THE NAIVETY OF HIV/AIDS PATIENTS TO ANTIRETROVIRAL DRUGS AND PATIENT SOURCING OF ANTIRETROVIRAL DRUGS IN DAR ES SALAAM

By

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CERTIFICATION

The undersigned certifies that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation titled: ***The naivety of HIV/AIDS patients to antiretroviral drugs and patient sourcing of antiretroviral drugs in Dar es Salaam,*** in partial fulfilment of the requirements for degree of Masters of Clinical Pharmacy of the Muhimbili University of Health and Allied Sciences.

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DECLARATION

I, Deus Charles Buma, declare that this dissertation is my own original work and that it has not been presented to any other University for a similar or any other degree award.

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DEDICATION

This dissertation is dedicated to Kwangu Shija Michembe, my mother. I still remember your torture in my upbringing to this level. Jessica Martin Gabagambi, my wife, for her patience and moral support. I love you very much.

ABSTRACT

Background

The first three HIV/AIDS cases in Tanzania were reported in 1983, and currently the prevalence is at 7%, with great variations across the regions. The uncontrolled sources of the antiretroviral drugs in Tanzania in private and public health facilities as well as community pharmacies pose challenges to rational use of these medicines. Irrational uses of ARVs eventually result in treatment failure, development of drug resistance and hence deterioration of quality of life to HIV infected individuals.

Objectives

The aim of this study was to determine the naivety to antiretroviral drugs among HIV infected patients before initiation of antiretroviral therapy at the HIV clinics and possible sources of antiretroviral drugs to HIV/AIDS patients in Dar es Salaam.

Methods

A structured questionnaire was used to determine naivety to ARVs of HIV infected patients before initiation of antiretroviral therapy at the HIV clinics. This was verified by analysing patient blood for nevirapine. Blood samples (4ml) from all HIV infected patients stating in the interview to have not used ARVs were collected, immediately centrifuged and stored at –20°C freezer until analysis. Nevirapine which is one of the drugs in the first line combination regimens recommended by the Ministry of Health and Social Welfare (MOHSW), was used as the surrogate marker for use of ARVs. The blood plasma analysis of nevirapine was carried out using validated high performance liquid chromatography (HPLC) with the limit of

quantification of 0.2 µg/ml, precision of 0.42% over the concentration range of 0.64 – 2.08 µg/ml and accuracy of 96.01%.

Simulated client method was used to investigate possible ARV drug outlets and dispensing procedures in the private community pharmacies.

Results

Among 480 HIV infected patients purported to be naïve to ART, 475 (99%) claimed to be naïve to antiretroviral therapy and 5 (1.0 %) were admitted being non-naïve (4 females and one male). Interviewed HIV infected patients non-naïve to ART started to obtain ARVs at the HIV clinics and stopped using them for a while due to side effects (20%), feeling of being cured (20%) and travelled (60%) away from their clinics. Among the 475 HIV infected patients interviewed 219 (46.1%) consented to provide blood samples for analysis by HPLC and out of these, 214 (97.7%) were naïve to antiretroviral therapy and 5 (2.3%) were non-naïve from analysis results. Those patients found to be non-naïve to ARVs according to analysis, only one (20%) had nevirapine concentration of 4.4 µg/ml, while 80% had nevirapine concentration range of 0.2-0.42 µg/ml below normal therapeutic concentration of 2-5 µg/ml.

In the assessment of ARVs dispensing practices, the study involved 202 private community pharmacies operating in Dar es Salaam city out of which, 3 (1.5 %) indicated willingness to dispense ARVs without prescriptions.

Conclusion

From this study, it can be concluded that most HIV infected patients are naïve to ARVs, with few patients sourcing ARVs from private pharmacies without going through HIV clinics,

implying the risk of irrational use of these medicines. The few pharmacies indicated willingness to dispense ARVs without prescriptions is an indication of malpractice in the dispensing practices of such drugs in the country, the consequence of which could be under dosing leading to treatment failure and/or resistance or overdosing resulting into ARV drug toxicity.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ARVs	Antiretroviral drugs
ATV	Atazanavir
AZT	Zidovudine
D4T	Stavudine
ddI	Didanosine
DMO	District Medical officer
DRP	Drug Related Problem
EDTA	Ethylenediaminetetraacetic acid
EFV	Efavirenz
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
LPV	Lopinavir
MLH	Mwananyamala Hospital
MNH	Muhimbili National Hospital

MOHSW	Ministry of Health and Social Welfare
MTCT	Mother to Child Transmission
MUHAS	Muhimbili University of Health and Allied Sciences
Na_2CO_3	Sodium carbonate
NACP	National HIV/AIDS Control Program of Tanzania
$NaHCO_3$	Sodium bicarbonate
NFV	Nelfinavir
NNRTIs	Non-nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NtARTIs	Nucleotide Analogue Reverse Transcriptase Inhibitors
NVP	Nevirapine
PIs	Protease Inhibitors
PIT	Provider Initiated Testing
PMTCT	Prevention of Mother to Child Transmission
RTV	Ritonavir
TACAIDS	Tanzania Commission for HIV/AIDS
TFDA	Tanzania Food and Drug Authority
TFDCA	Tanzania Food, Drugs and Cosmetics Act
UV	Ultraviolet
v/v	volume by volume
VCT	Voluntary Counselling and Testing
WHO	World Health Organization
USA	United States of America

CHAPTER ONE

INTRODUCTION

1.1 Global HIV/AIDS situation

The Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome (HIV/AIDS) pandemic pose the greatest challenge to global public health affecting every sector of humankind. A total of 33.2 million people were living with HIV by the end of 2007, of whom 30.8 million were adults (age above 15 years). Among adults 15.4 million were women, and 2.5 million were children aged 15 years and below. The estimated incidence of HIV infection by the end of 2007 was 2.5 million among which 84% were adults. It was estimated that the total mortality due to AIDS was 2.1 million people of whom 80.9 % were adults. Sub Saharan Africa is the world's most severely affected region contributing to 63% of all adults and children with HIV infection globally (UNAIDS, 2007).

1.2 HIV/AIDS situation in Tanzania

In Tanzania the first three cases were reported in 1983 and since then HIV epidemic has spread rapidly to all districts and communities affecting all sectors of the society. By the end of 2004 a cumulative total of AIDS cases were 192,532 since its discovery in 1983 (Annual Health, 2006). The Tanzania HIV/AIDS prevalence based on household surveys estimate the sero-positive prevalence in adults to be 7%, with a wide variation across the regions. Most infections of HIV are transmitted through hetero-sexual intercourse and hence the population most severely affected is the sexually active individuals between 15 and 49 years of age. Women have a higher risk of infection than men (Annual Health, 2006; NACP, 2005).

According to the WHO it was estimated that there were 1810000 people living with HIV; 840,000 males and 960,000 females in Mainland Tanzania in the year 2003. Four percent of the AIDS cases reported were below 15 years of age and most of these were likely to have acquired infection through mother to child transmission (MTCT). The age group 20-49 years was the most affected for both sexes. The observed clustering of cases in the age group was thought to suggest that the infection occurred during the age of maximum sexual activity. It is evident that there were more female AIDS cases than males in the age group 20-39 years (Annual Health, 2006).

1.3 The Impact of HIV/AIDS

The emergence of HIV/AIDS brought more sufferings to different ethnic groups in all affected countries (Bokazhanova, 2006). The AIDS epidemic is bringing additional pressure to bear on the health sector, increase in the number of orphans, school dropouts and decrease in labor force which result in family economy decline (UNAIDS, 2002; World Bank 2002). Government income also declines, as tax revenues fall and governments are pressured to increase their spending to deal with the rising HIV prevalence (Hartmut *et al.* 2003; Levy, 2006).

