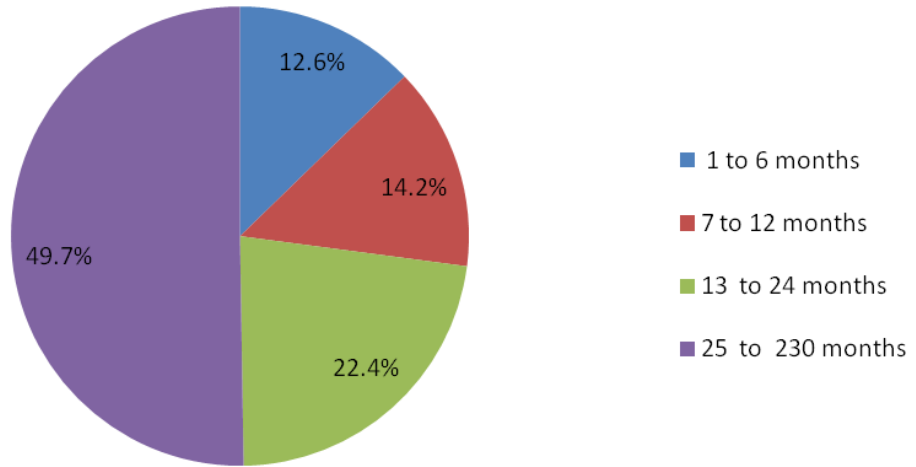
Figure 4.5 Distribution of participants by months on treatment

The mean duration since diagnosis was 38.4 (+/- 37.5) months and 50% had been

diagnosed over 2 years previously (Fig.4.6).
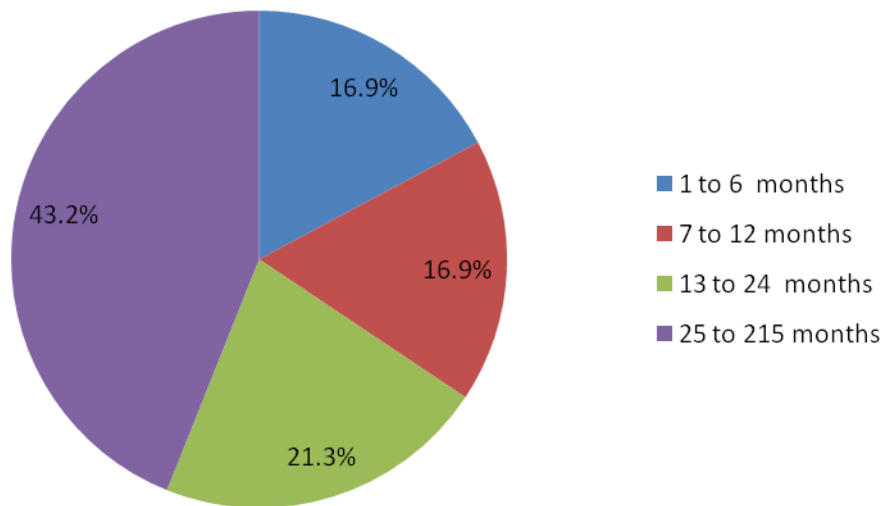
Figure 4.6 Distribution of participants by months since diagnosis

4.1.3 Knowledge, attitude, counseling and disclosure

Most participants were knowledgeable about HIV/AIDS and had a positive attitude towards their HIV positive condition; 60.7% reported that being positive was not a very serious problem to them, 77.6% believed that being HIV Positive didn't mean they would definitely develop AIDS, 99% believed that ART prolongs life for positive persons and 93.4% believed that ART would get rid of most of the virus in a patient's body. Most patients (95.6%) had received counseling before and during treatment and most (87.4%), had disclosed their status to someone. Spouse/sexual partner were the person disclosed to by most participants (47%) followed by close relative (32.2%), parent (24%), children (18%) and others such as sibling and non sexual partner (Fig.4.7).
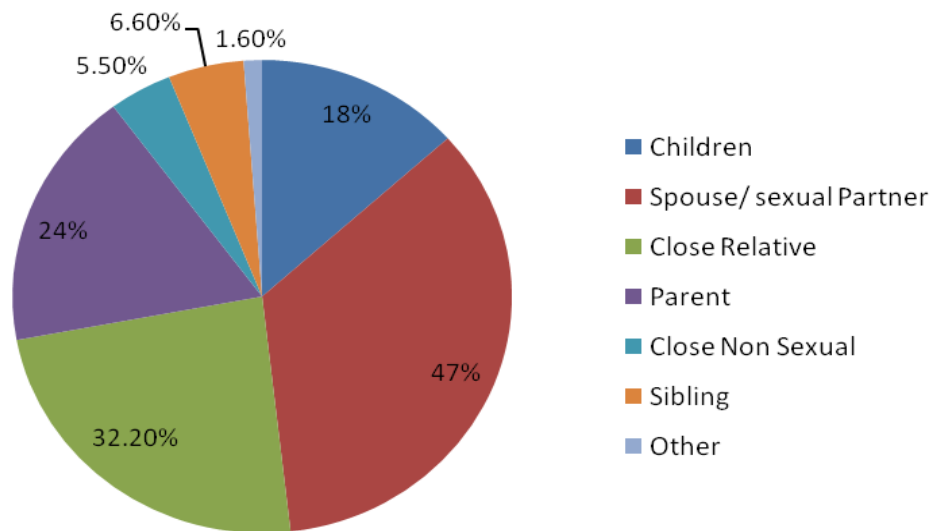
Figure 4.7 Distribution of persons to whom HIV status was disclosed

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4.2 Adherence

The mean short term (3 day) adherence was 96.4% while mean long term (1 month) adherence was 98.1%. Most patients (90.7%) reported being adherent (taking more than 95% of the prescribed dose) during the preceding 3 days while 95% reported being adherent during the preceding 1 month (Fig. 4.8).
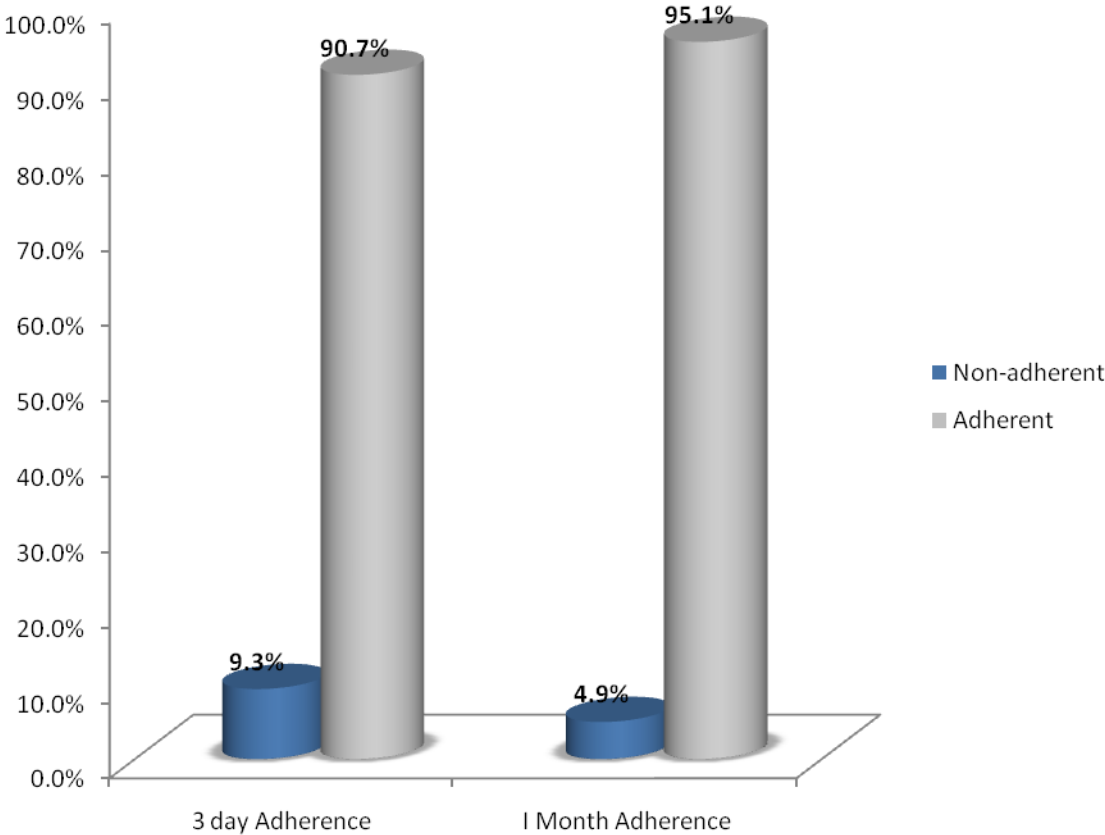
Figure 4.8 Adherence summaries by percent of respondents

