

CHAPTER ONE

1. INTRODUCTION

This chapter gives a brief overview of HIV/AIDS epidemic and treatment trends. Statements of the problem, objectives and justification of the study have been stated.

1.1 Background Information

The HIV/AIDS epidemic in Sub-Saharan Africa and Zambia

For more than two decades the Acquired Immune Deficiency Syndrome (AIDS) and its etiological agent, the Human Immunodeficiency Virus (HIV) has been a growing challenge worldwide. HIV/AIDS is recognized as a global emergency demanding the attention on the international health agenda and one of the most important public health issues (WHO, 2006). The spread of HIV/AIDS has reached a pandemic form within a short span of time. A total of 33 million people are estimated to be living with HIV across the globe, 2.7 million people became infected with the virus and 2 million people have lost their lives due to AIDS (UNAIDS, 2008).

Every day, more than 6,800 people become infected with HIV and more than 5,700 die mostly because they have no access to HIV prevention, treatment and care services (UNAIDS 2008). The United Nations included HIV in its sixth millennium development goal which aims at combating and reversing the spread of HIV/AIDS by 2015 as well as to achieve Universal access to treatment by 2010 (WHO, 2008).

Sub – Saharan Africa is more heavily affected by HIV/AIDS than any other region of the world. It is estimated that 22.5 million people are living with HIV. Around 1.5 million people died of AIDS and a further 1.8 million people became infected with HIV by the end of 2007 (UNAIDS, 2008). In this region, South Africa, home to more than 5 million people living with HIV/AIDS, is one of the countries hardest hit by the AIDS epidemic. The HIV/AIDS prevalence rate is at 18.1%, significantly higher than the rate in sub – Saharan Africa (5.0%) and globally (0.8%). In 2007, an estimated 350, 000 South Africans died of HIV/AIDS (UNAIDS/WHO, 2008).

Zambia, in southern Africa, has one of the world's most devastating HIV/AIDS epidemics. More than one in every seven adults in Zambia is living with HIV and life expectancy at birth has fallen to just 42 years with the prevalence rate of 15.2%. This compounded Zambia's existing economic problems. The first case of HIV in Zambia was diagnosed in 1984. By 1985, a survey of hospital patients in the capital city found that 17.5% were infected (AIDS Care, 2008). By the 1990s, it was estimated that 20% of the

population had become infected with HIV. This rise in prevalence led to World Health Organization (WHO) to develop a National AIDS Advisory Council in Zambia.

By the end of 2005, Zambia had a population of approximately 11.7 million people. In 2007, it was estimated that about 1.1 million Zambians were living with HIV/AIDS and that 57% of adult infections occurred in women. It was also estimated that 98,000 Zambians died of AIDS and projected that by 2015, AIDS will have increased the number of deaths by 83% bringing the cumulative total of AIDS death to 2.8 million (MOH, 2007).

Antiretroviral therapy (ART) for HIV/AIDS

HIV – positive people are individuals who are infected with human immunodeficiency virus. The virus is transmitted sexually, parenterally and perinatally. It infects the CD4⁺ cells and multiplies, weakens the immune system and increases risks of serious infections (Dennill and Roberts, 2005). When antiretroviral treatment is not taken, the average length of time for an adult to develop AIDS from the time of HIV infection is about 8 years or more. However, each person is different, and many factors such as nutrition, stress levels and emotional support influence a person's ability to remain healthy (MOH, 2007).

Antiretroviral therapy (ART) is the main type of treatment for HIV/AIDS. It is not a cure, but it can stop people from becoming ill for many years. The treatment consists of drugs that have to be taken every day for the rest of a person's life. The aim of antiretroviral treatment is to keep the amount of HIV in the body at a low level. This stops any weakening of the immune system and allows it to recover from any damage that HIV might have caused already. The drugs are referred to as antiretrovirals (ARVs). Taking two or more antiretroviral drugs at a time is called combination therapy. A combination of three or more anti-HIV drugs is referred to as Highly Active Antiretroviral Therapy (HAART) (UNAIDS, 2008). The highly active antiretroviral therapy consists of any of the following three combinations:

- 2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI).
- 2 NRTIs + 1 protease inhibitor (PI).

The aims of the combinations are to reduce the rate at which resistance would develop, making treatment more effective in the long term, reduce the viral load to undetectable levels, and improve quality of life by reduction of HIV-related illness and reduce transmission to others (MOH, 2007). The fixed dose combinations are carefully chosen based on considerations related to effectiveness, toxicity and availability. The fixed doses are multiple antiretroviral drugs combined into a single pill. This greatly

increases the ease with which they can be taken, which in turn increases adherence, and thus their effectiveness over a long term (MOH, 2008).

The recommended regimens for patients initiating HAART within Zambia National Guidelines, up to 2007 were as follows:

Table 1: Recommended Regimens in Zambia

FIRST LINE REGIMENS			SECOND LINE REGIMENS		FIXED COMBINATIONS
NRTI	NRTI	NNRTI	NRTI/NRTI	PI	- AZT/3TC
AZT or d4T	3TC	EFV or NVP	TDF/FTC	LPV/r	- d4T/3TC
		ALTERNATIVE REGIMENS			- AZT/3TC/NVP
					- d4T/3TC/NVP
ABC	3TC	NVP or EFV	ABC/ddI		- TDF/FTC or TDF/FTC/EFV

Source: MOH, 2007.

In Zambia, the ART programme started with the private sector. It then rolled to public facilities starting with Ndola Central Hospital and Lusaka University Teaching Hospital in 2002. At that time, very few people could afford the monthly payments towards the drugs. Provision of free treatment started in June, 2004 and this was made possible by an unprecedented amount of funding from the Global Fund which committed \$254 million for over 5 years (Lewis, 2005). As of September, 2004, an estimated 13,636 people were accessing antiretroviral therapy in Zambia. This was 1.2% of 1,100,000 HIV adult infected populations in the country (MOH, 2005). By then, there was an increase of government and mission health facilities offering antiretroviral therapy country wide and this included Choma general hospital, a government facility in Choma district, southern province.

Choma district is centrally located in southern province and shares borders with 5 districts namely Monze, Namwala, Kalomo, Gwembe and Sinazongwe. The district is situated along the line of rail, 289 km from Lusaka and 188 km north of Livingstone and it is on the major highway of the Great North Road. The district is on a plateau; in the east there is Gwembe valley which extends to southern east in Sinazongwe district. The land covers an area of 7, 300 km² with a population density of 31 per km² and the projected population was 241,796 for 2006 (Choma HMIS, 2006).

The district has good road network connecting neighboring districts and is a point of entry for several gravel and non-gravel feeder roads from surrounding rural communities. This has led to mass movement

of people engaged in various businesses including cross border-trading, contributing to an increase in commercial sex activities and a rise in crime. The six chiefdoms in the district define the cultural setting, values and norms in rural Choma. Early marriages are common and polygamy is an integral norm (Choma HMIS, 2006).

Choma district has a number of parastatal and private companies notably; Zamtel, ZESCO, SWASCO, Zampost, ZSIC, NAPSA, Choma Milling Company, Stanchart, Barclays, ZNBS, and ZANACO banks. These major companies provide various employment opportunities to the population. The town has an airstrip, land, mobile, and radio and internet facilities. The district is serviced by 3 hospitals; Choma general, Macha mission and Maamba hospitals. It has more than 30 health centers both in the urban and rural areas managed by the District Health Management Team (DHMT). Despite being one of the first government health facilities to provide free ART services in 2004, the district has had high levels of deaths mainly due HIV/AIDS leading to increased number of orphans and child headed homes.

1.2 Statement of the problem

Choma general hospital is situated within Choma town about 2 km from the main post office off Livingstone road. It offers 1st and 2nd level services to a catchment population of 241,796. 51.2% of this population is the adults of 15 years and above (Choma HMIS, 2006). All the surrounding districts have 1st level hospitals except Monze that has 2nd level services. Choma receives referrals from the 1st level hospitals. The hospital has a bed capacity of 184 and offers curative, palliative and preventive services. Besides the out-patient department, the hospital offers specialized clinics which include ART clinic which was established in 2004.

By the year 2006, with the adult HIV/AIDS prevalence rate of 16% in Zambia, the district had a high incidence rate of sexually transmitted infections (STIs) of 15.0 per 1000 population. The HIV infection was at an the incidence rate of 7.1 per 1000 population and case fatality rate of 195.1 per 1000 admissions (Choma HMIS, 2006). This revealed the high demand of Antiretroviral drugs (ARVs) and the need to scale up ART programme in order to increase accessibility to all the people in need of the ARVs.

Anti-retroviral drugs cripple enzymes that are crucial in the replication of HIV. When a patient with HIV starts taking these drugs, the concentration of HIV (viral load) drops rapidly as compared to a person with HIV who is not on ART, who might have an HIV concentration of 100, 000 copies per milliliter of blood. However, this can be reduced to below the level of detection by current technology within three to four months of taking ARVs. On stopping ARVs, HIV replication resumes and the viral load rapidly reverts to what it was prior to ART.

In the absence of ARVs the circulating virus progressively weakens the immune system, as reflected by the fall in the CD4 lymphocyte count. When taking one or two anti-retroviral drugs, the virus mutates to escape the drugs (resistance) after some time. The rate at which this happens is however vastly reduced when taking three drugs, although resistance eventually does occur, at which point new anti-retroviral drugs need to be used (WHO, 2004).

The first line recommendations are for individuals who have never received ARVs in the past, since past exposure to ARVs increases risk for drug resistance and one or more of these “first-line” regimens may be less effective. When resistance develops to the second-line regimen, increased viral replication occurs which leads to a progressive loss in CD4 lymphocytes and eventual progression to AIDS and death.