1.3.1 Health impact of HIV/AIDS

In Tanzania, data from annual health statistical abstract showed that HIV/AIDS ranks second (12 %) to malaria in the cause of death among patients aged five years and above that attend health facilities. The first being malaria in top ten diseases (Annual Health, 2006). Most

urban, district and regional Hospitals in Tanzania report a bed occupancy rate of up to 70% for HIV related conditions. The average, HIV-positive patients stay in Hospital four times longer than other patients (NACP, 2005).

The HIV pandemic has reduced resources and attention for other health problems thus adversely affecting quality of health care services delivered. In addition, health personnel are affected as well by the pandemic resulting in human resource crises in Hospital at a time that more resources than ever are needed to start care and treatment programs (Urassa *et al.* 2001; NACP, 2005).

Government expenditures in the health sector have increased significantly due to buying antiretroviral drugs that have to be used lifelong for patients to remain productive (Yonghua *et al.* 2007).

1.3.2 **Economic impact of HIV/AIDS**

HIV/AIDS negatively affects economic growth on one hand. On the other hand, a weak economy makes it difficult for the countries and individuals to mount adequate and comprehensive responses to epidemics. Reports show that poverty, is a powerful co-factor for the spread of HIV/AIDS. The economically and socially disadvantaged women, youth and other marginalized groups in the society are disproportionately affected by HIV/AIDS. Morbidity and mortality due to AIDS are reported to have reduced agricultural labour force, productivity and disposable income in many families and rural communities. Data from Kagera, one of the regions most severely affected by HIV/AIDS in Tanzania, indicate that the

annual Gross Domestic Product (GDP) declined from USD 268 to 91 between 1983 and 1994 (Urassa *et al.* 2001; NACP, 2005).

1.3.3 **Social impact of HIV/AIDS**

Although no part of the population is unaffected by HIV, it is often the poorest sector of society that is most vulnerable to the epidemic and for whom the consequences are most severe. In many cases, the presence of AIDS means that the household will break-up, as parents die and children are sent to relatives for care and upbringing. Materialist practices are on the increase; orphans are not only subjected to material, social and emotional deprivation, but also lack of opportunities for education and health care. Widows and orphans are deprived of their inheritance rights by relatives through the application of outdated traditional and customary laws. A study of rural South Africa suggested that households where an adult had died from AIDS were four times more likely to break-up than those where no deaths had occurred (Hosegood *et al.* 2004).

1.4 **Scaling up antiretroviral (ARV) drugs in poor resource settings**

The introduction of Highly Active Antiretroviral therapy provided HIV/AIDS patients with opportunities for quality of life improvement by inhibiting the replication of HIV (WHO, 2003; Battegay *et al.* 2006). Although these treatments are not a cure and present new challenges of side effects and drug resistance, they have dramatically reduced rates of mortality and morbidity and have revitalized community. By 2003, World Health Organization (WHO) had declared that the lack of access to HIV treatment was a global

health emergency and called for unprecedented action to ensure that by the end of 2005 at least 3 million people in need of antiretroviral therapy (ART) would have access to treatment (WHO, 2003; Rodriguez-Arenas *et al.* 2006). Tanzania, being one of affected countries, established a national policy on HIV/AIDS and has been mobilizing resources both locally and from developed partners to ensure access to free ARVs in both private and government health facilities (National Strategic Framework on HIV/AIDS, 2003). In addition the Tanzania Commission for AIDS (TACAIDS) advocates change in behavior for a successful fight against the AIDS pandemic (National HIV/AIDS Policy, 2005).

1.5 Management of HIV patients using ARV drugs in Tanzania

After a decade of slow progress in treatment of HIV infection, there have been dramatic advances in the development of ARVs in the last few years. This now offers extended patient survival and improved quality of life. Tanzania has a care and treatment plan for people living with HIV/AIDS as outlined in the strategies for the health sector response to the HIV/AIDS epidemic. The goal is to ensure that all patients who are eligible and willing have free access to ARVs in their nearby clinics (National Strategic Framework on HIV/AIDS, 2003).

1.5.1 Goals of antiretroviral therapy

According to WHO the following are the established goals of HAART (WHO, 2003):

1. Clinical goals: prolongation of life and improved quality of life

2. Virologic goals: reduce viral load, stop disease progression and prevent or reduce resistant variants.
3. Immunological goals: quantitative and qualitative immune reconstitution
4. Therapeutic goals: rational medicines use to achieve virologic goals, maintain therapeutic options, have relatively few side effects and have a realistic adherence probability
5. Epidemiologic goals: a reduction of HIV transmission.

1.5.2 **Criteria for initiation of antiretroviral therapy in adults**

The current WHO guidelines for ART recommend that in resource-limited settings, HIV-infected adults and adolescents should start ART when HIV infection has been confirmed and one of the following conditions is present (WHO, 2006)

1. WHO Stage IV HIV disease, irrespective of the CD4+ cells count;
2. WHO Stage III disease with consideration of using CD4+ cells count less than 350/μl to assist decision making;
3. HIV infected patients with CD4+ cells count less than 200/μl.

Besides clinical eligibility, it is important that the patient's willingness, readiness and ability to be on ART adherently be assessed and addressed. Psychosocial considerations (not exclusion criteria), therefore, need to be evaluated before initiation of therapy during several (three to six) pre-treatment visits (Ruiz-Perez *et al.* 2006; NACP, 2005).

1.5.3 **Criteria for initiation of antiretroviral therapy in children**

The current WHO guidelines for ART recommend that a child should not start treatment before the following issues are addressed (WHO, 2006):

A clearly defined caregiver, who must understand prognosis of HIV infection, side effects of medicines, how to administer and store medicines, implication of non-adherence and the fact that it is life-long therapy, accessibility of supportive processes, such as counseling services and family support groups, access to nutritional supplements and co-trimoxazole prophylaxis, and treatment of infected parents and siblings should be considered to preserve family unit; good health of the mother/caregiver is particularly important for survival of the child (WHO, 2006; Denis *et al.* 2004).

HIV exposed/infected children should start ART when HIV infection has been confirmed and one of the following conditions is present:

WHO Stage III & IV HIV disease, irrespective of the CD4+ cells count and WHO paediatric stage II, with CD4+ cells < 20% for children less than 18 months of age or CD4+ cells < 15% for children more than 18 months of age (Denis *et al.* 2004).

1.5.4 **Antiretroviral drugs used in Tanzania**

The introduction of ART has brought hope to people living with HIV/AIDS and managed to convert the formally known as "death sentence" to simply chronic illness which is manageable. HAART is a triple therapy and has proven to be effective as compared to mono

or dual therapy in terms of efficacy and delay of development of resistance (Thiebaut *et al.*2006).

The treatment guidelines in Tanzania recommend the use of nucleoside reverse transcriptase inhibitors (NRTIs) such as stavudine (D4T), zidovudine (AZT), lamivudine (3TC), abacavir (ABC), didanosine (ddI) and more recently) emtricitabine (FTC) and tenofovir (TDF, as the nucleotide reverse transcriptase inhibitor. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are nevirapine (NVP) and efavirenz (EFV) (NACP, 2007; Arts *et al.* 1996).

The third goup of ARVs is comprised of protease inhibitors (PIs) responsible for inhibiting protease enzyme which is required for virion maturation. The protease inhibitors (PIs) that have been included in the Tanzania guideline are lopinavir/ritonavir (LPV/r), saquinavir/ritonavir, nelfinavir and more recently atazanavir has been proposed as a replacement of saquinavir (NACP, 2007). Protease inhibitors are given as second line therapy with two nucleoside reverse transcriptase inhibitors, the backbone being didanosine and abacavir.