4.3 Reasons for Missing Drugs

Running out of drugs and being away from home were reported as the most common reasons for missing medications (44% and 35.6% respectively) while forgetting and wanting to avoid side effects accounted for 15.6% and 4.4% respectively of those who missed medications (Fig.4.9). Of all those who had missed their medication, 54.3% reported they had missed over a month previously (fig. 4.9).
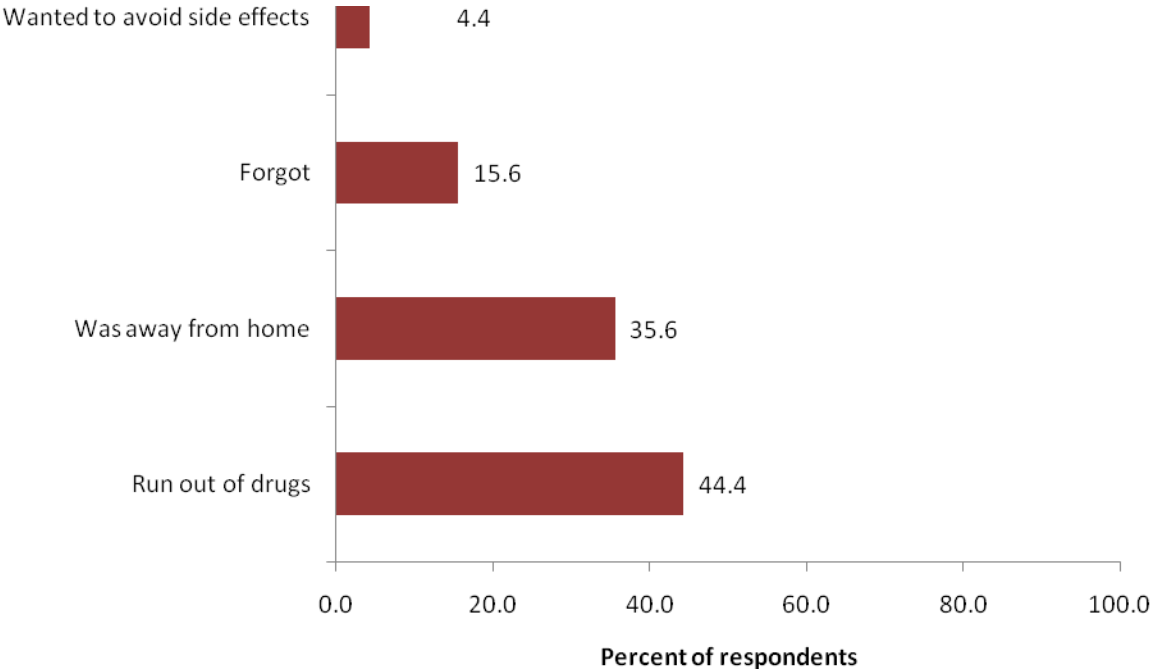
Figure 4.9 Reasons for missing drugs by percent of respondents

4.4 Predictors of Adherence.

On Univariate logistical regression, the last time a patient missed medication was significantly associated with 1 month adherence at 5% level of significance (OR 1.4,

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P=0.05). All other factors investigated such as socio-demographics, regimen, period since diagnosis or treatment, number and perceived intensity of side effects were however not associated with adherence (Table 4.2).

Table 4.2   Univariate logistical Regression for predictors of 3 day and 1 month adherence

Predictors	3 day Adherence		1 Month Adherence	
	OR	P-value	OR	P-value
Knowledge	0.23	0.13	0.42	0.36
Disclosed Status	1.56	0.51	0	1
Counseling Before Treatment	1.66	0.65	0	1
Counseling While on Treatment	1.65	0.65	0	1
No Of Side Effects	1.33	0.21	1	0.99
Age in Years	0.99	0.79	1	0.98
Months Since Diagnosis	1	0.56	1	0.96
Months On ARVS	1	0.69	1	0.72
Regimen	0.99	0.95	1.08	0.67
Sex	2.13	0.14	1.11	0.88
Education	0.97	0.87	0.71	0.17
Occupation	0.84	0.46	1.03	0.93
Perceived intensity Of Side Effects	1.02	0.98	0.65	0.57
Marital Status	2	1	0.99	0.98
last Time Missed Medication	0.82	0.44	1.4	**0.05**
Being HIV+ Effect on patient	0.69	0.3	0.85	0.75

On multivariate logistical regression, as with univariate analysis, the last time a patient missed medications was also significantly associated with 1 month adherence at 5% level of significance (OR, 1.7; P=0.03). Patients who had missed drugs during the past 2 weeks were more likely to be non-adherent compared to those who had not. All other parameters were not significantly associated with adherence (Table 4.3).

Table 4.3   Multivariate logistical Regression for predictors of 3 day and 1 month adherence

Characteristic	3 day Adherence		1 Month Adherence	
	OR	P-value	OR	P-value
Knowledge	0.23	0.18	0.37	0.4
Disclosed Status	2.85	0.22	0	1
Counseling Before Treatment	0.48	0.64	0	1
Counseling While on Treatment	4.3	0.37	0	1
No Of Side Effects	1.98	0.13	1.01	0.97
Age in Yrs	0.98	0.47	1	1
Months Since Diagnosis	1	0.92	1.03	0.61
Months On ARVS	1.01	0.78	0.96	0.54
Regimen	0.93	0.61	0.96	0.85
last Time Missed Medication	0.92	0.76	1.66	**0.03**
Being HIV+ Effect on patient	0.52	0.13	0.74	0.6
Sex	3.21	0.11	1.37	0.77
Marital Status	0.79	0.39	0.69	0.33
Education	0.91	0.7	0.73	0.25
Occupation	0.6	0.09	0.79	0.55

Majority of patients (54.3%) had missed medications over 3 months prior to the study, 13% and 15.2% had missed 2 to 4 weeks and 1 to 2 weeks previously while 17.4% had missed within the past week. A fisher's exact test of independence did not show any association between HAART regimen and either short term or long term adherence (P-value 0.28 and 0.29 respectfully).

4.5 Side Effects

ARV associated side effects were investigated as reported by the patients.

4.5.1 Number of HAART related side effects.

Of all the patients, 30.4% experienced at least 1 side effect. Eighteen percent experienced 1 to 3 side effects, 11% reported experiencing 4 to 6 side effects while 1.6% experienced 7 or more side effects. The majority of patients (69.4%) however did not experience any side effect (Fig.4.10).
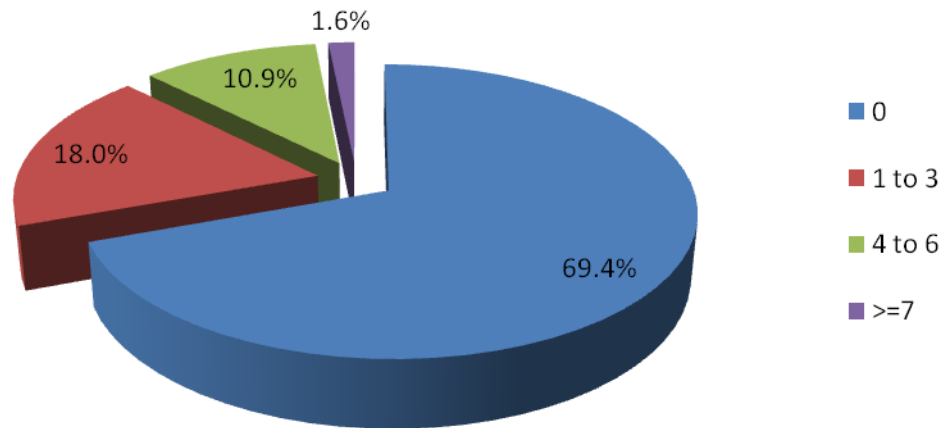
Figure 4.10 No. of ARV related side effects reported

4.5.2 Frequency of HAART associated side effects.

Figure 4.11 shows that Tiredness/General Malaise, rash and dizziness were the most commonly reported side effects at 21%, 20% and 17% respectively. Nausea and vomiting, stomach upsets, sleepiness and headache were also common each at 16 %. Other side effects experienced to a lesser extent were; Diarrhoea (5%), Peripheral