Therefore, this economic study interest was in the costs and effects of treating opportunistic infections (OIs) and HIV- related diseases with either ARVs or without ARVs in HIV-infected adults aged 15 years and above. The OIs which are common in Zambia are: *Mycobacterium tuberculosis* (TB), *pneumocystis carinii* pneumonia (PCP), oral candidiasis and cryptococcal meningitis. The coverage of HIV/AIDS infected patients being treated for OIs was 50% in 2005 (MOH, 2005).

The OIs which were to be considered in in-patient utilization were TB and cryptococcal meningitis. This was due to the fact that patients tend to be admitted for in-patient care with a number of different OIs together, and it is impossible to unpack the relative contribution of each OI to the total cost of a period of hospitalization (Sinanovic and Floyd, 2000).

The drugs being used for prophylaxis and treatment for these OIs are: Isoniazid/Ethambutol, Rifampicin and Pyrazinamide in TB; Amphotericin B and Fluconazole in cryptococcal meningitis. Other non-ARVs drugs such as co-trimoxazole, Ketoconazole, and Nystatin etc. given to eligible patients were also considered in the study.

In Zambia, the decision to initiate ART is guided by the patients' WHO clinical staging I, II, III and IV and CD4 count criterion: < 200, 200 – 350 and > 350 cells/ μ l (MOH, 2007). In this study, the Markov modeling construction was based on these WHO CD4 count criterion which was further divided into four: <50, 50 – 199, 200 – 350 and >350 cells/ μ l. in order to determine the four Markov health states of the cohort that gave significant survival levels which depended on the explicit length of time each patient occupied in a given state, assessed over a series of discrete time periods, called cycles.

1.3 Research Questions

- What opportunities exist for government to support one treatment option (No- ART) against another alternative intervention (ART) for population infected with HIV?
- How much does it cost the government to care for patients with HIV infection?
- How should resources be allocated within the competing needs of HIV/AIDS programmes (counseling and testing, preventive measures, treatment and care)?

1.4 Objectives of the Study

1.4.1 General Objective

To assess cost-effectiveness of providing HAART in a public health sector of Choma General Hospital and ART center from the provider's perspective by comparing treatment and prophylaxis of opportunistic infections without anti-retroviral drugs (No-ART) and with ART in terms of full economic costs by HIV infected adults aged 15 and above.

1.4.2 Specific Objectives

- i. To estimate the costs and effects of ARVs used in treatment of HIV infected persons.
- ii. To describe the costs of prophylaxis and treating of opportunistic infections in HIV infected adults.
- iii. To determine the incremental cost-effectiveness ratio of ARVs at Choma district ART center.

1.5 Justification of the study

HIV/AIDS infection has become a treatable chronic illness due to HAART intervention; however, many health-economic issues surround the use of the intervention. It is a complex and an expensive undertaking on the provider. This intervention undeniably draws resources away from other critical health and HIV/AIDS activities with a great impact on the finite budget of the health care system (Creese et al., 2002).

CEA has been used in industrialized countries as an evaluation tool for HAART intervention. The documentation reveals that CEA of HAART, in terms of reducing HIV-related morbidity and mortality, has been cost-effective (Beck et al., 2004). In Africa, little information exists on CEA studies done on HAART. However, a number of CEA studies on HAART done in South Africa have been documented

recently to show the effectiveness of the intervention (Badri et al., 2006; Clearly et al., 2006; Clearly and Maart, 2002).

In Zambia, so far, literature review does not reveal any cost-effectiveness studies on HIV/AIDS on use of HAART intervention. However, a comprehensive analysis study was undertaken in 2003, on the costs, budget, and resource requirements for the provision of HAART in the public health sector (Kombe and Smith, 2003). In Choma district, a cost-effectiveness study was done based on the assessment of CD4 count changes, weight gain and functional changes as well as prevalence of side effects of ARVs (Zulu, A., 2007, unpublished). However, the study did not undertake a comparative economic evaluation analysis in terms of costs and health effects of the HAART intervention.

Furthermore, treatment options continue to improve as additional new drugs enter clinical trials, hence the importance of evaluation studies for decision making on the best options to use in HIV/AIDS interventions.

CHAPTER TWO

2. LITERATURE REVIEW

2.1 Literature Search Strategy

The strategy was limited to published years from 1993 – 2008. The electronic journals, reports, research working papers and various studies done by other researchers were accessed “on line” by using Google. Published and gray literature by national, international, governmental and non – governmental organizations (NGOs) including Ministry of Health published materials was also searched.

2.2 Economic Theory

Economics is the social and policy science that analyzes the production, distribution, and consumption of goods and services. Economics aims to explain how economies work and how economic agents interact. Economic analysis is applied throughout society in many areas of human activity including health. The mainstream of economic theory relies upon a priori quantitative economic models, which employ a variety of concepts. The theory proceeds with an assumption of *ceteris paribus* which means holding constant explanatory variables other than the one under consideration (Mark, 2007). Economic writings date as far back as 14th century where notable writers such as Aristotle influenced the late scholastics of the 14th - 17th centuries.

2.2.1 Principles of Clinical Economics

To understand the role of economic analysis, it is imperative to distinguish between the different types of such analyses. There are four techniques of full economic evaluation and these are:

- Cost-benefit analysis (CBA) – attempts to incorporate both resources used for clinical interventions, as well as a measure of the value of those resources in terms of clinical benefits. As the outcome measure is currency, this methodology requires valuing clinical benefits, such as years of life saved (YLS) or disability-adjusted life years (DALYs) saved, in monetary terms.
- Cost-utility analysis (CUA) – it is a specialized form of CEA that includes a quality-of-life component associated with morbidity using common health indices such as quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs).
- Cost-analysis (CA) or Cost-minimization analysis (CMA) – this is a methodology which estimates the resources used for, or cost of, a particular type of care or a specific illness. The outcome of interest is cost, and these studies are used primarily for budgeting and planning purposes.

- Cost-effectiveness analysis (CEA) – this is a form of economic analysis that explicitly examines two outcome measures: costs in monetary terms, and effectiveness in YLs, DALYs, or QALYS. CEA is resource intensive and it is easier to understand and more readily suited to decision making. By convention different clinical interventions and strategies are compared in terms of their cost-effectiveness ratio, defined as $(C_A - C_B) / (E_A - E_B)$ where $C_A - C_B$ is the difference between the cost of interventions A and B, and $E_A - E_B$ is the difference between the effectiveness of these interventions. These ratios are a measure of value for money, the higher the ratio, the less cost-effectiveness the intervention (Gold et al., 1996).

2.2.2 Cost-effectiveness Analysis (CEA)

CEA, one of the economic evaluation techniques is commonly used in the field of health services, where it may be inappropriate to monetize health effects. CEA was created in 1970s as a tool for health care decision making, primarily to avoid controversy regarding valuation of health-related outcomes in dollars. The analysis was initially applied in the clinical arena but has recently been used to evaluate health policies, programmes and interventions. The decision makers can use CEA to identify the most cost-effective strategies from a set of options that have similar results (Denil et al., 2008).

In some developed countries, political decision making in medicine or public health is based on cost-effectiveness analysis. Many clinical trials are in progress which involves the collection of patient-level data on both the health outcome and resource use consequences of the health care interventions under evaluation. The overall aims of many such evaluations are to undertake a cost-effectiveness analysis, which often results in a cost-effectiveness ratio summarizing the value for money of the intervention in question (Briggs and Sculpher, 1998).

2. 2.3 Cost-effectiveness Analysis of HAART

Highly Active Anti-retroviral therapy (HAART) is the global standard of care in the treatment of HIV infection and is a combination of at least three ARV drugs. It has substantially improved the prognosis of HIV infected patients in industrialized countries as revealed from the documented studies done. In Switzerland and US, the cost-effectiveness studies on HAART, revealed an increase of health care costs. The incremental cost-effectiveness ratios in Switzerland study, ranged from Swiss Fr 33,000 to Swiss Fr 45,000 per life-year gained. In the US study, the incremental cost-effectiveness ranged from US\$13,000 – US\$23,000 per quality-adjusted life-year gained. In addition to health care costs, changes in productivity costs were considered from the societal perspective. As a consequence of their improved health status resulting from HAART, patients were able to return to work or work until later in their life. When these

productivity gains were included in the analysis, HAART was found to be a cost-saving strategy (Sendi et al., 1999).

Another study done in the US revealed that more health care resources were needed to provide appropriate medical care to all HIV-infected patients. This was because of an increase in the average direct costs per patient per month and an increase in the size of the infected population (Sendi et al., 1999).

In view of that, consideration must be given in decision making as to where these additional resources will come from if they are within the budget and then by definition some other health care programs can be either reduced or cancelled in order to free up resources for the HAART program. These programs should be chosen so that the health outcomes forgone by deleting the other programs will be smaller than the health outcomes gained by introducing the HAART program as in the concept of opportunity cost.

Another study done by Kenneth and others (2001) in United States, estimated the clinical benefits and cost-effectiveness of HAART regimen using the CD4+ cell count and HIV RNA levels as predictors of the progression of disease. The results of the study were that life expectancy adjusted for the quality of life, increased from 1.53 to 2.91 years. The results also revealed that per- person lifetime costs increased from \$45, 460 to \$77,300 with HAART as compared with no therapy. The incremental cost per QALYs gained was \$23,000. The cost-effectiveness ratio ranged from \$13,000 to \$23,000 per QALYs gained. The study concluded that treatment of HIV infection with HAART is a cost effective use of resources.