1.5.4.1 **Recommended first line ARV combination regimen for adults and adolescents**

The Ministry of Health and Social Welfare (MOHSW) recommends four different combination regimen (NACP, 2007);

1. D4T + 3TC + NVP in a fixed dose combination or singly formulated drugs. Unless contraindicated, all patients will commence therapy on this regimen.
2. However patients can start on
3. AZT + 3TC + NVP if a patient experiences peripheral neuropathy with D4T

4. D4T + 3TC + EFV if there is TB co-infection. Treatment should necessarily be initiated with both ARV drugs and anti-TB as well in patients experiencing anaemia (< 7.0 g/dl)
5. AZT + 3TC + EFV if there is TB but no anaemia
6. emtricitabine + tenofovir+ efavirenz if the patient cannot tolerate AZT and D4T

1.5.4.2 Recommended second line ARV combination regimen for adults and adolescents

Abacavir, didanosine and LPV/ritonavir, ABC + tenofovir (TDF) + Atazanavir/r and ABC + TDF + LPV/r. Didanosine is taken on an empty stomach while LPV/ritonavir is taken with food for the maximum absorption in the gut and ABC is taken irrespective of the gut contents.

1.5.4.3 Recommended first line ARV combination regimen for children

The MOHSW recommends four different combination regimen;

1. AZT + 3TC + NVP in liquid formulations, fixed dose combination or singly formulated drugs. Unless contraindicated, all children will commence therapy on this regimen.
2. However patients can start on
3. D4T + 3TC + NVP if a patient experiences anaemia with AZT
4. AZT + 3TC + EFV if there is TB co-infection for child with three years old and above (NACP, 2005; Denis *et al.* 2004).

1.5.4.4 Recommended second line ARV combination regimen for children

ABC + DDI + LPV/r, or ABC + ddI + Nelfinavir. didanosine is taken on an empty stomach while LPV/r is taken with food for maximum absorption in the gut.

1.5.5 Monitoring of patients on ART

In Tanzania, CD4+ cells count is one of the methods used to determine the time for initiation and change of therapy. Each patient should have a baseline lymphocytes count and viral load (optional) done before initiating treatment. Lymphocytes count should then be repeated at least every three to six months. Treatment will in most cases be associated with weight gain, reduced morbidity from opportunistic infections and improvement in the quality of life. Appearance or persistent opportunistic infections, or lack of weight gain could be due to treatment failure and so the need to consider changing regimens (NACP, 2005).

Treatment is to be considered successful if the viral load decreases by 10 to 100 fold from the baseline level. However, in most cases CD4+ cells count will be used instead of viral load thus a rise in lymphocytes count will indicate success. Treatment failure will be indicated by a 30% fall in lymphocytes count. The patient is monitored during every visit at the HIV clinics in which clinical assessment and pill counts are used to assess adherence to treatment, whereas immunological assessment is done every three to six months by determining CD4+ cells count (NACP, 2005).

1.5.5.1 Changing of ART

Antiretroviral therapy should be stopped and or changed when there is evidence of:

Treatment failure as evidenced by the patient becoming symptomatic and progressive decline of lymphocytes count or percentage and rise of viral load or both despite of good adherence to

antiretroviral treatment, lack of growth response or decline in growth over a six month period, after excluding other causes including tuberculosis in children, pregnancy, during the first trimester of pregnancy and also if the patient was on efavirenz (NACP, 2005) and toxicity or intolerance to one or all drugs.

1.5.5.2 **Side effects of ARV drugs**

Each of three traditional classes of ARVs (NRTIs, NNRTIs and PIs) has therapeutic set of toxicities that are not found with the other drug classes. On the other hand, lipodystrophy, which was thought to be specific to PIs, is now known to be common to all three classes of drugs (Mok, 2008). An understanding of drug specific, class specific and general toxicities and side effects of antiretroviral drugs will helps clinicians to tailor treatment regimens to individual patients (Rawlings *et al.* 2004).

Side effects or toxicities caused by ARV drugs are associated with increased non adherence to ART. These can be mild headaches, mild gastric upset, nausea, fatigue and the central nervous system disturbances seen with efavirenz (NACP 2005; Montessori *et al.* 2004).

The potential side effects of ARVs can be either short term, such as hypersensitivity reactions, drug-induced hepatitis, anemia and lactic acidosis or long term including dyslipidemia, cardiovascular disease, lipoatrophy, lipohypertrophy and diabetes (Wester *et al.* 2007; Tymchuk *et al.* 2008).

Antiretroviral drug related toxicities result into increased Hospitalization of HIV infected patients (Nunez *et al.* 2006). Liver toxicity is the most frequent complication of which one-

third is associated with NVP use. Other main ARV-related toxicities are bone marrow toxicity due to zidovudine (17%), pancreatitis (13%), and indinavir associated nephrolithiasis (6%). Some patients may present with symptomatic hyperlactemia, and some lactic acidosis (Nunez *et al.* 2006).

1.6 Problem Statement

According to treatment guidelines, it is recommended that HIV infected patients should be naïve to antiretroviral drugs and thorough assessment should be done before initiation of HAART. The eligibility criteria require that patient should be initiated ART when the CD4+ cells count is equal or below 350 cells/µl and in some cases until the CD4+ cells count are below 200 cells/µl. However, some patients may violet this rule and self initiate ARV treatment as soon as they are found to be HIV positive thinking that waiting until the CD4+ cells count falls below the required level for ART initiation is jeopardizing their survival. Such patients will try to access ARVs illegally from other sources rather than HIV clinics. The availability of ARVs in private pharmacies complements the government efforts of ARV access to many. However, if not monitored it may turn up being the loophole for accessing ARVs without meeting eligibility criteria. Those patients who decide to self medicate with ARVs without going through HIV clinic will eventually stop using the drugs after feeling better or after experiencing ARV toxicities ((Holkmann *et al.* 2007). Reports show that, patients infected with HIV who started ART and stopped for sometime were found to have worsened conditions when they reported back to HIV clinics (Ruiz-Perez *et al.* 2006). ART is life long, however, it has been reported that not all HIV infected patients adhere to this rule (Holkmann *et al.* 2007).

Since antiretroviral drugs cause adverse reactions in some patients, poor counseling will result into a patient stopping taking the ARVs and report back to HIV clinics when the health condition worsens. Worsened clinical cases have been reported where a patients who was

doing well immunologically and clinically decides to stop the ARV treatment (Wood *et al.* 2003; Plummer *et al.* 2006).

Stigma in HIV/AIDS patients may hinder utilization of available care and treatment services. Due to this, some patients look for alternative ways of getting ARVs for example sharing with other patients or buying the ARVs from other sources other than HIV clinics. Therefore, this research specifically investigated if patients attending HIV clinics purported naïve to ARVs were really naïve. The research also aimed at determining the possible drug outlets through which an HIV infected patient could access ARVs without visiting HIV Clinics (NACP, 2005). We were also interested in finding out the dispensing practices of ARVs from private outlets to HIV infected patients.

To our knowledge this is the first study that investigates the proportion of patients who are naïve to ARVs before treatment initiation and sources of ARVs other than HIV clinics in Tanzania.

1.7 Rationale of the Study

It is important to confirm whether the newly recruited HIV/AIDS patients are naïve to ARV treatment, because naïve patients have better prognosis to treatment when initiated ART than non-naïve HIV infected patients (Ruiz-Perez *et al.* 2006). The availability of ARVs in the private community pharmacies complements government efforts towards ARV drug access. However, there is need to determine the dispensing practices of such drugs in these drug outlets to avoid their misuse. The information is useful to Drug Regulatory authority and policy makers in the regulation of ARV uses so as to avoid drug resistance development and minimize toxicity incidences.

1.8 Research questions

The following are the research questions for this study:

1. Are the new HIV infected patients recruited at the HIV clinics really naïve to ARV?
2. What are the possible sources of ARVs other than HIV clinics?
3. What is the dispensing practice of ARVs if available in the private community pharmacies?

1.9 Objectives

1.9.1 Main objective

To determine the naivety to antiretroviral drugs among HIV infected patients before initiation of antiretroviral therapy at the clinics and possible sources of antiretroviral drugs to HIV/AIDS patients in Dar es Salaam

1.9.2 Specific objectives

1. To determine the proportion of patients found to have nevirapine in their blood before ART initiation at the HIV clinics
2. To determine sources of ARVs to HIV infected patients other than HIV clinics.
3. To investigate the dispensing practices of ARVs in the private community pharmacies.