Neuropathy (5%), Nightmares (4%), Hypersensitivity Reactions (3%), Lactic Acidosis (3%), Lipodystrophy (2%) and Insomnia (1%).
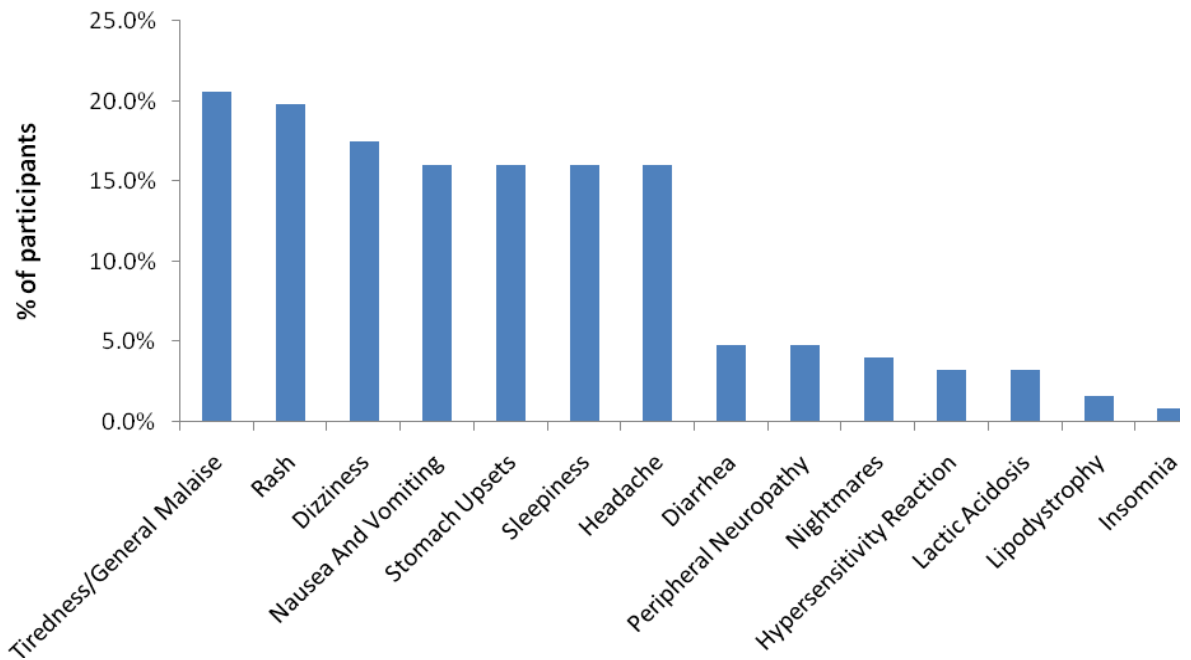
Figure 4.11 Frequency of HAART associated side effects by percent of respondents

4.5.3 Association between months since diagnosis and side effects

On chi square test of independence, the duration a patient had been on treatment was significantly associated with the number of side effects (P-value 0.04).Patients who had been on treatment for longer- 13 months and above- tended to have less side effects than those who had been on treatment for a shorter period (Table 4.4). The duration on treatment however was not significantly associated with the effect side effects had on patients (P-value 0.3).

Table 4.4   Association of duration of treatment and no. of side effects

Months on Treatment	No. of side effects				
	1 to 3	4 to 6	7 to 11	Total	%
1 to 6	8	3	2	13	23.2
7 to 12	6	5	0	11	19.6
13 to24	8	7	0	15	26.8
over 25	11	6	0	17	30.4

Chi-square p-value 0.04

4.5.4 HAART regimen effect on number and perceived intensity of side effects

There was no association between HAART regimen and either the number or perceived intensity of side effects on chi square test of independence (P-value 0.99 and 0.98 respectfully).

4.5.5 Effect of HAART associated side effects on Patients

Among patients who reported experiencing side effects, 5.3% reported being affected severely, 5.3% averagely, 40% mildly and 49% reported no effect at all (Fig.4.12).
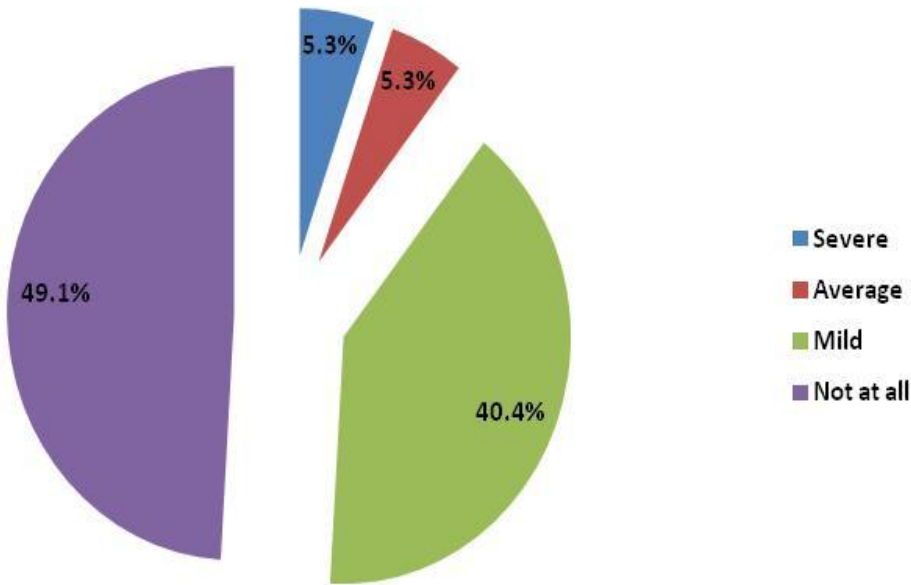
Figure 4.12 Effect of reported side effects on respondents in percentage

Only 14.2% of patients who experienced side effects reported that they influenced their medication taking behavior in any way, and of these, only 3(5.4%) stopped taking their medications as a result (Fig. 4.13).
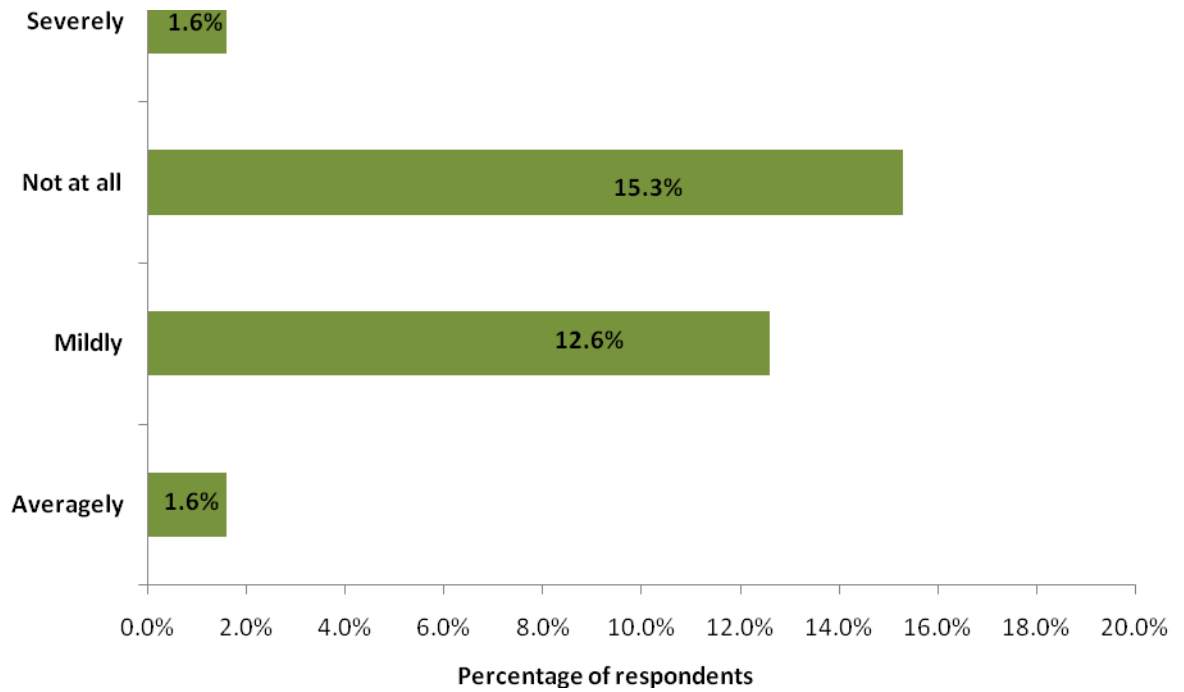
Figure 4.13   Influence of side effects on medication taking behavior

Based on chi square test of independence, neither the number nor the perceived intensity of side effects was significantly associated with adherence (Table 4.5).