In Africa, little information exists on cost-effectiveness analyses studies done on HAART. However, a number of cost-effectiveness analyses studies on HAART done in South Africa have been documented recently to show the effectiveness of the intervention. One of the studies evaluated the use and cost of services of HIV-infected adults in 1995-2000 in Cape Town. The study revealed that HAART is a cost-effective intervention and the estimates were based on direct costs.

In Zambia, so far, literature review does not reveal any cost-effectiveness studies done on HAART intervention. However, a comprehensive analysis study was undertaken in 2003, on the costs, budget and resource requirements for the provision of HAART in the public sector of health care system. The study included costs of treatment interventions of opportunistic infections (OIs) and HAART provision.

One of the key findings of the study was that provision of HAART to everyone who is clinically eligible would cost about \$50 million in the first program year (2002); rising to about \$160 million by the fifth year (2007), well over twice the entire annual public health budget. The study further revealed that the

average annual incremental cost per patient for a first-line HAART regimen in Zambia was \$488, with drugs and monitoring tests, accounting for 57% and 37%, respectively. Capital and training costs made up the remainder (Kombe and Smith, 2003).

2.3 The Multisectoral Impact of the HIV/AIDS Epidemic

The global HIV/AIDS pandemic continues largely unabated. If current trends persist, it is projected that 60 million more HIV infections will occur by 2015 and the annual number of new infections could increase by 20% or more by 2012. Beyond the substantial human toll, the epidemic has broader impacts throughout many parts of a society, largely because HIV remains a fatal disease that primarily affects those who are young and in their most productive years (UNAIDS, 2006).

Because of this, HIV is considered a threat to overall development in many of the hardest hit nations, complicating efforts to reduce poverty, improve access to education and health care, address gender inequality, and maintain national security. This broader “multisectoral impact” is one of the more unique and salient features of the HIV pandemic and is important to understand for informing policy and planning efforts at all levels of society.

Unlike many other infectious diseases which tend to have their biggest impacts on the very young or very old, HIV primarily affects adults in their most sexually active years which coincide with their most economically productive and reproductive years. Both the peak age of HIV infection and the greatest mortality are among those between the ages of 20 and about 40. Of the estimated 2.9 million deaths due to AIDS in 2006, most (90%) were among adults, aged 15 and over. Under normal circumstances, this is a population group that is less likely to be ill or die compared to other age groups (UNAIDS, 2007).

HIV has a very long incubation period, during which few, if any, symptoms are evident. The average time between infection and development of AIDS, is between 9 and 11 years in the absence of treatment—and, as a result, the epidemic continues to spread unknowingly. It is estimated that 8 in 10 people with HIV globally do not know they are infected. There is significant stigma related to HIV disease. Due to stigma, people may not see themselves at risk, may not get tested and, if infected, may not seek treatment or if they do, face barriers to accessing needed services—all of which exacerbate the epidemic.

2.3.1 Impact on Population Structure and Demographic

HIV is still considered a fatal disease that primarily affects people in their most productive and reproductive years, it has the potential to impact the structure of a country or region’s population. These

demographic effects can be seen most clearly on mortality rates and life expectancy which, in turn, can affect the ratio of men to women, fertility rates, age structure, and overall population growth.

Research studies done by UNAIDS (2006), have shown that mortality has been increasing in the developing countries highly affected by HIV/AIDS. HIV causes more deaths than most infectious disease in the world and it is the number one cause of death in sub-Saharan Africa. Whereas prior to the epidemic, those aged 20 -49 accounted for 20% of the region's overall deaths, they now account for 60% of deaths, largely due to AIDS.

Prior to the onset of the AIDS epidemic, many developing countries were experiencing significant gains in life expectancy. Studies done in the hardest hit countries indicate that those gains have slowed or even reversed in some cases due to HIV. Life expectancy in Southern Africa as a whole has fallen from 61 to 49 in the last 20 years. In Botswana, life expectancy dropped from nearly 65 years in the period of 1985 - 1990 to 47 years in 2000-2005 periods. South Africa, Swaziland, Zambia, and Zimbabwe have also seen drops in life expectancy (WHO, 2004, UNAIDS 2006).

There is the potential for HIV to alter the ratio of women to men since so many affected by HIV are women. Women account for almost half (48 %) of all adults living with HIV/AIDS globally; they account for 59 % of adults living with HIV/AIDS in sub-Saharan Africa. HIV infection rates typically peak among women 5 to 10 years earlier than men and women with HIV also tend to die earlier than men. Because fertility tends to be lower for women with HIV than uninfected women, fertility rates are expected to decline and also HIV-positive children born to infected mothers are not as likely to reach childbearing age (UN, 2006).

2.3.2 Impacts on Individuals, Households and Community

The impact of HIV/AIDS is felt most directly and deeply at the individual and household levels; this is worse in the poorest populations. For a person living with HIV/AIDS, there are obvious clinical and medical consequences. Due to the morbidity of HIV/AIDS, an individual's ability to work and generate income is affected at a time when the individual is likely incurring new costs, largely related to medical care. The combination of higher expenses and reduced income threatens the livelihood of a family, their ability to secure food, pay for education, save and invest. In response, households may "cope" by realigning their household expenses and making decisions that may have further implications. AIDS mortality also affects the composition of families (ILO, 2003).

A research study conducted by Booysen and Bachmann (2002) in Free State Province, in South Africa found that affected households had lower monthly incomes compared with non-affected households. Medical expenses related to HIV/AIDS in poor South African households consume up to a third of income whereas the national average household expenditure on health care was four percent per year. Funeral costs, on average, were four times the monthly income of households surveyed in South Africa.

Two-thirds of South African households' surveyed experienced decreases in income and 40% reported that the primary caregiver had taken time off from formal or informal employment or schooling to take care of an infected individual adding to the loss of household income, as well as under-schooling of children (Barnett and Whiteside, 2006). Other research studies have revealed that due to lack of support and treatment costs due to HIV, most of them are forced to sell assets and borrow from friends and relatives. A study done in Zambia revealed that female-headed households takes care of people living with HIV and orphans (ILO, 2003).

The impacts at community level in the most severely affected countries are that adults who are 20-49 years are dying in large numbers. Those are their most productive years in the work force. The soaring numbers of deaths have a profound impact on family livelihoods, community vibrancy, and the national economy (Net Aid, 2007). As adults pass away from complications of the disease, the number of orphaned children increases. The total number of orphans due to AIDS since the beginning of the epidemic was estimated at 14 million by the end of 2004 (Barnett and Whiteside, 2006).

In 2007, Zambia had approximately 600,000 AIDS orphans and this number was projected to rise to 895,000 by 2009 and 974,000 by 2014. This surge in the number of orphans comes at a time when the traditional roles of the extended family have already been breaking down with urbanization and prolonged economic pressures. At the community and national level, there is an increased burden on society to provide services for these children, including orphanages, health care and school fees (CBoH/MOH 1999).

2.3.3 Impact on Firms and the Private Sector

By affecting adults during their prime working years, HIV/AIDS has the potential to impact the labor supply and, therefore, businesses and firms in the private sector. AIDS-related illness and death among employees may increase costs, reduce productivity and change a firm's operating environment. Higher costs have significant implications for businesses, such as effects on profitability and competitiveness.

Research studies has shown that HIV/AIDS has raised costs for businesses through: absenteeism due to the ill health of a worker or a member of the worker's family; higher medical care and benefit costs; funerals costs for employees; employee attrition due to illness or death; and additional efforts needed to recruit new staff. Almost 10% of South African companies surveyed indicated that HIV/AIDS has already had a significant adverse impact on their business; more than 40% predicted a significant negative impact over the five years following the survey (Rosen et al., 2004).

Beyond impacts in the “formal” sector made up of larger business and enterprises, most developing countries have a vast “informal” sector of small, self-run businesses (often accounting for significant shares of GDP). A recent study focusing on South Africa's informal sector, which accounts for 50% of total employment and 30% of its GDP, found that poor health was significantly associated with business closure. While the study did not focus on HIV/AIDS, the researchers reported that the findings underscore the vulnerability of small businesses to HIV/AIDS (World Bank, 2007).

2.3.4. Impact on Governments and the Public Sector

Governments face some of the same issues as the private sector—illness and death of workers increases costs and reduces productivity. HIV/AIDS also poses special challenges for governments and the public sector. The epidemic increases demands on government and public services at a time when both human and financial resources may be compromised. HIV may also erode the revenue (tax) base of government by increasing mortality among adults in their prime productive years; revenue may be reduced further as the private sector; a key source of tax revenue is impacted by the epidemic (Haaacker, 2004).

These factors, when coupled together, have implications for how governments respond to the epidemic; the amount of resources available for addressing HIV/AIDS in prevention, treatment, care, and social support—as well as all the other areas governments are responsible for such as health, education, and justice; and the capacity of the governments to deliver services (Barnett and Whiteside, 2006).

2.3.5. Impact on the Health Sector

The sector most directly affected by HIV/AIDS is the health sector, both public and private. HIV/AIDS increases the number of people seeking services, the costs of health care for patients, and the need for health care workers. People living with HIV/AIDS need a wide range of health care services, often for many years. This increased demand is putting pressure on the limited health resources in many developing countries. Exacerbating this pressure is the threat to the supply of health workers already

severely short in number in many of the countries hard hit by HIV/AIDS who are themselves at risk for infection (UNAIDS, 2006).