CHAPTER TWO

DETERMINATION OF NEVIRAPINE IN BLOOD FROM HIV INFECTED PATIENTS

2 Background

Antiretroviral drugs are prone to resistance and must be rationally used without any interruptions. Once the patient is initiated on antiretroviral treatment the therapy must be for life. Better treatment outcomes have been associated with naivety of a patient on ARVs (NACP, 2007). The information on naivety is valuable in deciding the better treatment ARVs triple combination option for such patients. Research has shown that drug toxicities, availability and affordability contribute to stopping therapy (Inciardi *et al.* 2007). Interruption or stopping the treatment exposes the HIV to risk of developing drug resistance (Ruelle *et al.* 2007).

A study conducted by Scott *et al* revealed that patients who interrupted ART, experienced toxicities when they were re-initiated to ART (Scott *et al.* 1996).

It is recommended that the patient should remain naïve to ARVs until thorough assessment is done before he/she is put on ART. Naïve patients are less likely to develop drug resistance than those who make a lot of attempts in treating HIV infections. Switching from one regimen to another especially from first line to the second line may expose a patient to more side effects (Scott *et al.* 1996). Nevertheless, it is important for a patient to report the truth on the previous medications history as this helps the clinicians to decide the correct drug combinations for ART. This study was therefore undertaken to determine the naivety to ART of newly recruited HIV infected patients at the HIV clinics.

Determination of nevirapine was chosen due to its long half, and could be detected even if a patient has used the medicine for the past ten days (Jean *et al.* 2001). Also, according to the Tanzanian guidelines, most eligible HIV infected patients are initiated nevirapine based regimen (NACP, 2005).

2.1 Method

2.1.1 Study site

The study was conducted at Mwananyamala Hospital and Muhimbili national Hospital located in Dar es Salaam region.

2.1.2 Study design

A cross sectional study was undertaken involving HIV out patients attending HIV clinics but not on ARVs at Muhimbili National Hospital and Mwananyamala Hospital.

2.1.3 Study population

The study involved 480 HIV-infected out-patients (adults and adolescents, both males and females) attending HIV clinics, but not yet initiated antiretroviral therapy

2.1.4 Sample size of HIV infected patients to be interviewed

There is no study indicating the prevalence of HIV infected patients naïve to antiretroviral drugs, therefore the estimated prevalence was 50%. The sample size was calculated based on the following formula (Kothari, 2005).

$$n = \frac{z^2 p q}{\varepsilon^2}$$

n = sample size for patients to be interviewed

p= estimated proportion of naïve HIV patients = 50%

q= 100 - p

z= standard normal variate at 95% confidence interval =1.96

ε= estimated error = 5%

n= $[(1.96)^2 \times 50 (100-50)] / 5^2 = 384$ a minimum sample size

In this study the interviewees were 480 HIV infected patients.

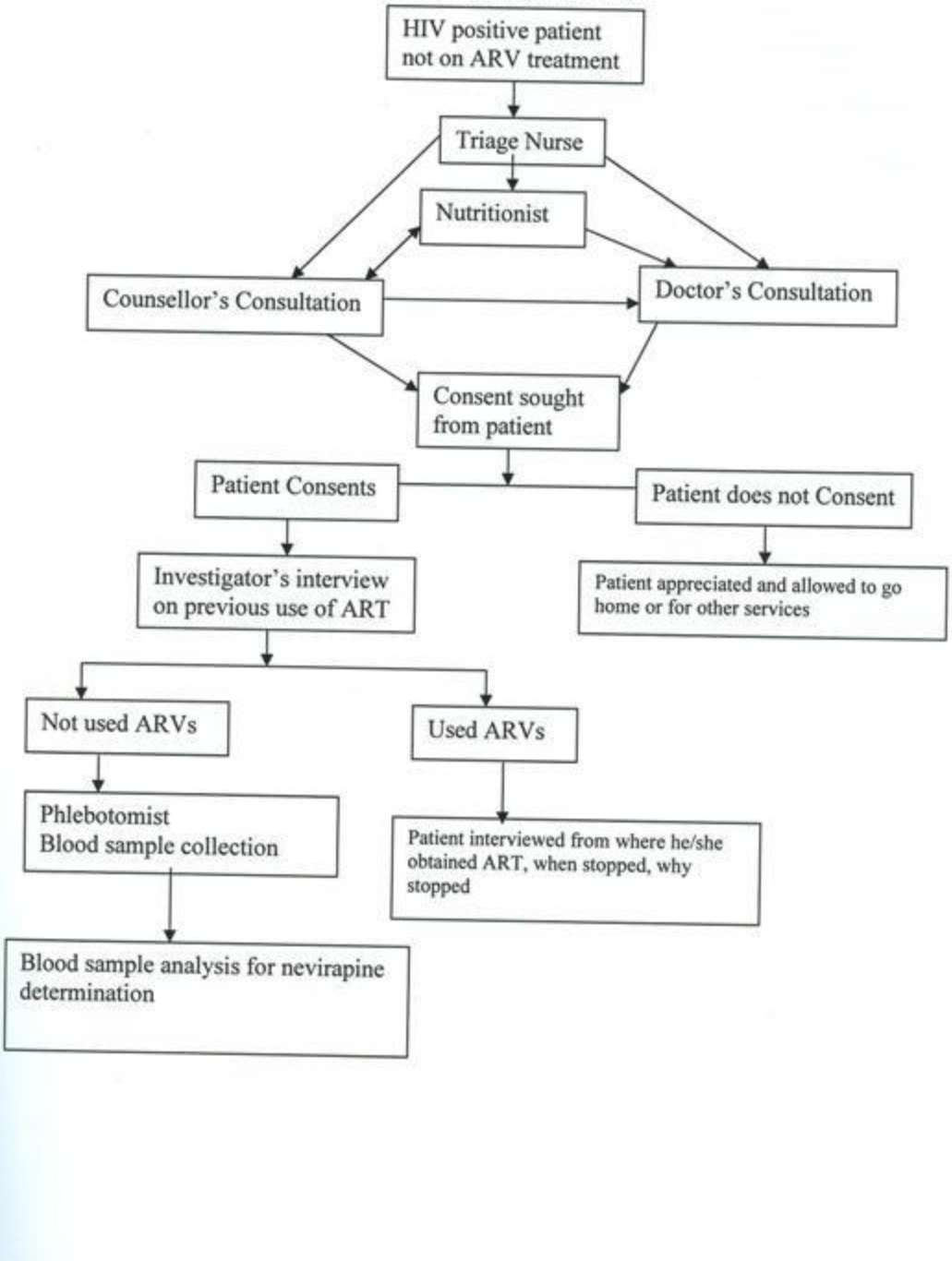
2.1.5 **Sampling technique**

Patients were selected based on the inclusion criteria, in which all patients who were not on antiretroviral therapy according to the registry information at the receptionist were interviewed.

2.1.6 **Patient recruitment and interview**

All patients purported to be naïve to ART were identified by the triage nurse during the registration and were directed either to the counsellor or to nutritionist according to the patient schedule. All newly recruited patients were directed to the nutritionist before consulting the physician. The flow of patients and interview is depicted in figure 1.

Figure 1. Patients flow for interview and sample collection



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The patients followed the normal procedures of the HIV clinics to avoid inconveniences that might happen during interview by the investigator. The investigator made interview with the patients using a structured questionnaire (Appendix III), after the patient had been counselled and/or consulted the nutritionist. Then the physician was informed about the identity of patients who consented to participate in the research. The sticker was attached on the patient's file to differentiate study patients from others. After the physician has made consultation with the patient, the patient was directed to go to the phlebotomy room for blood sample collection. The phlebotomists were informed about the identity of the patients that consented to participate in the research, by looking at the sticker on the file before they drew blood samples for research and/or other routine sample specimens according to the patient's visit schedule.