Table 4.5   Association between no. and perceived intensity of side effects on adherence

	n	Impact of no. of side effects on adherence		Impact of perceived intensity of side effects on adherence	
		Value	P-value	Value	P-value
1 month adherence	56	4	0.9	3	0.4
3 day adherence	56	3.8	0.9	1	0.8

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CHAPTER FIVE

5.0 DISCUSSION

The gender composition of the study group, 67.8% female and 32.2% male reflect the gender disparity in HIV infections in Kenya where prevalence is higher among women than men. The Kenya AIDS Indicator Survey (2007) found that women had a higher chance of being infected (8.4%) than men (5.4%).This finding was similar to those from most studies carried out in developing countries where women bear a higher burden of HIV infections than men; 54% female in Brazil, (Filho *et al.*, 2008), 59.8% females in Ethiopia (Alemayehu *et al.,* 2008) 53.3% females in Uganda (Byakika-Tusiime *et al.,* 2005) and an equal number of female and male subjects in Botswana (Weiser *et al.,* 2003). In Kenya, 57.4% of participants were female in a study at Kenyatta National Hospital (Evans 2008); 61.1% were female in an adherence study in Kericho (Njeru 2006); and females were 65% in another study in Mbagathi (Zachariah *et al.,* 2008), again displaying the trend of the distribution of HIV among the 2 genders. The higher HIV prevalence in women may be due to the biological predisposition that makes women more vulnerable to men. The lower socioeconomic status of women in low income settings may also lead women to engage in risky economic activities. The variation in HIV among the 2 genders in Kenya was further documented by the KDHS 2008-09 where, higher prevalence was observed in women than men (8% versus 5%). The higher prevalence of HIV among women in Kenya may, in addition to the factors prevalent in African settings, be fueled by traditional practices such as wife inheritance, which make women more vulnerable to new infections.This sex ratio was however

different from that from studies in developed countries where more males than females are often reported; 74% males in a study in four U.S. cities (Mallory *et al.,* 2005), 72% males in Italy (Ammassari *et al.,* 2001) and 76.2% men in Spain (Gordillo *et al*., 1999).This may be due to the fact that in western countries, HIV is more prevalent among intravenous drug users and homosexuals both of which practices are more common among men (Gordillo *et al*., 1999; Mallory *et al.,* 2005).

Average age of participants was comparable with most studies done in both resource rich and resource constrained settings; 42 years in USA (Mallory *et al.,* 2005), 36.3 years in Italy (Ammassari *et al.,* 2001), 35 years in Spain (Gordillo *et al*., 1999) 36 years in India (Sarna *et al.,* 2008). Among studies in the sub-Saharan Africa, mean age was 33.4 years in South Africa (Orrell *et al*., 2003), 36.7(±8.1) in another south African study (Malangu 2008), 38 years in Senegal (Laniece *et al.,* 2003) and ranged from 19 to 58 years in Ethiopia (Alemayehu *et al.,* 2008).In Togo, the age of patients ranged between 21 to 57 years, with an average age of 36.8 years (Yao *et al*., 2010), and 30-50 years in Botswana (Weiser *et al.,* 2003). In Kenya, the mean age of the participants in a study in Kericho was 37.8 years (range 19-70) (Njeru 2006), median age was 40 years in the Kenyatta National Hospital study (Evans 2008), and 31.5 years in a study in Bagathi District hospital in Nairobi.(Zachariah *et al.,* 2008). Majority of participants (72%) were aged between 26 to 45 years while 24.5% were between 46 and 75 years. Only a small proportion (3.3%) were aged between 18 and 25 years. This is comparable to age distribution in a study in Togo where the age group from 36 to 45 years was more representative (39.4%), followed by 26 to 35 years (34.3%).

Marital status composition in this study was comparable with most studies in similar settings, where a higher proportion of patients were married. A study in Sweden reported 59% of participants being married or partnered in a relationship like marriage (Nilsson *et al.,* 2006). In an Indian study however, 91% were married, 2% and 7% were single and separated/widowed respectfully (Sarna *et al*., 2008). This substantial dissimilarity may be due to differences in social cultural issues in the Indian setting. In Africa, 58% of participants were married in Botswana (Weiser *et al.,* 2003) and 54.5% in Uganda (J Byakika-Tusiime *et al.,* (2005).In Ethiopia, 45% were reported as married (Alemayehu *et al.,* 2008) while in Senegal it was 44%. (Laniece *et al.,* 2003). In Kenyan studies, 48.7% were married in Kericho (Njeru 2006) and 52.3% in Kenyatta National Hospital (Evans 2008). This variation in proportions married in some African countries, including Kenya may be due to response rates since the two settings are not significantly different. Notably, most studies in developed settings did not report marital status.

Low socio-economic status was prevalent among participants in this study i.e. low education level and employment status. Studies, from both developed and developing countries have reported varying levels of education which are consistently higher than that reported in this study except for a study in Senegal where 32% of the patients had never been to school (Laniece *et al.,* 2003), and in Kenya, where 6.3% did not have formal education (Njeru 2006). Dissimilar results were however reported by majority of studies. In Italy, only 10% of participants had an education level below or equal to 8 years (Ammassari *et al.,* 2001), over half of participants in Sweden had a

university degree (Nilsson *et al.,* 2006) and in the USA, 25% of participants reported

less than high school graduation (Mallory *et al.,* 2005). In Botswana, 46% of participants

had some form of higher education (many of whom had taken brief training courses after

secondary school), and an additional 37% of patients completed at least 3 years of

secondary school (Weiser *et al.,* 2003). A half of patients had attended secondary

education in Ethiopia (Alemayehu *et al.,* 2008) while 63% had post-secondary education

in Uganda (Byakika-Tusiime *et al.,* 2005). In South Africa, 73.9% of participants had a

high school level of education (Malangu 2008).This difference in education levels may

be due to the fact that this study was done in a rural public hospital, which serves mainly

the lowest income bracket of the community.

Concerning employment, studies report a wide range of occupation situations.

Notably, the level of unemployment reported by most studies was consistently higher

than that reported in this study. In Italy, 26% of respondents were unemployed while

68% had an income of less than $350 per month (Ammassari *et al.,* 2001). In Togo,

occupations included service, administrative, government, custodial, and professional

(Weiser et *al.,* 2003). In Ethiopia, 35.8% of participants had no job and 37% of the

survey participants had no monthly income (Alemayehu *et al.,* 2008), while in Senegal

41% were not in paid employment   (Laniece *et al.,* 2003). Eighty seven percent were

unemployed in South Africa (Malangu 2008) whereas in Uganda 87.8% of participants

had a monthly income below 250$ (Byakika-Tusiime *et al.,* 2005).This may be

explained by the design of the study in comparison to others where casual employment

and very small businesses were reported as a form of employment.

The mean duration on HAART (32.1 months (2.6 years), was comparable to most studies done in both developed and developing countries where mean duration on treatment was 1.6 years in Italy (Ammassari *et al.,* 2001) and 2.4 years in USA (Mallory *et al.,* 2005). Thirty one and twenty six percent of patients had been on treatment for more than 2 years in India (Sarna *et al.,* 2008) and Botswana (Weiser *et al.,* 2003) respectively. In Kenya the mean duration on treatment was 10 months in one study (Njeru 2006) and the median number of months on treatment was 32 (range12 – 56) in another study (Evans, 2008).The duration on treatment was much longer though in Brazil (7.6 years) (Gordillo *et al*., 1999).

The regimen composition and distribution is comparable to that observed in many studies in the African setting. Notably in Togo, where the first line therapy was used by 89.9% of patients while in South Africa, 99.8% of patients were using this first line regimen (Malangu 2008). In a Kenyan-Kericho study, all patients were on the first line triple therapy out of which 16.1% were using the fixed dose combination - Lamuvidine + Stavudine + Nevirapine (Njeru 2006).In the Kenyatta national Hospital study, 99% of participants were on this first line regimen based on 2 NRTIs and 1 NNRTI and only 1% was on a protease inhibitor based regimen (Evans, 2008). It was also reported in India where 80% of respondents were on a first line Nevirapine based regimen. A Ugandan study however, reported only 58% of patients on this regimen (Byakika-Tusiime *et al.,* 2005). This may be mainly because the study was done when large scale ART was just starting in Africa and a standard approach to therapy had not been established. These 2 NRTIs and 1 NNRTI based regimens are available in many

sub-Saharan African countries and are recommended as first-line regimen because of their efficacy and ability to enhance adherence as there is an available fixed-dose combination (Lamuvidine + Stavudine + Nevirapine). This fixed-dose combination, used by 22% of patients in this study, was highly appreciated because it requires only 2 daily doses of one tablet each, reducing the pill burden significantly.