Studies done by UNAIDS (2006), in various countries revealed the following findings: in one hospital in Nairobi, Kenya, HIV prevalence among patients rose from 19 % in 1988/89 to 40% in 1997, hospital bed occupancy rose from 100 to 190%. In Rwanda, a study found that HIV positive patients visited health facilities 11times on average in one year as opposed to 0.3 times for the general population. In South Africa, a study estimated that nearly 16% of health workers in both public and private facilities in four provinces were living with HIV/AIDS in 2002 and that among younger health workers (18 -25), the prevalence rate was estimated at 20%.

In Lusaka, Zambia, HIV prevalence was 39 % among midwives and 44 % among nurses in the early 1990s. Botswana, a country with one of the highest HIV prevalence rates in the world, lost approximately 17 % of its health care workforce due AIDS between 1999- 2005 (UNAIDS, 2006). In many southern African countries, death from AIDS is the largest reason for exiting the health workforce. Those who remain experience increased workloads, which can lead to burnout and absenteeism. While access to antiretroviral treatment is expanding in many hard hit countries, the labor and resources needed to deliver treatment puts additional pressure on the health system.

2.3.6. Impact on Education

Education is critical for development and the generation of human capital. However, HIV has affected both the demand for (number of students) and supply of (number of teachers) education and this is particularly the case in some African and Asian countries that already face significant challenges in their educational systems. Ultimately, the quality of education may be compromised. AIDS orphans are at risk of ending their education before completion or never entering school. Girls' education often suffers the most from the AIDS pandemic (UNAIDS, 2006). Research studies done has shown that deaths of children born with HIV and the removal of AIDS orphans and other children affected by the epidemic from school, result in smaller numbers of children needing education.

In India, a study done by Pradhan et al. (2006) revealed that children aged 6 -18 living in households with an ill family member were more likely than children in households without HIV to drop out of school in order to get a job or take care of younger siblings and other household work. The epidemic has also created a population of children with new special needs (orphans, children living with HIV, children taking care of parents with HIV/AIDS).

In Zambia, a study done by World Bank (2005) revealed that personal illness or taking care of family members (including attending family funerals) accounted for over 60% of teacher absences. A survey carried out among teachers found that a five percent increase in a teacher's rate of absence, reduced students' average gains in learning by four to eight percent per year.

In Tanzania it was estimated that 45,000 additional teachers were needed to make up for those who have died or left the system because of AIDS. At a time when teacher resources are declining, there are reports that the number of teachers being trained is not enough to fill the gaps in African countries. Besides that, the average age, and the level of training of teachers, was expected to fall, meaning that teachers may be less experienced (ILO/GTZ, 2004).

2.3.7. Impact on Agriculture and Food Security

The majority of people in countries most-affected by HIV live in rural areas, with many relying on farming and other rural occupations for subsistence and income. In fact, the agriculture sector is often the single largest source of employment in developing countries. Given agriculture's reliance on labor, illness and death directly affect productivity and, therefore, affect crop yields, the types of crops being cultivated, income, and, ultimately, food security. This sector already faces many challenges like drought, existing food shortages, and the extreme poverty of farmers, all of which are worsened by HIV/AIDS (FAO, 2004).

Research studies have shown that by the year 2000, the agricultural workforces in high-prevalence African countries were between 3 and 13% smaller than they would have been in the absence of AIDS. It was estimated that by 2020, the loss could be 10% in some countries and over 20% in hard hit countries like Botswana, Mozambique, Namibia, and Zimbabwe. In Zimbabwe it was found that agricultural output declined by nearly 50% in HIV-affected households. In Kenya, it was found that poor households in rural areas do not recover quickly when the head of household die resulting in reduced crop production and income (UN, 2004).

Other studies done in some of the most affected countries in Africa showed that slow growth in agricultural productivity and the overall economy resulted in growing food insecurity. For example, in Tanzania, grain production in 2010 was projected to be 34% less than the amount needed. Food insecurity can heighten susceptibility to HIV exposure and infection and, for people living with HIV/AIDS; illness can be worsened by poor nutrition (Barnett and Whiteside, 2006).

2.3.8. Impact on the Macro economy

The impact on economic growth of HIV/AIDS is a critical area to examine, yet difficult to measure. Economic growth is tied to job creation, higher living standards, and the resources governments have available—all of which have implications for overall development. Studies in this area have also looked at broader social development and welfare factors, such as human capital to assess the potential impacts.

Most recent studies have indicated that AIDS has had some impact on the economic growth of some of the worst-affected countries. The findings were that their gross domestic product (GDP) grew more slowly than it would have without AIDS. A preliminary analysis of South Africa's economy indicated that the country's GDP could be 17 % lower by 2010. A study in Botswana indicated that the country's economy could be 24 - 38 % smaller by 2021 (World Bank, 2006; Casale and Whiteside, 2006 and UN, 2007).

2.4. Antiretroviral Therapy Program

Antiretroviral therapy began in the late 1980's with the introduction of the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (AZT). The benefits were shown in patients with late disease but were not sustained due to development of resistance. In the early 1990's more drugs in the same class became available, and combination therapy with two agents was shown to be more effective than monotherapy. Although the dual therapy resulted in a longer duration of benefit, resistance developed within a few years (Dennill and Roberts, 2005).

In 1996, a powerful new class of ARV drugs, the protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) were developed. When these were combined with two nucleoside reverse transcriptase inhibitors (NRTIs), viral replication was completely suppressed and mutations that led to drug resistance did not occur. Hence, the new treatment strategy was adopted which use ARVs in combinations of at least three drugs from two different classes with the goal to decrease the amount of HIV in the body as much as possible for as long as possible. This type of treatment is known as Highly Active Antiretroviral Therapy or HAART (MOH, 2007).

Globally, antiretroviral therapy program shows that at present there are an estimated 38.6million people living with HIV infection, including 6.8million who need antiretroviral therapy (ART); of these, 1.65million (24%) were receiving ART but with great regional disparities: 5% in North Africa, 13% in Eastern Europe, and 65% in Latin America (Bartlett, 2006). By the end of 2007, the number of people estimated to be in need of ART, were 9.7 million and only 3.0 million were receiving ART globally (WHO, 2008).

In developed countries, anti-retroviral treatment has been shown to be effective in reducing morbidity and mortality in patients infected with HIV/AIDS. In sub-Saharan Africa where 25.8 million are HIV-infected, only 17% of those in need of ART were using treatment by the end of 2005, (UNAIDS, 2006). However, by the end of 2007, the estimated number of people in need of ART increased to 7.0 million and only 2.1 million were on ART program. Similarly, in South Africa, the people in need of ART were 1.7 million and only 460, 000 were receiving ART (UNAIDS/WHO, 2008).

In Zambia, the government's national antiretroviral therapy programme began in 2002 with 2 pilot sites at University Teaching Hospital and Ndola Central Hospital. As of March, 2005, 54 government and mission health facilities in Zambia, were offering ART in the country. In September, 2005, there were close to 110 sites providing ART across the country.

At the end of 2004, the Central Board of Health reported that 15, 328 Zambians were receiving ART, mostly through the public sector. By November, 2005, 43,964 people were receiving ART in Zambia in the public sector with an estimated additional 2,000 accessing treatment through private-sector sources. Some companies, such as the Konkola Copper Mines, also provided ART to their employees at a subsidized rate (WHO, 2005).

2.5. Antiretroviral Therapy Scale-up and HIV/AIDS Care

According to the UNAIDS report of the General Assembly of the United Nations, held in March, 2006, the world leaders acknowledged the dire need to scale-up HIV/AIDS strategies in its own right to prevent the suffering of individuals, and to alleviate the impact of AIDS and address the spiraling costs of HIV treatment. A great emphasize was made on the importance of HIV/AIDS prevention, treatment, care and support of vulnerable persons infected by the HIV virus. Leaders of the member states realized the importance of a renewed emphasize on scaling up HIV strategies and took it as a critical need globally.

Worldwide, it was estimated that between 250,000 and 350,000 deaths were averted in 2005 as a result of increased treatment access (UNAIDS, 2006). Although access to antiretroviral treatment has increased dramatically since December 2003 in low- and middle-income countries, only 31% of people living with HIV/AIDS in need of ARVS were estimated to be receiving treatment as of December, 2007 (UNAIDS/WHO, 2008).

A study done in Thailand, on a scale-up of HAART, revealed an increase of patients' enrollment for ART from 1200 in 2001 to 99,220 by June 2006. Data were reported for 746 hospitals with 42,135 patients and a median follow-up of 7.7months. The median age of patients was 34 years and the median CD4 cell

count at baseline of 46 cells/ μ l. The conclusion was that the scale-up was rapid and successful; most patients stay on their original ART regimen; and AIDS mortality is significantly reduced (Bartlett, 2006).

One of the first study of CEA based on primary costs, to estimate the cost-effectiveness of comprehensive HIV care including ART done in South Africa, revealed that decisions to scale-up ART across sub-Saharan Africa, have been made in the absence of incremental lifetime costs and cost-effectiveness data which seriously limits attempts to secure funds at the global level for HIV treatment or to set priorities at the country level (Clearly et al., 2006).

In Zambia so far, there are notable successes in scaling up ARV treatment national wide. The government has involved faith-based organizations, civil society and NGOs, and has also entered into a partnership with the private sector to administer some of the treatment. In the quest to improve access to ARV treatment, the government introduced the free ARV policy in mid 2005.

In addition to that, the government managed to scale up the ART program through the expansion of voluntary counseling and testing (VCT) centers and antiretroviral therapy centers countrywide. VCT sites are an entry points into other HIV intervention programmes such as TB, STI, PMTC, Future Vaccine trials and HAART administration (MOH, 2006). Currently, by the end of 2007, 46% of the 330,000 people needing ARV treatment were receiving it. Furthermore, the HIV prevalence rate has reduced from 15.6 in 2002 to 14.3 in 2007 (ZDHS, 2001/2002 and 2007).