2.1.7 **Inclusion criteria for questionnaire administration.**

- Age 15 years and above
- HIV infected patient
- Patient attending HIV clinics, but not on ARVs
- Have registration number at the respective clinic
- Able to give verbal informed consent (patients below 18 years their consent were obtained from their parents)

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2.1.8 Inclusion criteria for patients to provide blood sample

- Age 15 years and above (age between 15-49 years is the most affected by HIV/AIDS)
- States to have not used ARVs before attending HIV clinics
- Able to give written informed consent

2.1.9 Exclusion criteria for patient to provide blood

- Resident outside Dar es Salaam region
- No registration number
- Does not provide verbal /written informed consent
- Patient on ARVs according to HIV clinics eligibility
- States to have used ARVs before attending HIV clinics
- Too ill patient (wheelchair ridden patient and unable to communicate due to psychosis)

2.2 Ethical considerations

The blood samples were collected using single use vacutainers and the site of blood drawing was sterilized with a methylated spirit soaked cotton swab. There was no serious pain expected to be felt by patients in the process of bleeding. The patients were informed about the purpose of the research and the confidentiality of the information obtained. Verbal informed consent was sought from the participants before questionnaire was administered

whereas written informed consent (Appendix IV) was sought before blood was taken. Patients were informed that declining to participate would not jeopardize getting services at the clinic. In order to maintain confidentiality, patients' registration number was used to identify patients at the waiting place. Permission to conduct the study was granted by municipal Chief Medical Officer of Mwananyamala Hospital and Director of clinical services for Muhimbili National Hospital. At the level of HIV clinics, all the in-charges and administrators of the HIV clinics were informed of the study. The ethical clearance was provided by MUHAS ethical committee.

2.3 Blood Sample collection for nevirapine determination

Four millilitres (4.0 ml) of venous blood were collected using single use syringes.
The blood was collected in EDTA tubes and the samples were immediately centrifuged at a speed of 1500g for 10 min. The obtained plasma samples were kept at -20 ̊C until assay.

2.4 Determination of nevirapine in blood samples

The collected blood samples were determined for presence and levels of nevirapine using below described HPLC method.

2.4.1 Chromatographic conditions

The chromatographic conditions used in this study were adopted from Bregt *et al* 2003 and modified to suit our environments. The detection (Shimadzu system controller SCL-10A, Japan) and quantification of nevirapine in the samples was done by reverse-phase HPLC

(Varian Prostar model 310 serial 01302, Stockholm, Sweden) fitted with Spherisorb C_{18} column (Agilent, 150 mm length x 4.6 mm I.D, United States of America) and fixed wavelength of 282 nm UV detector. The detector was connected to a computer installed with ELDS PRO software (Huddinge Sjukhus version 951001, Stockholm, Sweden) that was used to calculate peak area ratios of the analyte in relation to internal standard. The mobile phase with a pH 7.5 was composed of 15 mM sodium dihydrogen phosphate monohydrate (Stockholm, Sweden) and acetonitrile (Merck, USA) (80:25 v/v, respectively) at a flow rate of 0.7 ml/min.

2.4.2 **Analytical procedure**

Nevirapine plasma concentrations were determined using a HPLC method. In-house method involved liquid-liquid extraction procedures. The method was the adoption and modification of the method developed by Bregt *et al* in 2003, with the 95.86% recovery, limit of detection and quantification were 0.02 µg/ml and 0.2µg/ml respectively (Bregt *et al.* 2003). Into a polypropylene tube of 12 ml, 100 µl of plasma were put followed by addition of 25 µl internal standard (carbamazepine 11.6 µg/ml) and 200 µl sodium bicarbonate buffer with a pH 9.7. The contents were vortexed for 20 sec then 500 µl of diisopropyl ether (Merck, USA) were added, followed by shaking using automatic shaker at a speed of 100 rpm for 10 minutes and centrifugation at a speed of 4000 g for 10 min. Then 380 µl of the organic layer were transferred into other tubes and dried with a current of air followed by reconstitution with 120 µl mobile phase containing 15 mM sodium dihydrogen phosphate monohydrate and

acetonitrile (80:25 v/v, respectively) with a pH 7.5. Into the chromatograph, 90 µl of the resulting solution were injected and peak area ratios between analyte and internal standard were recorded. The solutions were stored at -20 °C.

2.4.3 **Calibration solution: Stock**

A stock solution of nevirapine with concentration of 430 µg/ml was made by weighing about 4.3 mg of NVP reference standard into 10 ml volumetric flasks and dissolving into about 5 ml methanol. The mixture was sonicated for 5 min and the resulting solution was diluted to mark with water. For calibration purpose, 8.6 µg/ml was prepared by taking 50 µl stock solution and diluting with 2500 µl water. The solution was stored at -20°C.

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2.4.4 **Calibration solution: Control**

Control solution of nevirapine with concentration of 120 µg/ml were made by weighing 1.2 mg of NVP reference standard into 10 ml volumetric flasks and dissolving into about 5 ml methanol. The mixture was sonicated for 5 minutes and the resulting solution was diluted to mark with water. For recovery purpose, 12 µg/ml was prepared in which 100 µl stock solution was made up to 1000 with water. The solution was stored at -20°C.

2.4.5 **Calibration solution: Internal**

Carbamazepine was chosen to be an internal standard according to Bregt (Bregt *et al.* 2003). Solution of internal standard cabarmazepine with concentration of 1160 µg/ml were made by

weighing 11.6 mg of NVP reference standard into 10 ml volumetric flasks and dissolving into about 5 ml methanol. The mixture was sonicated for 5 minutes and the resulting solution was diluted to mark with water. For calibration purpose, 11.6 µg/ml was prepared in which 50 µl stock solution was made up to 5000 with water. The solution was stored at -20°C.

2.4.6 **Standard curve**

The standard curve was prepared by adding 10, 20, 30 and 40 µl of nevirapine (working standard 8.6 µg/ml) to 100 µl blank plasma to make concentrations of 0.64, 1.19, 1.66 and 2.08 µg/ml respectively. To each of the test tube 25 µl carbamazepine (internal standard) was added. The resulting peak areas are indicated in Table 1.

Tab 1. Mean calibration values

Nevirapine concentration (µg/ml)	*Peak Areas*
0.64	238.5
1.19	444
1.66	716.5
2.08	950

The calibration curve was calculated based on the following formular:

$y = 431.74x + 0.1$, $R = 0.984$

2.4.7 **Recovery**

To determine the recovery, 20 µl control nevirapine (12 µg/ml) was added to 100 µl plasma to give a recovery of concentration of 1.66 µg/ml after four injections. Samples were worked up according to the in house method described and the peak areas were compared to those of directly injected standards Table 2. The formula for calculating recovery was taken as a ratio of recovered amount to expected amount multiplied by hundred.

Table 2. Within and between day assay precision and recovery.

Concentrations (µg/ml)	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Inter-day*
c1	1.60	1.64	1.57	1.61	1.61
c2	1.63	1.5	1.61	1.64	1.60
c3	1.62	1.65	1.64	1.58	1.62
c4	1.54	1.48	1.62	1.53	1.54
Mean	1.60	1.57	1.61	1.59	1.59
Standard deviation	0.04	0.08	0.03	0.04	0.03
Precision (%)	2.52	4.97	1.58	2.55	1.87
Recovery (%)	96.23	94.43	96.99	95.78	95.86

c1, c2, c3 and c4 = number of injections run for control solution

2.4.8 **Precision and Recovery**

Quadruplet samples of 100 µl blank plasma were spiked with 20 µl control nevirapine (12µg/ml) standard to give a predetermined concentration of 1.66 µg/ml. The internal

standard was added to each sample and extraction was carried out as described above (section 2.4.3). Peak areas were calculated using ELDS PRO software; from the peak areas precision and recovery were determined. The concentrations are given in Table 2. The formular for precision was standard deviation divided by the mean multiplied by hundred.

2.4.9 **Interference**

Interference of nevirapine with other analytes was studied by adding the different compounds (stavudine, lamivudine, zidovudine, sulfamethoxazole, trimethoprim, sufadoxine and pyrimethamine) to blank plasma and the samples were analysed according to the method (section 2.4.3). The results are summarized in Table 3.