The regimen characteristics observed in this study however, are drastically different from those reported by studies in most developed countries where Protease inhibitors are more commonly prescribed; close to two-thirds were taking a protease inhibitor in Sweden (Nilsson *et al*., 2006), 50% in a study in USA (Mallory *et al.,* 2005), and all patients in a study in France were on a protease inhibitor (Carrieri *et al*., 2001). Some studies in Africa have also reported use of protease inhibitors to a large extent. In Senegal, most antiretroviral treatments prescribed during the study period included a protease inhibitor (Laniece *et al.,* 2003). Regimens containing protease inhibitors were also used by 41.5% of patients in Uganda (Byakika-Tusiime *et al.,* 2005).In South Africa, 41.5% of patients were on protease inhibitors containing regimens.(Orrell *et al.,* 2003).

Excellent knowledge and attitude towards HIV/AIDS was similar to that observed in USA (Holzemer *et al.,* 1999), Brazil (Filho *et al*., 2008), Botswana (Weiser *et al.,* 2003), Togo (Yao *et al*., 2010) and in Kenya (Njeru 2006). The high level of understanding and positive attitude may be attributable to the fact that most patients had received counseling before and during treatment, and most, had disclosed their status to

someone. Disclosure helps a patient to share their worries with someone in addition to supporting adherence (Alemayehu *et al.,* 2008; Filho *et al*., 2008; Gordillo *et al*., 1999).

The high mean short term and long term adherence was somewhat comparable to that observed in developing and middle income countries. Adherence was reported to be 94.3% in Ethiopia (Alemayehu *et al.,* 2008), 94% among adolescents in Brazil (Filho *et al.,* 2008), 93.5% in South Africa (Orrell *et al*., 2003), 91% in Senegal (Laniece *et al.,* 2003) and 90% in China (Wang *et al*., 2008). Although reported adherence was relatively high in these studies, it was still less than the recommended 95% level necessary to prevent drug resistance and treatment failure.

Some studies in developing countries however reported much lower adherence, 68% in both Uganda and Cameroon (Akam *et al.,* 2004, Byakika-Tusiime *et al.,*2005), 54% in Botswana (Weiser *et al.,* 2003) and 40% in Cote d'Ivoire (Eholie *et al.,* 2004). This difference in levels reported from other studies could be explained by the fact that patients in this setting also reported to be very knowledgeable about HIV/AIDS, having positive attitudes towards the disease and most had disclosed their statuses. These factors may have contributed to the high levels of adherence. On the other hand, most of these other studies were prospective in design and were therefore more likely to encounter non adherence during follow up time, compared to the cross sectional design used in this study.

The adherence level reported in this study was also considerably higher than that observed in most studies in developed countries -less than 90% among HIV-positive adults on ARV therapy in four U.S. cities, 69.2% across seven cities in the USA

(Holzemer *et al.,* 1999), 57.6% among intravenous drug users in Spain (Gordillo *et al* 1999) and 31.4% in France (Carrieri *et al*., 2001). This difference could be due to methods used to determine adherence, this study used self reports that are often associated with over reporting adherence. Most developed countries used electronic drug monitoring and drug levels which are more accurate than self reports albeit more expensive. Patients in poor resource settings may additionally be more motivated to be adherent because they are provided the otherwise expensive drugs free of charge. Studies in Kenya observed varying levels of adherence, In a Kericho study it was 98.8%, (Njeru, 2006), 87% among pediatric patients in Kenyatta ((Ng'eno, 2008) and 62% in Nyeri Provincial General Hospital ((Mutugi *et al.,*2010). This is despite the fact that the latter two are public health facilities with no donor support, consequently comparable to the current study setting. The high level of adherence observed in this study may be attributable to the good knowledge, positive attitude and the counseling that patients had received before and during treatment. In addition, the fact that most patients had disclosed their status to at least one person may have added significantly to the high level of adherence, as disclosure helps in supporting patients' adherence (Gordillo *et al*., 1999., Alemayehu *et al.,* 2008; Filho *et al*., 2008;).

The finding of running out of drugs and being/travel away from home as the most common reasons for missing medications, was consistent with that from studies in Botswana, Uganda Ethiopia and Togo (Weiser *et al.,* 2003, Byakika-Tusiime *et al.,* 2005, Alemayehu *et al.,* 2008, Yao *et al.,* 2010). Desire to avoid side effects accounted for 4.4% of those who missed medications.

Regarding association with adherence, although a number of studies in the past have found many patient related factors, such as socidemographic characteristics to be associated with adherence (Ammassari *et al.,* 2001; Laniece *et al.,* 2003; Orrell *et al.*2003; Oyugi *et al.,* 2004; Gill 2005; Njeru, 2006; Aspeling *et al* 2008; Malangu 2008), this study did not find a significant association between these factors and adherence. Many studies have found an association between age in particular and adherence. In Nairobi Kenya, Wakibi and others reported that younger respondents were more likely to be non-adherent to HAART (Wakibi *et al*, 2011). Bruno and others found that younger age, poor housing conditions, lack of social support were associated with lower adherence (Bruno *et al*, 2002). A Spain based study reported that patients aged 32-35 years had better adherence (Gordillo *et al*., 1999). Irrespective of this, age did not predict adherence in this setting. This finding was similar to that by Ammassari and others who found no association between age and adherence (Ammassari *et al.,* 2001).

The finding of no association between adherence and marital status was in contrast to work by Byakika and others in Uganda who found marital status to predict lower than optimal adherence (Byakika-Tusiime *et al.,* 2005). It was however similar to that by Wakibi and others who did not find any relation between the two (Wakibi *et al*., 2011). Less than university education and being unemployed were associated with less than optimal adherence in an Indian study thus contrasting findings from this study (Sarna *et al*, 2008). On the other hand, findings by Weiser and others in Botswana were similar to this study in respect of no association between adherence with education and employment status (Weiser *et al*, 2008). Inconsistent findings between adherence and

most socio-demographic characteristics however have therefore been reported by various studies.

Findings in this study are comparable to findings from some previous studies where patient factors were not found to be associated with adherence (Fogarty *et al.,* 2001; Byakika-Tusiime *et al.,* 2005). This is probably due to improved counseling, disclosure of HIV status and increased understanding of the risks of non-adherence. Aspeling and others in South Africa found Lack of HIV education, facilitating reversion to traditional customs to be negatively influence adherence while adequate preparation for treatment enhanced adherence (Aspeling *et al,* 2008).

Similarly, this work found no association between adherence and duration on treatment, which differs from various studies which reported significant association between duration on ART and adherence behavior. Adherence has been reported to decline over time in most studies (Alemayehu *et al*., 2008; Akam *et al*., 2004; J Byakika-Tusiime *et al*., 2005). Constant counseling of patients might be a possible explanation for this difference. Furthermore, regimen type was not found to be associated with adherence unlike in the work by Laniece and others, where some regimens notably Efavirenz based regimens, had better adherence than Indinavir based regimens (Laniece *et al.,* 2003). The fact that some drugs that were frequently associated with serious side effects were removed from standard regimens could explain this difference in findings. HAART related side effects were not associated with either short term or long term adherence.

The last time a patient missed medication was significantly associated with 1 month adherence; patients who had missed drugs during the past 2 weeks were more likely to be non-adherent compared to those who had not. This finding was similar to that reported by studies in Cameroon and Ethiopia where adherence was low for those who had missed medications in the recent past (Akam *et al.,* 2004; Alemayehu *et al.,* 2008).This might be explained by the fact that patients' adherence pattern at any point in time is likely to reflect a patient's general medication taking practices.

Commonly reported side effects were comparable to those reported in other studies, both in developed and developing countries. Tiredness/general malaise was reported by various studies in both resource rich and resource poor settings; these include studies in the U.S, Kenya, South Africa and France (Mallory *et al.,* 2005, Evans, 2008, Malangu 2008, Mutugi *et al.,* 2010, Brian Boyle 2010); Rash was reported by a US study (Mallory *et al.,* 2005) and two studies in Kenya (Evans, 2008, Mutugi *et al.,* 2010); while dizziness was cited by a study in Kenya (Evans, 2008). Most studies reported that nausea and vomiting were major side effects; among these are studies in the U.S (Mallory *et al.,* 2005), Italy (Ammassari *et al.,* 2001) and Kenya (Mutugi *et al*., 2010). Stomach upsets were reported by Mallory and colleagues, (2005) in a US study and Malangu (2008) in South Africa. Sleepiness was found to affect patients in Italy (Ammassari *et al.,* 2001) and South Africa (Malangu, 2008), while headache was reported in South Africa (Malangu 2008), and in two Kenyan studies (Evans, 2008, Mutugi *et al.,* 2010). Notably, although diarrhea was not reported in this study, it has been reported by many studies (Mallory *et al.,* 2005, Evans, 2008, Mutugi *et al.,* 2010.