2.6. Financing and Priority Setting for HIV/AIDS

Worldwide, financial resources for addressing HIV/AIDS in low- and middle-income countries have increased notably over time, but a significant resource gap remains. From UNAIDS' launch in 1996 until 2005, available annual funding for the response to AIDS in low- and middle-income countries increased 28-fold, from US\$ 300 million to US\$ 8.3 billion. Existing pledges, commitments and trends suggest the rate of increase may be declining and that available funds will be US\$ 8.9 billion in 2006 and US\$ 10 billion in 2007. Those amounts will be far short of meeting the estimated requirements of US\$ 14.9 billion in 2006, US\$ 18.1 billion in 2007 and US\$ 22.1 billion in 2008. Looking beyond 2007, an effective response will depend on sustained growth in annual funding until the epidemic is stopped and reversed (UNAIDS, 2005).

In Zambia, the provision of free treatment started in June, 2004 and this was made possible by an unprecedented amount of funding from the Global Fund; in 2004 it committed US\$ 254 million over 5 years (up to 2009). Zambia is one of the most highly funded focus countries, receiving US\$ 149 million

in 2006 alone and other sources. The delivery of the programmes relies on the involvement of many NGOs, churches and communities (UNAIDS, 2008).

In the donor community, governmental and NGOs accounting, expenditures on prevention and treatment compete with one another within the same budget. Despite of the large international aid flows for HIV/AIDS, the needs for prevention and treatment in low-income countries outstrip the resources available because these countries face myriad of health and other development needs and can least afford both large-scale HIV prevention and treatment strategies. Therefore, the governments of these countries are forced to prioritize their HIV program allocations (Stone, 2007).

However, in Zambia, currently, one of the major successes in its response to HIV epidemic is credited to its coordination mechanism of the national response to HIV/AIDS by the National AIDS Council (NAC) with cooperating partners. Because of clarity in coordination and division of labor, Zambia has attracted steady inflows of funds from various sources at home and abroad. The Global Fund channels funding are through four institutions known as Principal Receipts. These are Ministry of Finance and National Guidance and Planning, Ministry of Health, Churches Health Association of Zambia (CHAZ) and Zambia National AIDS Network (ZNAN) (Mwiinga, 2008).

2.7 Costs and Affordability of HAART

At the beginning of the 21st century, very few people in the developing world had access to HIV treatment. This was in large part because of the very high prices of ARVs drugs and the international patents that stopped them from being manufactured at cheaper prices. In 2001 drug manufactures in developing countries began to produce generic drugs under special terms in international trade law (WHO, 2006).

In Africa, Asia, and South America, where 90% of people with HIV/AIDS live, access to HAART was limited largely because of the costs of ARVs regimens. State leaders noted that there was further need for price declines in order to sustain and expand treatment access initiatives (Sherpard, 2006; Dabis, 2005 and Yazdanpanah, 2004). In sub-Saharan Africa, countries including Kenya and South Africa passed bills that made it legal for them to purchase generic drugs abroad. The vast reduction in price made possible by manufacturing of generic drugs led to expansion of treatment on a globe scale (WHO, 2008).

The falling prices of proprietary drugs, the increasing availability of generic formulations has been made possible through the launch of initiatives by international agencies, including the World Health Organization's (WHO's) "3 by 5" programme, the Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR). Pharmaceutical companies also reduced the prices of some ARV drugs for

developing countries by up to 90%. This has enabled some countries in sub-Saharan Africa to initiate HIV/AIDS treatment programs (Bartlett, 2007).

In high-income countries, the cost of HAART ranges from US\$10,000 to US\$15, 000 per patient per year. Compared to many drugs on the market, HAART is perceived to be very expensive. A study done by Yazdanpanah et al. (2002) revealed that for HIV disease the cost of care per person-year has increased over time, especially for patients in the early stages of the disease. Because of this increased costs in the early stages, and longer patient survival, the total lifetime costs of HIV disease are increasing.

In low-income countries, although there is evidence of feasibility and efficacy, HAART regimen is not widely accessible partly because of social, logistics, and overwhelming costs barriers. At more than US\$ 10,000 per patient-year, treatment was clearly unaffordable. However, the efforts of treatment activists, combined with the increased availability of generic combinations, this led to multinational pharmaceutical manufactures to lower the prices of their medications in the low-income countries. The antiretroviral therapy formulations started costing as low as US\$350 per person-year (Hogg et al., 1998).

The cost of making HAART available remains extremely high, and exceeds the per capita national health expenditures in many countries. In addition to the drug costs, the provision of treatment to patients living with HIV in the low-income countries involves other major expenses, such as those of sustaining health care structures, laboratory facilities, health care technologies and distribution channels. These countries with limited financial resources cannot afford these costs, which must therefore be met, at least in part, by high-income countries (UNAIDS, 2006).

Without a cure or the availability of a viable vaccine, the HIV/AIDS pandemic will have claimed a total of 65 million lives by 2020 (NetAid, 1999 – 2007). Current estimates show that the rate is increasing in every part of the globe, including the United States of America. Despite advances in treatment, most people with HIV/AIDS can't afford medicine or healthcare, speeding the impact of the disease. Through the Millennium Development Goals, the international community pledged to halt or reverse the spread of HIV/AIDS by 2015 (UNAIDS, 2006).

The literature review has brought out key issues and challenges faced by governments, especially those in the developing countries, in the HIV/AIDS, prevention, treatment and care. The overwhelming challenge is that HAART intervention is very expensive, hard to access, and requires more cost-effective strategies to address the global health crisis. In addition to that the literature review has also shown the integral role of CEA in policy-decision making in the health systems and the urgent need to address the stated issues and challenges in order to strengthen the whole spectrums of health systems through collaborative

approach to achieve the millennium development goals. However, numerous efforts are being made to reach universal access of HAART intervention to HIV infected people globally.

CHAPTER THREE

3. RESEARCH METHODOLOGY

3.1 Perspective Analysis

This economic study undertook both cost-utility and cost-effectiveness analyses (CUA/CEA) framework from the provider's perspective, Ministry of Health (MOH), which incurs direct costs on HIV healthcare utilization by HIV/AIDS infected people. This framework is useful from a budgeting point of view because it can calculate the cost per life years (LYs) gained with the disability.

3.2 Economic Evaluation

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences and is concerned with choices. Economic evaluations use commonly accepted methodology to establish the costs and the outcomes of different courses of action, in order to provide clarity to the decision-making process. Economic evaluations of health interventions use common outcome measures that have only one dimension; life years (LYs) gained with a disability, taking into account the remaining life expectancy at the point of each averted death (Drummond et al., 2007).

3.2.1 Cost-Utility Analysis (CUA)

The cost-utility analysis (CUA) is a specialized form of the cost-effectiveness analysis (CEA). These terms (CUA/CEA) in this study will be used interchangeably. The cost-utility analysis is a far more appropriate form of economic evaluation when comparing No-ART to ART. It uses a multi-dimensional outcome measure, quality-adjusted life years (QALYs), and can capture the different effects of No-ART and ART in terms of both quantity and quality of life.

3.2.2 Cost-Effectiveness Analysis (CEA)

Cost-effectiveness analysis (CEA) is a type of economic evaluation that examines both costs and health outcomes of alternative strategies. CEA compares the cost of an intervention to its effectiveness as measured in natural health outcomes (years of life saved). Therefore, in economic evaluation of ART, one is concerned with the costs over a patient's entire lifetime on ART, and also the effectiveness of the intervention in terms of the average life expectancy and the quality of life lived with the disability. CEA results are presented in cost-effectiveness ratio, which expresses cost per health outcome (cost per life year gained) (Denil et al., 2008).

3.2.3 Importance of Cost-effectiveness analysis

CEA is a tool that provides the clearest simple way to promote 'value for money' in health as it compares the cost of an activity, termed an 'intervention' with the known or expected health gain. CEA is important because decision makers are often faced with the challenges of resource allocation which are scarce and must be allocated judiciously. Decision makers constantly face resource constraints in HAART intervention, therefore, it is particularly important that they know if there are less expensive ways ('alternatives') by which infected people can benefit from ARVs (Canning, 2006).

Making choices is a necessity in any life situation where resources are limited, and this includes health systems. The best choice dictated by economic circumstances of poor resources and budget constraints, is to find the most efficient combination of resources and to use each resources in the most efficient way. CEA has a strong point in priority-setting process of strategic planning in health-care and can be used in responding to HIV/AIDS epidemic by making known to decision-makers the costs and consequences of initiatives proposed in HIV/AIDS interventions. This would make possible the best use of scarce resources (Drummond et al., 2007).

In medicine or public health, there is always a status quo for drugs, treatments or policies even if it means 'doing nothing'. The status quo and new drugs, treatments or policies are substitutable. Thus we have to compare these two alternatives and discuss which is better from the view point of cost-effectiveness (Ohkusa and Sugawar, 2006). In this study the status quo was treatment of opportunistic infections and HIV related diseases with No-ART and the new treatment was use of HAART to HIV-infected people.

3.2.4 Costs in Economic Evaluation

Costs - refer to the resource expended for the intervention, usually measured in monetary terms such as dollars or pounds. On the cost side, economic evaluations include all recurrent and capital costs required to deliver an intervention. Costing can be done from a number of different perspectives (such as society, or health system) and depending on the perspective chosen, different categories of costs are included. In societal perspective, costs would include to the health system and to the patient (e.g. patient waiting time and travel costs). In health system perspective, all direct costs are considered including the opportunity costs of the alternative intervention (Drummond et al., 2005).