Table 3. Drug and retention time for drugs used for selectivity testing

Drug	*Retention time (minutes)*
Nevirapine	3.94
Pyrimethamine	11.82
Sulfamethoxazole	1.92
Trimethoprim	4.57
Sulfadoxine	1.82
Lamivudine	2.58
Stavudine	2.42
Zidovudine	2.74
Carbamazepine	8.52

2.4.10 **Data analysis**

The results of plasma analysis from blood of patients were used to determine the proportion of HIV infected patients who were naïve to ARVs. The obtained results were compared to the patients' responses obtained during interviews.

2.5 **Results**

2.5.1 **Intra-day and inter-day precision and recovery**

The intra-day and inter-day precision of the method were 2.91% and 1.87% respectively and intra-day and inter-day recovery were 96.01% with the coefficient of variation of 0.03-0.08%.

2.5.2 **Calibration curve**

The coefficients of calibration curves prepared were always between 0.97- 0.99 indicating linearity of the method.

2.5.3 **Selectivity of the method**

The retention time of some medications were determined as indicated (Table 3). Endogenous substances did not interfere the peak of NVP and internal standard.

2.5.4. **HPLC plasma analysis results**

The majority of respondents 475 (99%) out of 480 HIV infected patients reported not to have used ARVs (Table 4). The interview revealed non-naivety in 1% of respondents who obtained

ARVs at HIV clinics. Among those who declared non-naïvety through the interview, 4 (80%) were females and one (20%) was a male and therefore were not eligible for provision of blood samples for drugs analysis (Table 4).

Out of 475 patients eligible for blood sample provision, 219 (46.1%) provided blood samples for analysis. out of which 214 (97.7%) of samples did not contain nevirapine and five (2.3%) had nevirapine in their blood. All HIV infected patients whose blood were shown by HPLC to have used ARVs were females (Table 5)

Table 4. Distribution of the interviewed HIV infected patients by sex and naivety to antiretroviral drugs.

	Male	*Female*	*Total*
	n (%)	***n (%)***	*n (%)*
Naïve	124 (99.2)	351 (98.9)	475 (99.0)
Non-naïve	1 (0.8)	4 (1.1)	5 (1.0)
Total	125	355	480 (100)

Majority of interviewees 332 (69.2%) attended HIV clinics as early as within four weeks after HIV test, 129 (26.9 %) delayed from five weeks up to one year and 19 (3.9 %) of the 480 respondents delayed for more than one year.

Majority of interviewed HIV infected patients (415, 86.5%) knew their serostatus in the period between 2007 and June, 2008, while 52 (10.8%) knew their serostatus in the period between 2004 and 2006, while very few patients (13, 2.7%) found out their serostatus in the year between 1998 and 2003.

Majority (363, 75.6%) interviewees knew their serostatus at voluntary counselling and testing (VCT) centres while antenatal clinics account (101, 21.1%) of the patients and the rest were test during admission at the hospital.

The reasons for HIV testing were illness (269, 54.1%), pregnancy (115, 24%), advise from relatives/friend (52, 10.8%), presidential campaign (25, 5.2%) and the death of spouse (28, 5.8%).

2.5.5. Demographic characteristics of patients

The demographic characteristics of the 480 interviewed HIV infected are reflected in Table 5. Most of the respondents were in the age group of 15-45 years (86.6%). The overall mean age of the respondents was 35.4 (median 34.0 years) with the oldest respondent being 70 years and the youngest being 17 years old. Most of respondents 355 (74.0%) were females; men were older than women (mean 39.3 year and 34 years for male and female respectively). High proportion of male respondents 66.4% were above 35 years old whereas female respondents 65.9 % were equal or below 35 years old.

Majority of respondents 354 (73.8%) had primary school education, followed by 76 (15.8%) who had secondary school education. Those who attended vocational training were 16 (3.3%) and 26 (5.4%) of respondents did not attend any formal education. None of the respondents had university education and only 8 (1.7%) had diploma education.

Majority of study sample were self employed 255 (53.1%) followed by unemployed 132 (27.5%) and 93 (19.4%) were employment. Among unemployed respondents, there was large proportion of unemployment in females than males (36.6% and 1.6 % respectively).

Table 5. Age, education level and occupation of the HIV infected patients under study.

	Hospital		
Characteristic	MLH, n=408	MNH, n=72	Total, n=48(
Age group (years)	n (%)	n (%)	n (%)
15-25	46 (11.3)	8 (11.1)	54 (11.3)
26-35	193 (47.3)	29 (40.3)	222 (46.3)
36-45	114 (27.9)	25 (34.7)	139 (29.0)
46-55	32 (7.8)	9 (12.5)	41 (8.5)
56 +	23 (5.7)	1 (1.4)	24 (4.9)
Education level			
No formal school	25 (6.1)	1 (1.4)	26 (5.4)
Primary school	310 (76)	44 (61.1)	354 (73.8)
Secondary school	59 (14.5)	17 (23.7)	76 (15.8)
Post secondary school (certificate)	11 (2.7)	5 (6.9)	16 (3.3)
College education (Diploma)	3 (0.7)	5 (6.9)	8 (1.7)
Occupation			
Not employed	116 (28.5)	16 (22.2)	132 (27.5)
Self employed	223 (54.7)	32 (44.4)	255 (53.1)
Employed	69 (16.8)	24 (33.3)	93 (19.4)

2.6 Discussion

When HIV infected patients were interviewed, majority 475 (99%) of 480 reported not to have used ARVs in their life time. Five patients reported to have previously used ARVs decided to stop the treatment due to various reasons (Table 4), while other 5 patients denied to have previously used ARVs although they had detectable levels of NVP in their blood samples. The 5 patients who reported that they previously used ARV drugs, decided to stop therapy for some reasons such as travelling (3) away from their normal HIV clinics, side effects (1) and feeling of being cured (1). For a successful treatment outcome the HIV infected patients should continue using ARVs for life without any interruption to treatment. Studies have shown that, patients who were on ART and stopped the treatment, experienced toxicities when they were re-initiated (Scott *et al.* 1996; Ruelle *et al.* 2007). Naïve HIV infected patients are less likely to develop drug resistance than those who make a lot of attempts in treating HIV infections (Scott *et al.* 1996; Ruelle *et al.* 2007). The patients' self decision to stop the treatment has got not only the risk of development of resistant HIV or drug related toxicities, but also undermines government efforts in the provision of effective ARVs. Such practices also waste the limited resources of the government. It is therefore stressed that patients should follow the HIV clinic care and receive ARVs under proper hands of trained health providers. This minimizes the chances of defaulting from ART and provides the patient with adequate knowledge on reporting of adverse drug reactions (ADR), managing some of the ADR at home and avoiding drug interactions.

The study showed 5 patients had nevirapine in their blood, and 4 out these had low levels of NVP (0.2-0.42 µg/ml), while one of them had high levels of NVP (4.4 µg/ml). These patients denied to have used ARVs in the interview. Reporting to have not used ARVs while actually one used creates difficulty for the clinician in deciding whether there is treatment failure or not and complicates deciding the correct dose to give in case of high levels of the drug remaining in blood. In a study conducted by Nsimba in 2002 on the mothers reporting on an antimalarial drug they gave to their children, as many as 98% of the children had detectable levels of chloroquine (CQ) and 16% of them already had high blood concentrations of the drug despite their mothers denying to have given CQ at home prior to interview (Nsimba *et al*. 2002) indicating that our communities still have poor tendency of storing medication use records. Misinformation on the ARVs use may expose patients to drug overdosing if re-administered the same medications. Patients' correct information is important in history taking and it helps the clinicians to decide the right treatment options. In this study one patient was found to have 4.4 µg/ml nevirapine which is within the therapeutic range of 2-5µg/ml (Donnerer *et al.* 2003). This means that it is possible that the patient has been receiving ARVs from other sources.