Brian Boyle 2010. This may be because most patients in this study had been on treatment for a long duration, whilst diarrhea is mostly reported by patients who are starting therapy. (Ammassari *et al.,* 2001, Mills *et al*., 2006, Filho *et al*.,2008). Abnormal fat distribution and peripheral neuropathy were not commonly experienced in this study either, though they had previously been reported in earlier studies (Ammassari *et al.,* 2001; Mallory *et al.,* 2005; Evans 2008).This may be due to the recent revision of first line regimens to exclude stavudine, a drug now known to cause these side effects, for all new patients and to switch for any patient with early symptoms of fat maldistribution and peripheral neuropathy.

Other side effects that were cited in other studies but were not reported in the current study include, anxiety, confusion, vision problems, anorexia, insomnia, taste perversion (Ammassari *et al.,* 2001); Pulmonary conditions, fever, colds, wounds and oedema (Mutugi *et al.,* 2010); nightmares and lactic acidosis (Evans, 2008). Some of these adverse effects especially those associated with neuorological effects like confusion, vision problems and insomnia could be attributed to the nature of the drugs patients were taking, notably Efavirenz which was not used to a large extent in the current study is associated with these adverse effects.

Side effects were experienced by 30% of patients in this study in varying levels of perceived intensity; 5.4% of patients were affected severely, 5.4% averagely, 41% mildly and 48% were not affected. Only 5.4% stopped taking their medications as a result. This finding is comparable to that found in several studies. In a cross-sectional study in four U.S cities, over 85% of respondents reported at least one problem that they

attributed to their ARV medications. A study in France reported that most patients (89.9% to 91.3% for the duration under observation) self-reported at least one symptom that may have been related to HAART during the month before the visit, with the median number of HAART-related symptoms being 3 (Carrieri *et al*., 2001).

A study in Pretoria, South Africa also found that 94% of respondents reported at least one side effect and the mean number of self-reported side effects was 2.6. Respondents reported 19 different side effects (Malangu 2008).
Mutugi and colleagues working in Nyeri provincial hospital, Kenya found that patients related certain conditions with ARVs (Mutugi *et al.,* 2010). In Kenyatta National Hospital, the prevalence of adverse drug effects (ADR) was 49% - with some patients reporting more than one; ADR was the most common reason for change of regimen accounting for 59% of all regimen changes (Evans, 2008).

In the current study, the duration on treatment was found to be associated with the number of side effects. Patients who had been on treatment for 13 months and above reported less side effects than those who had been on treatment for a shorter period. This observation was differed with that reported by Evans in a study at Kenyatta National Hospital. (2008), who found that one of the most commonly reported risk factor for adverse drug effects was being on HAART for more than 32 months. In that study, the time to develop ADR ranged from 2 months to 29 months and side effects generally increased with time. Mallory and others working in a USA study (2005), on the other hand found that patients experienced toxicity mostly within the first 3 months of therapy. This difference may be explained by the fact that at the time Evans did the study,

regimens that were used in the Kenyan setting were associated with adverse effects that generally take long to develop while those associated with regimens used in the US setting are associated with fast developing adverse effects. However, at the time of the current study, drugs that were associated with side effects that took long to develop were being withdrawn and only a third of patients were using it.

The lack of association between HAART regimen and either number or perceived intensity of side effects finding was different from that from several studies which demonstrated an association between regimen and side effects, especially those containing protease inhibitors (Ammassari *et al.,* 2001; Mallory *et al.,* 2005; Malangu 2008).In an Italian study, 57% of participants had changed their first ART regimen because of toxicity (Ammassari *et al.,* 2001). Studies in which majority of patients were on a non-protease inhibitor regimen did not report any association between regimen and side effects (Orrell *et al.*2003; Oyugi *et al.,* 2004; Gill 2005; Njeru, 2006; Aspeling *et al* 2008; Malangu 2008).This difference could be explained by the fact that only one patient in the current study was on a protease inhibitor based regimen as opposed to patients in most studies that report this association.

Similarly, the lack of significant association between both the number and the perceived intensity of side effects in this study with adherence was remarkably different from what most studies have reported in both developed and developing countries. Majority of studies have demonstrated that side effects had a negative effect on adherence to ARVs. A cross-sectional multicenter study in Italy found that the frequency of moderate/severe symptoms or medication side effects in non adherent participants

ranged from 3.6% to 30%. Non-adherent persons had a higher mean overall symptom score (12.3 versus 8.1; $p < .001$) and mean medication side effect score (2.9 versus 1.9; $p < .001$) when compared with adherent participants (Ammassari *et al.,* 2001).In a US study, respondents with less than 90% adherence reported greater numbers and severity of adverse effects. Nausea, skin problems, vomiting, and memory adverse effects were independently related to less than 90% adherence over the prior three days(Mallory *et al.,* 2005). Another study in the US across seven cities found that HIV-positive clients with higher symptom scores, particularly depression, were more likely to be non-adherent to medication, not to follow provider advice, and to miss appointments (Holzemer *et al.,* 1999).A study in France found that the risk of being non-adherent at any visit increased 6% for each additional reported symptom. There was however no significant association between the total number of drug side effects medically reported, the number of severe side effects, and adherence at any visit. Self-reported symptoms were more likely to be associated with non-adherence behavior than medically confirmed side effect (Carrieri *et al*., 2001). In Brazil, adherence to treatment regimens was reduced for patients who reported adverse effects (Silveira *et al.,*2000).

In Africa, most studies have reported side effects to have a significant effect on adherence. A study in South Africa reported barriers to self-reported adherence (=> 95%) to include headaches (28.6%) symptoms such as insomnia (27.3%) and abdominal pain (20.8%) (Malangu 2008).In Togo, side effects were the 4th barrier of non adherence (11.6%); The perceived presence and severity of medication adverse effects was related to an increased likelihood of non-adherence (Yao *et al*., 2010). In Kenya, a study in

Kericho identified the fear of side effects as the most important barrier to adherence at 76% (Njeru, 2006). Another study in Nyeri reported side effects perceived by patients to be associated with ART as chest pains, coughing, headache, diarrhea and malaise- as contributors to poor adherence (Mutugi *et al.,* 2010).Some studies however report that patients who have experienced AIDS-related symptoms perceived as serious are usually more adherent than patients who never had symptoms, or who consider their symptoms unimportant (Gao *et al.,* 2000; Steele *et al.,* 2001). A study in France found that the number of HAART side effects was relatively high in both adherent and nonadherent patients (Gordillo *et al*., 1999), while another study in Botswana reported that side effects did not pose a large barrier to adherence. Whereas 51% of patients noted some side effects associated with the use of ARVs, less than 10% reported side effects as a significant barrier to treatment. There is therefore contradicting findings on the influence of side effects on adherence with most studies reporting a negative relationship (Weiser *et al.,* 2003).

The number of patients who discontinued treatment because of side effects was negligible, this is again, markedly different from studies done in the past in which toxicity of ARVs was implicated in about 58% of treatment discontinuations in a study in the USA (Mallory *et al.,* 2005; Ammassari *et al.,* 2001).

Findings from this study could perhaps be explained by the fact that the study was cross-sectional and may therefore not detect participants who discontinued ARV due to adverse effects or who never initiated treatment for fear of adverse effects. It could also possibly be because only one patient was on a protease inhibitor, and the fact

that there has been a drastic revision of ART regimen to exclude very toxic drugs. Notably, Stavudine which was widely used in sub-Saharan Africa ART programmes was being faced out at the time of the study and only patients who hadn't experienced any side effect related to stavudine were currently using it. This could explain the difference in findings of previous studies in African countries where stavudine was largely in use at the time the studies were done. Difference in findings from developed countries could be due to the fact that most patients in these developed countries used protease inhibitors. Patients on protease inhibitors (PI) have reported a higher rate and greater severity of adverse effects than those on NNRTIs (Miller *et al.,* 1998; Mallory *et al.,* 2005; Ammassari *et al.,* 2001). It is also possible that patients in this setting had been well educated about ART and side effects given the high level of knowledge and positive attitude towards HIV/AIDS and the fact that most had been counseled both before and during treatment.