Opportunity cost - refers to the economic cost of an intervention: the value of the next best opportunity foregone. Choices must be made between desirable yet mutually exclusive actions. It expresses the basic relationship between scarcity and choice. The opportunity cost of an activity is an element in ensuring that scarce resources are used efficiently and the cost is weighed against the value of the activity.

3.3 Research Design

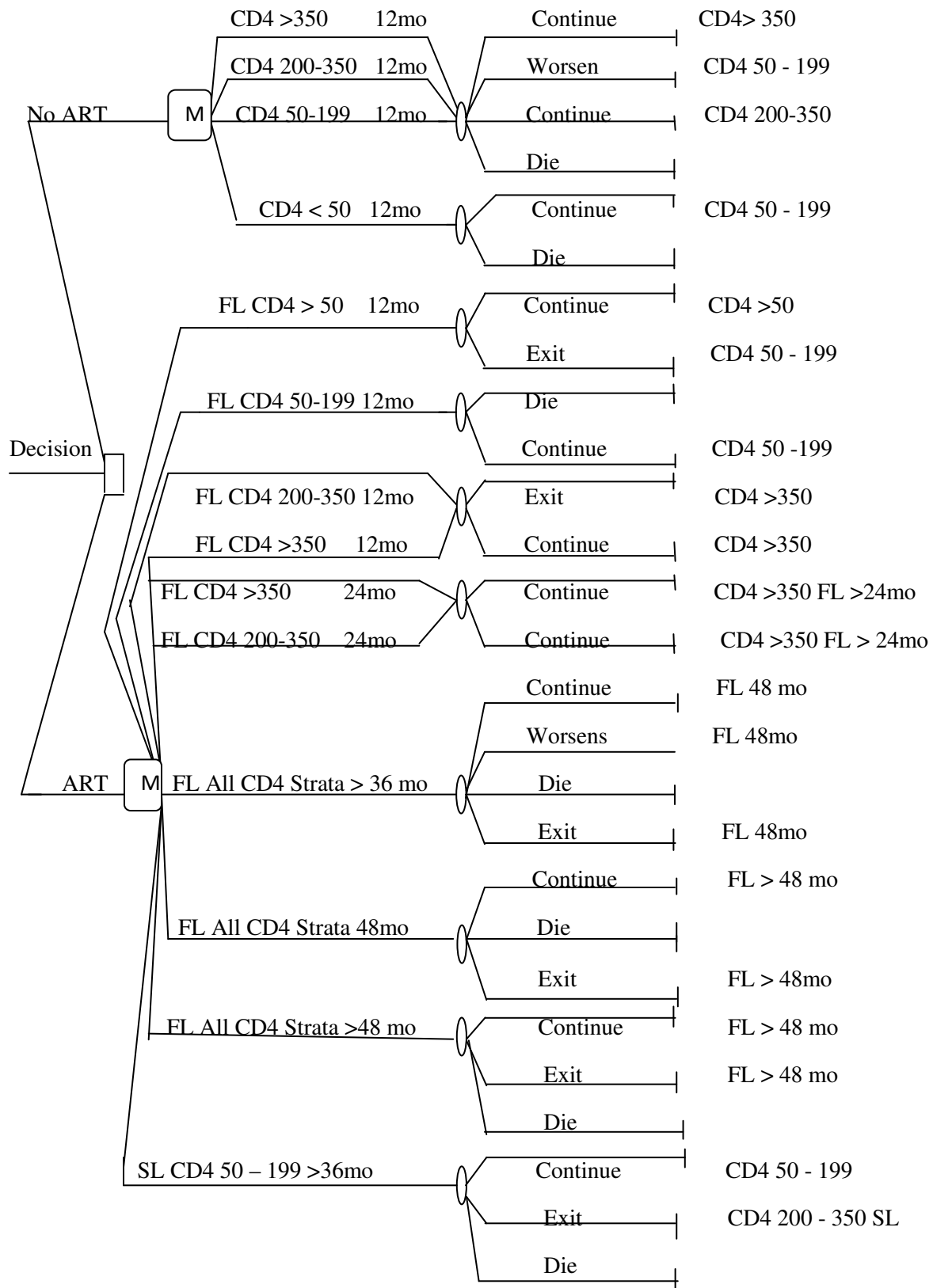
Use and cost of healthcare utilization by HIV/AIDS infected adults was determined by a retrospective cohort application of **pre-treatment** (Pre-ART) and **treatment** (ART) **person-time observation** study design. This means that ART patients were used as their own control, i.e. the pre-ART period, was used to calculate No-ART utilization of health services and the ART period, the time when the patient was initiated on ARVs to the time-period of the study. The time of enrollment of a patient in the service to initiation of ART permitted evaluation of use and costs effects and health outcomes of No-ART and in the ART period respectively. However, all individuals assigned to the **pre-treatment person-time observation**, they subsequently received ART. This study design was based on the following criteria:

1. Cohort Simulation based on CEA approach using the Markov Modeling to calculate life time costs and health effects of ART versus No-ART intervention.
2. CEA was done on a five year No-ART and ART cohort exposure of HIV/AIDS infected adults aged 15 and above.
3. Valid effectiveness data used in Markov Modeling was from:
 - Primary data from ART facility over the five year period of 2004 – 2008.
 - Key informants were clinicians whose selection was based on their more than five years experience of management of HIV/AIDS infected persons.






3.4 Markov Modeling for HIV/AIDS

The Markov modeling approach was based on four health states defined by the four CD4 cell count categories: <50, 50 – 199, 200 – 350 and > 350 cells/ μ l and WHO clinical stages 1, 2, 3 and 4, with death being 0. This was used to extrapolate data used to calculate lifetime costs and life years gained with a disability as shown in figure 1.

Figure 1: Application of Markov Model Decision Tree - ART vs. No-ART



Legend for Markov Decision Tree

1. The Decision node represented by a square  is a point where the clinician has to make a decision.
2. After the Decision node, cohort members are randomized into one of the two Markov nodes  labeled ART or No-ART in the diagram.
3. The lines — to the right of the Markov nodes depict the full set of Markov states in each model. Once patients have been randomized into ART or No-ART, all patients start in a Markov state reflecting any of the CD4 count strata as a baseline. The lines emanating from the Markov states describe the possible transitions in the model.
4. Chance node  is a point where the clinician must wait to see the outcome.
5. Terminal lines  and sometimes nodes  are used, to represent subsequent prognosis for a particular combination of patient characteristics and events. There are various ways in which a decision analyst can assign values to these terminal nodes/lines as outcome measures such as life years (LYs) gained. In this study the researcher used QALYs measure.
6. FL – First Line ARV
7. SL – Second Line ARVs.

3.5 Transition Probabilities in Markov Model

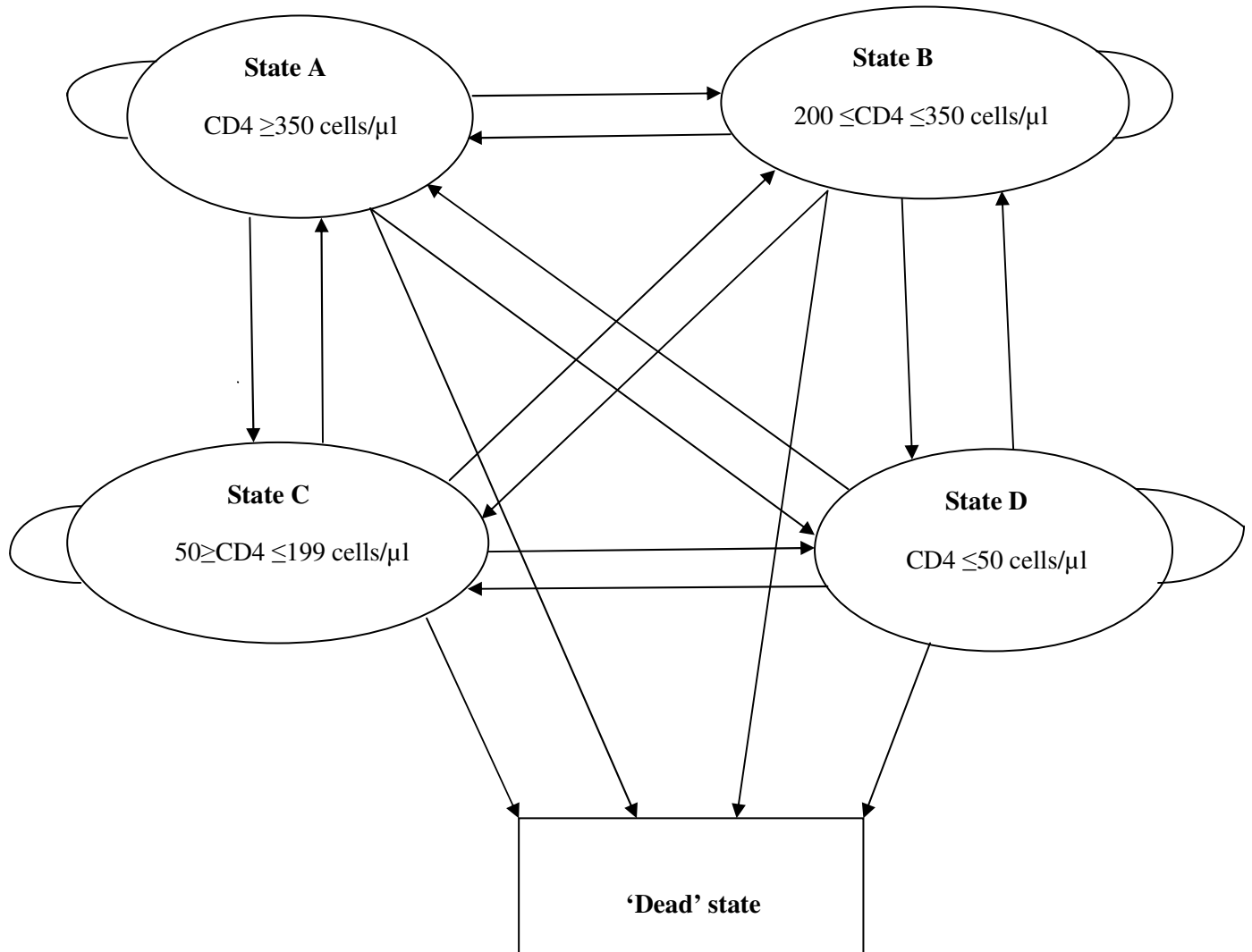
Transition probabilities in a Markov model defined all relevant movements between Markov health states and were calculated from transition rates (i.e. the number of occurrences of an event for a given number of patients per unit). Transition probabilities between Markov states determined the speed at which the cohort moved through the model towards the absorbing state ‘Dead’ which is death and were the basis of the of the calculation of cost-effectiveness in the interventions.