This work has confirmed by the use of HPLC, that some patients though few (2.3%) had used ARVs before visiting HIV clinic to seek care and finally ART initiation. It is possible that, these patients feared to report previous ARV use thinking that they could be denied the service. However, it is important to trace where these patients could have sourced the ARVs. It is also possible that some of these patients were already taking the drugs from other HIV clinics and were getting additional doses for selling or giving to their relatives at home.

Currently, the NACP has established patient cards for every patient on ART. However, it is difficult to control patients who may want to be registered and have patient cards from more than one HIV clinic.

In this study, 4 out of 5 patients found to have NVP in blood had low levels of the NNRTI. It is possible that such patients were in the past recruited to undergo ART in one of the HIV clinics but defaulted and resumed attending a different HIV clinic after their conditions worsened. Defaulting from ART has been reported to be caused by many factors including inadequate counselling, drug toxicities and even poor performances of care providers and the HIV clinics in providing good services to patients.

The study was conducted in only one region (Dar es Salaam) where Tanzania Drug and Food Authority is also housed. Such malpractices may be much higher in the rural areas.

From the findings of this study, it can be concluded that the community still needs to be educated on the importance of relying on HIV clinics as the right point for sourcing care and treatment. It is also important that the community is educated on right procedures to undertake until one is identified to have met ART initiation criteria.

CHAPTER THREE

SOURCING OF ANTIRETROVIRAL DRUGS BY HIV INFECTED PATIENTS

3 Background

Increased access to antiretroviral drugs is vital in developing countries with high rates of HIV infection. Unless treatment is properly controlled, these drugs could rapidly lose potency. According to Brugha, only 5% of the 5.5 million people in developing countries who need antiretroviral treatment got it in 2003, this is a report of 2003. Since then there have been massive effort to scale up ARV provision and this figures must be much higher. New initiatives and global partnerships are trying to increase access to antiretroviral drugs (Brugha, 2003). However, people who suspect that they have a sexually transmitted infection seek care in the private sector and traditional healers because of stigma (Katabira *et al.* 1999). Studies have shown that drug provision in developing countries are often unregulated and some of the drug outlets dispense drugs illegally (Brugha , 2003). Therefore for drugs like ARVs which require stringent dispensing regulations, proper drug handling and dispensing only to eligible patients is of paramount importance. Studies have shown that there are benefits of private-public partnership in expanding access to ARVs to HIV infected patients rather than the burden being laid to the government only (Ramiah *et al*. 2006; Dreesch *et al*.2007). This means the private sector, are key partners in the fight against HIV pandemic. According to Tanzania HIV/AIDS policy, the access of ARVs from Hospitals, whether public or private, is free of charge to whoever is eligible (National Strategic Framework on HIV/AIDS, 2003).

This enables all people regardless of their economic status, to have access to care and treatment of HIV/AIDS infection. (National HIV/AIDS Policy, 2005).

However, due to stigma associated with HIV infection and stringent ART initiation criteria from the HIV clinics, some patients may decide to seek for ARVs from uncontrolled sources. Therefore, this study wanted to identify other possible ARVs drug outlets than HIV clinics and their dispensing practices.

3.1 Method

3.1.1 Study area

The study was conducted in Dar es Salaam region in Ilala, Temeke and Kinondoni districts.

3.1.2 Study design

A cross sectional study was undertaken involving private community pharmacies in Dar es Salaam region.

3.1.3 Study population

The study population involved private community pharmacies operating in Dar es Salaam.

3.1.4 Ethical Clearance

Ethical clearance was provided by MUHAS ethical committee.

3.1.5 Site characteristics

This study was conducted in Dar es Salaam city. This is the largest city in Tanzania and is the main business centre in the country. Dar es salaam region has three districts of Ilala, Kinondoni and Temeke.

The city is situated along the Indian Ocean, bordered by the Coastal region on the west, north and south. Dar es Salaam is the second largest harbour along the eastern border of the Indian ocean, after Durban harbour of South Africa. The city can be accessed through the ocean, airport, railways and roads. The city has a total population of 2,497,940 of whom males are 1,261,077 and females are 1236863. Total household number is 596,264. The average household size is 4.2 and the growth rate from 1988-2002 is 4.3%. Dar es Salaam is one of the most hit regions by HIV/AIDS in the country. It has AIDS case rate of 88.9/100, 000 population for the year 2003 being the third, the first is Kagera, followed by Arusha (Population Census, 2002).

3.1.6 Sample size and sampling of private community pharmacies

The Tanzania Food and Drug Authority has registered 293 pharmacy premises in Dar es Salaam (TFDCA, 2003). Initially, TFDA set criteria to be met by the interested private pharmacies which wanted to sell ARVs. This included the capacity of the pharmacy to supply ARVs continuously, certified premises and trained dispensers to handle ARVs (TFDCA, 2003). However, until this study was being conducted, there was no list of premises from TFDA specifically designated to sell ARVs, and was not a criteria for disqualifying a premises to stock ARVs but only being firstly registered by the Drug Regulatory Authority in

the country to conduct a business of the pharmacy. Of 293 private pharmacy premises, 192 were retail and 101 were wholesale pharmacies. Two hundred and two private community pharmacies were included in this study that 151 pharmacies were randomly selected from the cluster of retail pharmacies and 51 pharmacies were randomly selected from the cluster of wholesale pharmacies. Selection of the premises was such that from the list of 192 retail pharmacies each ballot paper was printed a particular name, put into a large box and then rotated five times. The research assistant selected 151 out of 192 papers, similar procedures was carried out in selecting 51 wholesale pharmacies

3.1.7 **Data collection from private community pharmacies**

The investigator and research assistant visited private pharmacies to carry out simulated client interview with the dispenser at the pharmacy premises and then the investigator and/or the research assistant filled the check list after leaving the premises (Appendix II). The questions asked by the investigator/research assistant aimed at determining whether the premises stocked ARVs and the possibility of accessing ARVs from these pharmacies without showing a prescription from accredited HIV clinics (Appendix I).

3.2 **Data processing**

3.2.1 **Data entry**

The principal investigator checked the quality of data daily and then questionnaire were coded. Data was entered in the computer using software programme Excel 2003. Data

cleaning was done after running initial frequencies of variables using SPSS programme, eight questionnaires were cleaned.

3.2.2 **Data analysis**

The simulated client interview data obtained from the private community pharmacies were used to determine the proportion of premises that were selling ARVs and to determine the proportion of private community pharmacies that dispense ARVs with or without prescription.

3.2.3 **Ethical consideration**

The ethical issues were considered during data collection in the private pharmacies in which the researcher did not take any photo to identify the premises that dispensed medicines without prescription. In case the researcher was famous to certain premises, the research assistant took over to visit such premises.

3.3 Results

The study sample involved 202 (69 %) out of 293 private community pharmacies operating in Dar es Salaam city. The general procedures of dispensing ARVs according to their responses when interviewed are summarized in the Tab 6 overleaf.

Out of 202 private community pharmacies, 51 (25.2%) and 151 (74.8%) were wholesale and retail premises, respectively. Most of premises (184, 91.1%) did not stock ARVs and few of them 18 (8.9%) did, of which 9 were wholesalers and 9 retail pharmacies.

Most of respondents/dispensers 126 (62.4%) wanted to know the age of the patient before dispensing ARVs. The respondents from wholesales showed greater interest 70.6 % in knowing the age of the patient than their counter parts in retail premises 59.9 % although there was no significant difference between the two categories of premises ($p > 0.5$). Majority of dispensers 200 (99%) would like to know whether the client has tested for HIV before seeking ARVs rather than depending on the symptoms related to AIDS. According to Table 6, most of the dispensers 200 (99%) required and/or advised to know the CD4+ cells count before using ARVs and few 2 (1%) indicated willingness to dispense the medicines without knowing the CD4+ cells count (Table 6).