There were notable limitations in this study; the use of self-reported data has been associated with over-reporting due to recall and social desirability biases which could have inflated adherence from the true level. The study minimized this by validating responses to some key questions on adherence and side effects by asking these questions twice in two different ways. This aimed at establishing that the participants were consistent in their responses. In addition, the cross-sectional data did not allow for detection of participants who discontinued ARV regimens in the past in response to adverse effects or who never initiated treatment out of concern over adverse effects.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMEDATIONS

Short term and long term HAART adherence levels were above 95% level in this setting. The person most likely to be least adherent was one who had missed medication the preceding 2 weeks. Socio demographic characteristics did not differ significantly between those who were adherent and those who were non-adherent, both on the short and long terms.General Malaise, Rash, Dizziness, Nausea and Vomiting, Stomach Upsets, Sleepiness and Headache were side effects commonly experienced by HAART patients.This study further demonstrated that medication-related characteristics and side effects are not reasons for non-adherence to HAART.

This is encouraging given that in the future, it is certain that HIV-infected persons will continue to be exposed to adverse drug symptoms due to the need for use of combination ART over a long period and the fact that new HIV infections continue to be documented everyday. This notwithstanding, patients who had gaps in taking medication during the preceding 2 weeks were likely to be nonadherent, and the duration on treatment was found to be associated with side effects. Further studies however are needed to elicit these relationships clearly, as this study did not study them exhaustively.

Although from this study side effects were not a major problem to patients, ART programs still need to appreciate the importance of educating and supporting patients in dealing with side effects as this helps patients to cope better. Further, given the complex nature of adherence, ART programs need to tailor their approaches in addressing

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resulting issues based on each patient in order to address multiple patient and drug

related factors that may vary from one individual to another.

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APPENDICES

APPENDIX 1 QUESTIONNAIRE

Date ……//………//...………...

Patient no

PART 1: SOCIO-DEMOGRAPHIC PROFILE

Sex: Male   ☐   Female   ☐

Age in years

1.1 What is your marital status?

a) Married/co-habiting	☐
b) Single	☐
c) Divorced/separated	☐
d) Widowed	☐

e) Others (specify) ………………………..

1.2 What is the highest level of education you reached?

a) None	☐
b) Primary – incomplete	☐
c) Primary – complete	☐
d) Secondary – incomplete	☐
e) Secondary – complete	☐
f) College/university – incomplete	☐
g) College/university – complete	☐

1.3 *What is your occupation*?

a) Business/Self employed	☐
b) Formal employment	☐
c) Informal employment (casual worker)	☐
d) Housewife	☐
e) Unemployed	☐

1.4 *How long has it been since you were diagnosed to be positive? (Months)..........*

1.5 *For how long have you been taking ARVs? (Months) ....*

PART 2: KNOWLEDGE, ATTITUDES AND BELIEFS ABOUT HIV AND ART

Please respond appropriately	Yes	No	S/how
1) Being HIV positive is a very serious problem for me	☐	☐	☐
2) Being HIV positive does not mean I will definitely develop AIDS	☐	☐	☐
3) ART Prolong life of HIV positive persons?	☐	☐	☐
4) ART will be able to get rid of most of the virus in my body.	☐	☐	☐

(S/how = somehow

PART 3: DISCLOSURE, COUNSELLING, SOCIAL SUPPORT AND STIGMA

3.3 *Have you disclosed your HIV status to anyone?*

Yes ☐   No ☐

3.4 *If yes to whom?*

a) Children	☐
b) Spouse/sexual partner	☐
c) Close relative	☐
d) Parent	☐
e) Close (non sexual) friend	☐
d)sibling	☐
e) Others (specify)…………………………	☐

3.6 *Did you receive any counseling before you started your treatment*?

      Yes ☐   No ☐

3.7 *Have you received any adherence counseling during your treatment?*

      Yes ☐   No ☐

PART 4: ADHERENCE

4.*1What ARV drug(s) are you taking and how?*

4.2 *Please tell me how many pills you have missed over the durations indicated*.

Drug name(s) /Abbreviation	No. of Pills/dose	No of times taken/day	No. of pills missed over	
			Last 3 days	Last one month

Anti-retroviral drugs.	
1. Lamivudine (3TC)	6.Tenofovir (TDF)
2. Efavirenz (EFV	7. Didanosine (ddI)
3. Nevirapine (NVP)	8.Lopinavir/Ritonavir (LPV/r)
4. Zidovudine (AZT)	9.Abacavir (ABC)
5.stavudine (D4T)	10.Triomune (3TC/D4T/NVP)

When was the last time you missed any of your medications?

a) Within the past week.	☐
b) 1-2 weeks ago.	☐
c) 2-4 weeks ago.	☐
d) 1-3 months ago.	☐
e) More than 3 months ago	☐

4.4 *If you reported missing the drugs, what reason(s) made you miss?*

a) Forgot	☐
b) Was away from home	☐
c)Wanted to avoid side effects	☐
d) Run out of drugs	☐
e) Other	☐

PART 5: SIDE EFFECT PROFILE

5.1 *What unpleasant effects have you experienced due to your ART medications within the last one month?*

    i. …..………………………………………………………

    ii. …………………………………………………………..

    iii. …………………………………………………………..

    iv. …………………………………………………………...

5.2 *Have you encountered any of the following side effects to your ARV medication, within the last 4 weeks? If so, what was the intensity?*

Side Effect	Not at all	Mild	Moderate	Severe
1)Dizziness	☐	☐	☐	☐
2) Nausea and vomiting	☐	☐	☐	☐
3) Rash	☐	☐	☐	☐
4) Stomach upsets	☐	☐	☐	☐
5)Tiredness/General malaise	☐	☐	☐	☐
6) Feeling sleepy	☐	☐	☐	☐
7)Nightmares	☐	☐	☐	☐
8) Headache	☐	☐	☐	☐
9)Diarrhoea	☐	☐	☐	☐
10)Peripheral neuropathy	☐	☐	☐	☐
11) Hypersensitivity reaction	☐	☐	☐	☐
12) Lactic acidosis	☐	☐	☐	☐
13) Lipodystrophy	☐	☐	☐	☐
Other (Specify)				

(Lactic acidosis = nausea/vomiting + abdominal pain + difficulty breathing +severe weakening of muscles in the legs and arms, occurring together.
Lipodystrophy = Fat distribution abnormalities.)

5.3How did e these side effects make you feel and/or affect you?

a) Didn't affect me at all	☐
b) Mildly	☐
c) Averagely	☐
d) Severely	☐

5.4 *Did you stop or skip taking medications because of these side effects?*

Yes ☐　No ☐

THANK VERY MUCH FOR YOUR TIME.

Interviewer's name _____

Sign --

APPENDIX 2a INFORMED CONSENT DOCUMENT

Study Title: *Influence of Self-reported HAART Side Effects on Adherence in Persons with HIV Infection attending Tigoni District Hospital, Kenya.*

Institution: Jomo Kenyatta University of Agriculture & technology (JKUAT), Institute of Tropical & Infectious diseases (ITROMID).

Investigator; Helen W Kiarie- Msc Public Health; JKUAT-ITROMID. Tel: 020-
2726765

Supervisors; 1) Prof M. Mutugi-JKUAT - Jomo Kenyatta University of Agriculture &
technology   Tel (067) 52095 or 52711

2) Dr P. Wanzala – KEMRI-Centre for public health research.

Tel; 020-725017/8

Our aim is to survey how patients take their HIV drugs (ARVs), and to help identify the factors that make patients miss their medications and specifically investigate the side effects that patients experience, how they affect patients and their medication taking behaviour.

The study involves obtaining information from you so that we can better understand why some people are unable to adhere, in order to form strategies to help them.

The study has been approved by the KEMRI Scientific Committee and the National Ethical Committee, which checks to make sure all studies are appropriate and don't endanger the health of participants like you. Please note that the choice of participating in this study is entirely yours.

Alternatives to participating in the study

If you are not comfortable participating in this study, you can opt not to participate. If you choose not to participate, you will not be questioned further. If you choose to participate, you have the right to withdraw from the study at any time without needing any explanation or loss of benefits you get from the hospital. The decision not to take part in the study will have no impact on the future treatment and care you receive from this hospital.

Procedures to be followed

There will be an interview that will be conducted in private so that nobody will hear your answers. If you agree to take part in the study, you will be asked some questions about yourself, your family, how you have been taking your ARV medication, the side effects you have experienced and the difficulties you have been experiencing while taking them. The interview will take an average of 15 minutes.

Potential risks

The major risk associated with this interview is a breach of confidentiality. We will work to minimize this by not including your name on any notes resulting from the interview. Any summary of data records relating to your participation will remain confidential to the interviewer and investigators. All the data obtained about you as an individual will be considered privileged and held in confidence; you will not be identified in any presentation of the results. The consent forms and the survey forms will be maintained in

a secure location until all the data are analyzed, and destroyed on completion of the study.

Benefits

You will not directly benefit from participating in this study but it will help in improving the management of your HIV disease. The information you provide will be used to design strategies to improve the current and future ART programs.