3.6 Markov Health States

The Markov model was based on a four health states that a patient occupied at a given point in time. Time elapsed explicitly with a Markov model and the probability of a patient occupying a given state was assessed over a series of discrete time periods, called cycles. In this study the time horizon of the model was divided into equal cycles which had a length of 12 months. This length of time was chosen because it

represented a clinically meaningful time interval. All patients assigned to a given state incurred similar economic costs and QALYs.

Figure 2: Markov Model Health States in HIV/AIDS cohort.



Definition of Markov Health States

- State A – represents the healthiest patients with relatively high CD4 counts: ≥ 350 cells/ μ l.
- State B – patients have relatively lower CD4 counts: $200 \leq \text{CD4} \leq 350$ cells/ μ l.
- State C – patients have CD4 counts: $50 \geq \text{CD4} \leq 199$ cells/ μ l and are/or progressing to AIDS.
- State D – patients have very low CD4 counts: ≤ 50 cells/ μ l and mostly have AIDS.
- 'Dead' State – this is an absorbing state of the patient where the patient dies.
- The arrows in the model show how patients progressed through the model health states.

3.7 Costing Methodology

This study interest was exclusively on incremental costs of the comparator (No-ART) and the new intervention therapy (ART), i.e. costs associated with intervention requirements that were not typically already included in the government's health budget. Certain costs were excluded since they would have been incurred whether an ART intervention existed or not.

3.7.1. Inclusion Criteria

1. Recurrent costs - These were variable costs that reoccurred throughout the costing procedure and the success of the intervention critically depends on the availability of these items such as drugs, salaries, supplies (syringes, x-ray films, stationary, etc) and training these were included.

2. Exchange rates – These were determined in order to facilitate a more meaningful comparison across regions and industrialized countries. Prices in local units (Zambian Kwacha), were converted to US\$ using the average exchange rates for the years under study (2004 – 2008).

3. Incremental Cost-effectiveness Ratio

By switching from a current level of one health intervention strategy to another new strategy, a new (and incremental) health outcome is obtained; the CEA ratio is considered as the 'price' incurred by making this change in strategy. In this study, the incremental cost-effectiveness ratio (ICER), through the use of ART versus No-ART intervention was calculated using the following simple equation:

Formula:

$$\text{ICER} = \frac{C_1 - C_0}{E_1 - E_0} = \frac{\Delta C}{\Delta E}$$

- No-ART denoted by **C₀**
- ART denoted by **C₁**.
- Health outcome effects of two therapies are denoted by **E₀** and **E₁**.
- **ICER** is the change in C divided by change in E.

4. Health Effects Measure

Cost-effectiveness analysis in policy for medicine or public health evaluates life and its quality; quality of life (QOL), numerically. QOL measures severity of illness or disability which defines death as zero and perfect health as one. The most commonly used health outcome measure is quality-adjusted life years

(QALYs). This is the summary measure that represents an implicit trade-off between quantity for quality of health in a fairly transparent and consistent way and attempts to combine the value of the health effects attributes into a single index number (O’Brien, 1994; Ohkusa and Sugawara, 2006). Moreover, QALYs measures the ‘usefulness’ or utility of a particular health state and the length of life lived under that state.

Quality-adjusted life years (QALYs)

QALYs, is the health summary measure used in this study and it was determined by use of Euro Quality of life (Euroqol) scores referred to as EQ – 5D. The scores were calculated by subtracting the relevant coefficients from 1.000. The constant term used for dysfunction was 0.081. In this study, the dysfunction was HIV infection.

EQ-5D Scoring Formula

Table 2.

Coefficient for Time Trade Off (TTO) tariffs

Dimension	Coefficient
Full health	1.000
Constant	0.081
Mobility	
Level 2	0.069
Level 3	0.314
Self-care	
Level 2	0.104
Level 3	0.214
Usual activity	
Level 2	0.036
Level 3	0.094
Pain/discomfort	
Level 2	0.123
Level 3	0.386
Anxiety/depression	
Level 2	0.071

Level 3	0.236
N3	0.269

The classification of system of EQ-5D has three level dimensions (level 1 to 3) and five attributes defining possible health outcomes which are: mobility, self-care, usual activity, pain/discomfort, anxiety/depression. The full health state coefficient is 1.000. The constant dimension is the term used if there is any dysfunction at all and it is 0.081. The N3 is a term used if any dimension is at level three e.g. if the estimated value for a patient's health state is estimated at the value of 11223, then the utility function is 0.255. Drummond et al. (151, 156, 163:2007).

3.7.2 Exclusion Criteria

1. Capital costs - These are fixed costs that do not vary with the intervention size and are allocated across various interventions being carried out under the given scenario and these are:

- Buildings,
- Equipment,
- Vehicles

2. Amortized capital costs - These are costs of construction and ongoing maintenance, they were also excluded since these costs generally would not be incremental because they are already part of Zambia's existing health budget allocation.

3. Overhead costs - These were not considered because the inputs needed to produce the interventions (ART and No-ART) were shared with the production of other interventions and were not incremental.

3.8 Study Setting

Choma ART center is established within the hospital buildings and provides easy accessibility to patients who are referred for admission for TB treatment and other HIV-related diseases. This center has been in operation since 2004 to date and patients are also referred to the hospital ART center from urban and rural health centers. The ART center (out-patient utilization) provides treatment and prophylaxis of HIV-related and opportunistic infections and counseling (VCT) services. Severely ill patients are referred to the wards for in-patient utilization.

The ART centre is run by qualified staff trained in HIV/AIDS management of patients. The staff includes Doctors, Clinical Officers, Nurse/Midwives and counselors. The clinic runs from Monday to Thursday, starting from 08.00 to 12.30hrs and 14.00 to 15.00hrs.

3.9 Study Population

The study population was HIV/AIDS infected adult persons enrolled at the ART center, aged 15 years and above. This group was sampled because it is the economically productive and sexually active in whom HIV infection is highly prevalent. The following table is an overview of enrollment and eligibility of patients (adults) at the ART center between 2004 and 2008:

Table 3: Patients Enrolled and Eligible for ART (2004 -2008)

Year	Male	Female	Total
2004	57	71	128
2005	142	221	363
2006	260	401	661
2007	337	588	925
2008	449	756	1, 205
Totals	1, 245	2, 037	3, 282

Source: ART Center – Choma General Hospital Records (2008)

3.10 Calculation of Sample Size

The researcher calculated the sample size from the enrolled ART population by using the following:

$$\text{Formula: } n = \frac{t^2 \times p \times q}{d^2}$$

Where: n = first estimate of sample size

t = confidence (for 95% - 1.96 was used)

d = precision (0.05 was used)

p = proportion of the target population with the characteristics being measured:

HIV/AIDS prevalence rate in Choma is 16%

$$q = 1 - p$$

$$\text{Calculation: } n = \frac{1.96^2 \times 0.16 \times 0.84}{0.05^2}$$

$$\begin{aligned}
& 0.05^2 \\
& = \frac{3.8416 \times 0.16 \times 0.84}{0.0025} = \frac{0.51631104}{0.0025} \\
& = 206.52 \qquad \qquad \qquad = \mathbf{207}
\end{aligned}$$

The sample size was **207**, the percentage of males and females was calculated from the total enrolled patients for the study period and this came to 38% (79) for males and 62% (128) females of 207. The proportion of males and females for each individual year under study was calculated.

3.11 Sampling Technique

Simple random sampling technique was employed and this gave an equal chance for each file to be selected:

- Enrollment registers for the study period were used to compile a list of all file numbers.
- A numerical number sequence was assigned to each one of them.
- The file numbers were then randomly selected using statistical random numbers according to the calculated proportions for both males and females for each individual year of the period of study.

3.12 Data Collecting Tools and Techniques

The researcher used the following instruments to collect data:

Check list:

- to review patient's records in the files.
- to review records in the pharmacy, laboratory, radiology and accounts to ascertain recurrent costs.

Questionnaire:

- a semi - structured interview questionnaire translated into Tonga (the ethnic language in the district) was used to interview the respondents in order to determine their quality of life with the HIV disability.

Questions for discussion with Key Informants:

- a list of six questions for discussion with six key informants was compiled.