Antiretroviral drugs are prescription only medicine, some of dispensers 3 (1.5%) indicated willingness to dispense them without a prescription if the researcher would have money to buy the medicines and most of them 199 (98.5%) out of 202 did not indicate willingness to dispense without prescription. The antiretroviral medicine available in the community pharmacies were stavudine, zidovudine, lamivudine and nevirapine.

Among premises that stocked ARVs majority 17 (94.4%) did not indicate willingness to dispense ARVs without knowing the CD4+ cells count and 1 (5.6%) premises indicated willingness to dispense ARVs depending on the serostatus results only without CD4+ cells count results. When the respondents in the wholesale pharmacies were asked about whether or not would dispense ARVs without prescription, the finding indicated that none of them indicated willingness to dispense without a prescription. This was probably due to closer supervision of wholesale pharmacies by the pharmacist compared to retail pharmacies.

Table 6. Responses of dispensers in the private community pharmacies.

Responses	*Retail* *n=151* *n (%)*	*Wholesale* *n=51* *n (%)*	**Total** **n=202** **n (%)**
Dispenser asked the age of the patient			
Yes	90 (59.6)	36 (70.6)	126 (62.4)
No	61 (40.4)	15 (29.4)	76 (37.6)
Dispenser advised to test for HIV			
Yes	150 (99.3)	50 (98.0)	200 (99.0)
No	1 (0.7)	1 (2.0)	2 (1.0)
Premises stocking ARV drugs			
Yes	9 (6.0)	9 (17.6)	18 (8.9)
No	142 (94.0)	42 (82.4)	184 (91.1)
Request/advise to have CD4+ cells count results before taking ARV drugs			
Yes	150 (99.3)	50 (98)	200 (99)
No	1 (0.7)	1 (2)	2 (1)
Request of prescriptions before dispensing ARV drugs			
Yes	148 (98)	51 (100)	199 (98.5)
No	3 (2)	0 (0)	3 (1.5)

3.4 **Discussion**

Most of premises 184 (91.1%) did not stock ARVs and few of them 18 (8.9%) stocked. The possible reason for ARVs being stocked in few private community pharmacies was due to the fact that HIV infected patients obtained free medications from public Hospitals and even from accredited private Hospitals (Nyazema *et al.* 2000; Ramiah *et al.* 2005).

Antiretroviral drugs are prescription only medicines, among 202 private community pharmacies visited 199, (98.5%) requested prescription from recognized institution before dispensing ARVs. Our study revealed the presence of some pharmacies indicated willingness to dispense ARVs without prescriptions though few (1.5 %). The possibility of ARVs being obtained from the private community pharmacies without a prescription implies that, the patients may not be thoroughly assessed by medical personnel to obtain proper baseline information regarding ART initiation. Without baseline information during ART initiation such as CD4+ cells count, ineligible patients may start using ARVs. Patients could be using medications on and off depending on whether they experience drug toxicities or due to financial status especially those who buy from the community pharmacies. In this situation development of HIV resistant to ARVs and treatment failures become inevitable.

We also found out that even some of the wholesale pharmacies would dispense ARVs as retail pharmacies if a patient could show an ART prescription. Wholesale pharmacies are designated to carry out bulky sales to other premises involved in provision of drugs for instance dispensaries, retail pharmacies, medical shops, but are not allowed to dispense doses to patients. The willingness of wholesale pharmacies to dispense a monthly doses to HIV patients is an indication of irrational use of ARVs in the country and a prognosis of patients

accessing the drugs even without meeting the criteria for ART initiation stipulated by HIV clinics.

The private health sectors dealing with service provision to HIV infected patients target in maximizing profit. Irrational dispensing of ARVs in both retail and wholesale pharmacies undermines the government effort of fighting the pandemic (Goel *et al.* 1996; Michelle, *et al.* 2000; Ford *et al.* 2007).

Government authorities responsible for regulating the use of medicines in the country should put more efforts to ensure that drug dispensing regulations are adhered to. The drug dispensers working in both retail and wholesale pharmacies should be educated on the consequences of dispensing ARVs to patients who have not fulfilled the ART initiation criteria and the dangers of by-passing the HIV clinics in HIV treatments.

In general the study found few pharmacies indicated willingness to dispense ARVs without demanding a prescription. The presence of even a single premises dispensing ARVs without a prescription is a risk to those patients who want to by-pass the HIV clinic recruitments especially those who think waiting until the CD4+ cells count falls to less than 200 could be too late. Patients living around the same district especially those affected by HIV infection normally share information. Therefore, the availability of even a single centre with uncontrolled ARV drug provision is enough to create high influx of patients who would not like to visit HIV clinics for thorough checking and ultimately ART initiation. This in turn will have negative impact on the control of ARV drug use and finally it could jeopardise the government political will to eradicate the pandemic.

The National AIDS Control Program in collaboration with stakeholders should set mechanisms of ensuring that the ARVs are used as per guidelines and TFDA should make sure that the pharmacies in the country do not act as centres for illegal sourcing of ARVs by HIV patients.

CHAPTER FOUR

4 GENERAL DISCUSSION, CONCLUSION AND RECOMMENDATIONS

4.1 Conclusion

This study has revealed that some HIV infected patients newly recruited at the HIV clinics were already using ARVs, despite the fact that they denied using ARVs during the interview. Although few patients were found to have used ARVs in blood and also few private community pharmacies indicated willingness to dispense ARVs without prescription, it does not rule out that the problem could be perpetuating. Patients infected with HIV are affected by stigma and discrimination and if no measures are taken to educate the community and the patients, effective utilisation of the free services provided by the government through the National AIDS Control Program will be anecdotal. Most patients think that the moment one is diagnosed to have been infected with HIV, the immediate step is ART initiation. Antiretroviral drugs are toxic and have high potentials of interacting with other drugs and therefore the need of adequate counselling before ART initiation. Furthermore, baseline information is required to assure that the patients do not have diseases like hepatitis, diabetes mellitus, skin hypersensitivity to some of the ARVs. There are some studies which also indicate the dangers (such as adverse effects) of starting using ARVs in patients with high levels of CD4+ cells (Opravil *et al.* 2002).

The current ART initiation guidelines in Tanzania require that the patient should indicate the name of a relative as treatment support and also that there must be assessment of the health status of the patients and his/her social life and even the presence of a social group to support

that patient. In addition, the baseline CD4+ cells count and the body weight should be documented to enable making assessment of the treatment progress once ART is initiated. It can therefore be seen that, it is not simply being HIV positive but other factors should be considered before a decision is reached to put a patient on ART.

Patients need therefore to be educated through mass media and other campaigns on the dangers of self-medicating with ARVs.

This study revealed that some private pharmacies that stocked ARV drugs indicated willingness to dispense the medications without prescription. This implies that some patients will continue bypassing HIV clinics as long as they can access ARVs from these premises. This on the other hand poses a risk of irrational use of ARVs which ultimately will result into development of drug resistance.

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4.2 **Recommendations**

From this study it is recommended that regulatory authority should ensure that regular inspection in all community pharmacies to check the ARVs dispensing practices in order to safeguard the public against dishonest business people. Some patients had already been on ART therefore clinicians have to take detailed clinical history and recommend blood assay of ARVs before initiation of ART. This will prevent early occurrence of HIV resistance to the regimen which is important to patients and ARVs. The community pharmacies should ensure that all prescription medicines including ARVs are dispensed with prescription and keep

records of the dispensing register for inspection when needed. Antiretroviral drugs should not be used without attending HIV clinics where guidelines are followed during ART initiation. The study was conducted in Dar es Salaam city only, therefore further studies should be conducted countrywide to reveal the magnitude of the problem..

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4.3 **Study limitations**

In some cases respondents were not willing to provide required information. Recall bias among patients was another source of study limitation. In order to overcome these limitations the purpose and benefits of the study was clearly explained to the respondents and they were assured that the information provided would be strictly confidential. The time and funds were limited for the study to be conducted in other parts of the country. In those cases where the investigator was known by some workers in the community pharmacies during data collection, the research assistant was used to access such premises.

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