CONTACT PERSONS

For any additional questions or concerns about the study, contact the following;

1. **The Secretary, KEMRI/National Ethical review Committee,**

   P.O. Box 20752 NAIROBI, Kenya

   Tel. (254)(020) 2722541. 0722205901

   Email; ckithinji@kemri.org

2. Prof M. Mutugi - Jomo Kenyatta University of Agriculture & technology

   Tel (067) 52095 or 52711; Email; mwmutugi@yahoo.com

3) Dr P. Wanzala – KEMRI-Centre for public health research.

   Tel; 020-725017/8 Email; pwanzala@kemri-nuitm.or.ke

CONSENT FORM

Influence of Self-reported HAART Side Effects on Adherence in Persons with HIV Infection attending Tigoni District Hospital, Kenya.

Helen W Kiarie, Msc Public Health- JKUAT (ITROMID)

I have read the consent form, received a detailed explanation and I have understood about the study. Any questions that I had have been answered to my satisfaction. I understand that my participation is voluntary and that if I fail at any time to participate in this study, I will not be denied any future healthcare from the hospital.

I hereby give consent to research staff to collect my personal medication data, including sensitive information for the purposes of the study.

I have been assured that all the information will be confidential and no personal details about me will be revealed at any time.

_____   _____

Participant's Signature or left thumbprint   Date

_____   _____

Investigator's Signature   Date

APPENDIX 2b KANUNI ZA FOMU YA IDHINI

Athari ya makali ya madawa kwa Ufuasi wa madawa ya kuthibiti makali ya ukimwi kati ya wagonjwa katika hospitali ya Tigoni.

Kituo Chuo kikuu cha Jomo Kenyatta cha kilimo na teknologia (JKUAT), idara ya ITROMID.

Mtafiti; Helen W Kiarie- Chuo kikuu cha Jomo Kenyatta cha kilimo na teknologia (JKUAT), idara ya ITROMID.Simu: 020-2726765

Wasimamizi; 1) Prof M. Mutugi- Chuo kikuu cha Jomo Kenyatta cha kilimo na teknologia (JKUAT;)

Simu (067) 52095 or 52711

2) Dr P. Wanzala – Idara ya utafiti ya KEMRI

Simu; 020-725017/8

Ninakushukuru Kwa kukubali kupata muda kidogo ili kushiriki katika utafiti huu.

Haja yetu ni kujua vile wagonjwa wanatumia madawa yanayokabiliana na makali ya ukimwi, matatizo yanayowakabili wakati wa kufuatilia matibabu, madhara ya madawa yanayowakabili na vile inaathiri Ufuasi wa madawa.

Habari hii itatusaidia katika kupanga mbinu zinazoweza kukusaidia, na wengineyo wanaotumia matibabu haya ili kuweza kuyatumia vyema na hivyo kupata manufaa kamili pamoja na kuimarisha na kurefusha maisha.

Utafiti huu umeruhusiwa na *KEMRI Scientific Committee na National Ethical Committee*, kuhakikisha kuwa utafiti wowote ule hauhatarishi maisha ya mshiriki kama wewe.

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Tafadhali jua kuwa uamuzi wa kushiriki kwa utafiti huu niwako pekee wala hautalazimishwa kushiriki.

Mbadala ya kushiriki katika mradi

Kama utaamua kutoshiriki katika mradi, hautaulizwa maswali zaidi. Uko na uhuru wa kujiondoa katika mradi wakati wowote bila ya kushurutishwa kutoa sababu kwa mtafiti. Uamuzi huu hautaathiri matibabu na utunzi unaopata kwa hospitali au tahasisi yingine.

Taratibu itakayofuatwa

Iwapo utajiunga na utafiti huu, utaulizwa maswali ya kibinafsi kuhusu familia yako, jinsi unavyotumia madawa na madhara unayopata wakati unapotumia madawa haya.Majadiliano yatafanywa mahala pa faragha ili pasiwe na mtu atakayesikia majibu yako Majadiliano yatafanyika baada ya kupitia taratibu za kawaida za klinki na itachukua muda wa dakika ishirini.

Athari

Athari ya kushiriki kwa mradi huu ni kujulikana kwa habari ulizotoa. Kuzuia jambo hili, habari zote zinazohusiana na kushiriki kwako zitahifadhiwa kisiri na anayejadiliana nawe pamoja na watafiti wengine. Matokeo ya mradi yatatolewa kwa mukhtasari na hakuna wakati wowote majina yako yatatumika.Makaratasi yote yanayotumika kukuhoji yatahifadhiwa mahala salama na yataharibiwa baada ya mradi kuisha.

Manufaa

Ingawa hautapata maufaa sasa hivi kwa kuhusika katika utafiti huu, habari unazotoa zitasaidia ili kuunda mikakati ya kuimarisha matibabu kwa wakati huu na katika siku za usoni.

FOMU YA IDHINI

Nadhibitisha kuwa nimepata maelezo kuhusu mradi huu na nimepewa nafasi ili kuuliza maswali niliyo nayo. Nimeelewa kuwa kushiririki kwa mradi ni kwa hiari yangu, na nina uhuru wa kujiondoa katika mradi kwa wakati wowote bila kutoa sababu yoyote, na jambo hili halitaathiri matibabu au utunzi wangu baadaye katika hospitali hii.

Ninakubali kushiriki katika mradi, watafiti wanaweza kutumia habari kutokana na utumizi wangu wa madawa, na pia habari za kibinafsi ili kufanya itafiti. Nimehakikishiwa kwamba habari nitakazotoa zitahifadhiwa kisiri na hakuna wakati wowote habari zinazoweza kunitambulisha zitatolewa.

_____   _____

Sahihi/ alama ya mshiriki   Tarehe

_____   _____

Sahihi ya mtafiti   Tarehe

Kwa maswali zaidi wasiliana na;

1. **The Secretary, KEMRI/National Ethical review Committee,**

   P.O. Box 20752 NAIROBI, Kenya

   Tel. (254)(020) 2722541. 0722205901

   Email; ckithinji@kemri.org

2. Prof. Mutugi - Jomo Kenyatta University of Agriculture & technology

   Tel (067) 52095 or 52711; Email; mwmutugi@yahoo.com

3) Dr P. Wanzala – KEMRI-Centre for public health research.

   Tel; 020-725017/8 Email; pwanzala@kemri-nuitm.or.ke

ESACIPAC/SSC/5040   3rd December, 2009

Hellen Kiarie

Thro'

    Director, CPHR
    NAIROBI

Forwarded
02/12/2009

REF: SSC No.1705 (Revised) – Influence of self-reported HAART side effects on adherence among persons with HIV in Tigoni District Hospital, Kenya. Hellen Kiarie (CPHR).

I am pleased to inform you that the above-mentioned proposal, in which you are the PI, was discussed by the KEMRI Scientific Steering Committee (SSC), during its **161st meeting** held on **29th September 2009** and has since been approved for implementation by the SSC.

Kindly submit 4 copies to the Secretary SSC as soon as possible.

The SSC however, advises that work on this project can only start when ERC approval is received.

C. Mwandawiro, PhD
SSC SECRETARY

KENYA MEDICAL RESEARCH INSTITUTE

KEMRI/RES/7/3/1   October 8, 2010

TO: **HELEN KIARIE (PRINCIPAL INVESTIGATOR)**
             ITROMID STUDENT

THRO':   **DR. YERI KOMBE,**
             THE DIRECTOR, CPHR,
             NAIROBI

RE: **SSC PROTOCOL NO. 1705 (*RE-SUBMISSION*): INFLUENCE OF SELF
             REPORTED HAART SIDE EFFECTS ON ADHERENCE AMONG PERSONS
             WITH HIV IN TIGONI DISTRICT HOSPITAL, KENYA.**

Make reference to your letter dated September 28, 2010 received on September 29, 2010. Thank you for your response to the issues raised by the Committee. This is to inform you that the issues raised during the 174th meeting of KEMRI/National Ethics Review Committee held on Tuesday 19th January 2010, have been adequately addressed.

Due consideration has been given to ethical issues and the study is hereby granted approval for implementation effective this **8th day of October 2010,** for a period of twelve (12) months.

Please note that authorization to conduct this study will automatically expire on **7th October 2011.** If you plan to continue with data collection or analysis beyond this date, please submit an application for continuing approval to the ERC Secretariat by **26th August 2011.**

You are required to submit any amendments to this protocol and other information pertinent to human participation in this study to the ERC prior to initiation. You may embark on the study.

Yours sincerely,

R.C.Kithinji.

R. C. KITHINJI,
FOR: SECRETARY,
KEMRI/NATIONAL ETHICS REVIEW COMMITTEE