3.13 Pilot Study

The pilot study was conducted at Shampande health urban ART center in order to test the validity and reliability of the questionnaire instrument. 10 subjects were used for the pilot study and these were not included in the main study.

3.14 Data collection/field activities

Five research assistants were engaged, trained and collected data after approval to proceed by UNZA Ethics Committee. Data collection was done within a period of three months after the pilot study. Patient's records were reviewed from the randomly sampled files. A purposive sub-sample of 95 randomly sampled files was selected based on their clinical appointments that were within the study period. Subsequently, as the listed patients came for their reviews, a structured interview schedule questionnaire was administered to them directly to determine their quality of life with the HIV disability. This was done in order to supplement the reviewed data of the cohort in their files. Those who were not met during their clinical appointments, follow-ups were done to their residence using their contact addresses.

3.15 Data processing and analysis

Data was screened to ensure consistency and completeness whilst in the field and there after was entered into computer in Excel spread-sheet template where recurrent costs were tabulated after calculation of the exchange rate for each particular year of study. There after data was entered in the Cost Model template in line with WHO CostIt Intervention Software Template (2007). Transition probabilities between health states were calculated in Excel and tabulated per year giving a total of ≤ 1 .

3.16 Ethical Consideration

Approval to conduct the study was sought from the Research Ethics Committee of the University of Zambia. Authorization to conduct this study at Choma General Hospital ART center and hospital level was obtained from the Ministry of Health and the Executive Director of the hospital. Written consents were obtained from the patients after explaining to them about the study and the benefits. They were further informed that their participation in the study was voluntary and they could refuse if they felt that they were not ready. No names were written on the questionnaires in order to maintain anonymity of the subjects and the collected data was kept as confidential as possible.

CHAPTER FOUR

4. RESULTS

The data presented in this study was obtained from the record reviews of 207 randomly selected files and the sub-sample of 95 of a semi structured questionnaire administered to the patients to determine their quality of life with the disability which was compared with the reviewed data in the files. Data was also obtained from six key informants of Choma General Hospital and ART center. The data has been presented as:

Section A – Transition probabilities of ART and No-ART.

Section B – Rating of quality of life of No-ART and ART cohort using Euro Quality of life (EQ – 5D).

Section C – Cost-Effectiveness Analyses (CEA) results.

Section D – Life – Time Cost and Life Years gained.

Section E – Matrix for Qualitative data obtained from key informants.

4.1 Section A: Transition Probabilities of ART and No-ART Cohort

Table 4:

Stage transition	No-ART	ART
I - II	0.3316	0.2427
II - III	0.22316	0.1220
III - IV	0.1669	0.1358
II - IV	0.1874	0.0714
I - IV	0.24917	0.1239
I - V	0.0678	0.0125
III - V	0.1169	0.0906
II - V	0.15613	0.00001
IV - V	0.1874	0.0801

Table 4 shows transition probabilities of patients on ART and No-ART. The transition probabilities of patients with No-ART, moving from stage 1 – 4 was 0.24917 and in ART it was 0.1239. Similarly, the

transition probability of patients with No-ART, moving from stage 1 – 5 was 0.0678, higher than in ART and that was only 0.0125.

Table 4, further reveals that patients in stage II, on No-ART moved to severe stage IV with the probability of 0.1874 than those in ART with less probability of 0.0714. The same patients in stage II, in No-ART move to stage V with the probability of 0.15613, more than those in ART whose probability was 0.00001. In stage III – IV, the transition probability of No-ART was 0.1169 and in ART was 0.0906. In stage IV – V, in No- ART, the probability was 0.1874 and in ART, it was 0.0801.

4.2 Section B: Euro Quality of life (EQ – 5D) Health Status Rating

In Pre- ART and ART period (No-ART and ART cohort)

Table 5:

CD4+ Count Stage	Health Status Rating
1 - >350 cells/μl	0.847239
2 - 200 – 350 cells/μl.	0.73288
3 - 50 – 199 cells/μl.	0.568529
4 - <50 cells/μl	0.281107

Table 5 shows that the average rating for asymptomatic patients in stage 1 which was 0.85. In stage 2, 3 and 4, the ratings were 0.73, 0.56 and 0.28 respectively.

4.3 Section C: Cost – Effectiveness Analyses (CEA) Results

Table 6:

Effect (QALYs)			Cost (US\$)		Cost – Effectiveness Ratio	
NO-ART	Mean	Standard Deviation	Mean	Standard Deviation	Delta	ICER
	3,381	850	\$10,166,199	\$271,925	2,692	-
ART	6,073	111	\$12,226,813	\$38,055	2,060,614	765.46

Table 6 shows cost-effectiveness results of No-ART and ART. For No-ART, QALYs were 3,381 and 6,073 for ART, with standard deviations of 850 and 111 respectively. The mean cost of No-ART utilization was \$10, 166,199 and for ART was \$12, 226, 813. The standard deviations of costs are \$271,925 for No-ART and \$38,055 respectively, giving the ICER of \$765.46.

4.4 Section D: Lifetime Costs and Life Years gained

Table 7:

	Lifetime Cost/ patient	LYs gained	QALYs	Cost per LY	Cost per QALY	Incremental Cost/ QALY gained
NO-ART	\$10,166,199	3.25	3,381	\$1,166	\$272	\$765.45
ART	\$12,226,813	8.50	6,073	\$1,223	\$38	

Table 7, shows costs of No-ART and ART per patient per year and per 10 – year period. In No-ART the costs per year per patient were \$1,166 and for ART they were \$1,223. On a 10 - year period for No-ART, the costs were \$10,166,199 and \$12,226,813 for ART. The mean life years gained for patients with No-ART was 3.25 and for ART patients it was 8.50 years.

4.5 Section F: Qualitative Findings from Key Informants

The discussion with key informants comprised of 2 doctors, 3 clinical officers and 1 ART In-Charge who had more than five years experience in managing HIV infected patients with OIs at Choma General Hospital before the era of ART intervention. The information collected from the three categories of key informants has been summarized and tabulated in the matrix.

4.5.1 Matrix: Key Informants Views

NO-ART PERIOD	Doctors	Clinical Officers	ART In Charge
Opportunistic Infections (OIs).	The common OIs patients presented with at the hospital were oral candidiasis, pneumocystis carinii pneumonia (PCP), mycobacterium tuberculosis (TB).	Other OIs were rash mostly due to fungal infection, cryptococcal meningitis, and increased incidences of herpes zoster.	Most of the patients repeatedly visited the hospital with recurrent OIs despite taking prescribed antibiotics such as phenoxymethylpenicillin.

Non ARV drugs	Antibiotics, antifungal tablets and creams were prescribed depending on the type of OIs. In patients suspected to have TB, Anti-TB drugs were prescribed along with multivitamin supplements and analgesics.	Antiviral creams and tablets were prescribed to patients with herpes zoster and analgesics to relieve pain. Laboratory and imaging investigations were done to ascertain the causative organism and diagnose accurately the OIs.	Information, Education, Communication (IEC) was specifically given per individual needs, e.g. adherence on drugs, nutrition, hygiene. The family was involved for physical and emotional support. Referrals for nutrition and community support were done to patients in need.
Quality of Life	Patients were assessed according to their ability to do activities of daily living (ADL) i.e. able to eat, cook, bathing and dressing. Some patients responded for a while to Non ARVs and were able to do ADL normally.	Others despite of taking non ARVs drugs, their health did not improve and continued seeking treatment for OIs and were not able to carry out ADL normally. Most of the time they would be sick and not able to work.	Those with poor nutrition status used to be severely ill and would depend on their families to help them carry out ADL. Most of the time they were in pain and anxious to perform ADL.
In-patient Utilization	There was high in-patient utilization in the medical and TB wards. TB patients were hospitalized for a longer period. Cryptococcal meningitis was very common. There was a high incidence of morbidity and mortality in the wards.	Other patients would be admitted for severe bacterial and fungal OIs. The hospital was spending more on consumables for various investigations coupled with costs of drugs and a high number of patients.	The increase of patients in medical and TB wards lead to inadequate bed space. Usually there were problems of staffing in the wards, i.e. one qualified staff to ten patients.
ART PERIOD			
ARV drugs	Patients initiated on ARVs with CD4 count >350 cells/ μ l responds rapidly than those with CD4 count of <50 cells/ μ l. Laboratory, imaging and ultrasound investigations are done to know the patients' CD4 count and to rule out OIs.	50% of patients on ARVs experience minor side effects. Others, moderate, and are put on alternative 1 st line ARVs. Based on our clinical experience we've noticed that most patients stay on 1 st line ARVs and very few ends on 2 nd line drugs.	Issues of adherence to ARVs drugs are critical and therefore measures are put in place such as adherence sessions at each return visit the patient makes to avoid drug resistance. Emotional and physical stability plays an integral part in cost-effectiveness of use ARVs drugs.

Opportunistic Infections (OIs).	ARVs drugs are used along with Non ARVs drugs to minimize reoccurrence of OIs such as PCP and Co-trimoxazole is a drug of choice. Amphotericin B and Fluconazole are used as prophylaxis drugs for cryptococcal meningitis.	Co-trimoxazole is a Non ARV drug and is given to patients with CD4 count <650cells/ μ l. It is continued until CD4 count is above 650. Besides that patients are prescribed antibiotics such as Amoxycillin whenever they have OIs in spite of being on ARVs. If the OIs are of fungal infection, antifungal drugs are prescribed.	IEC is continuously given on importance of completing the course and side effects of drugs to avoid drug resistance and to promote patients' well being. Referrals are done for nutrition and community support. Family support is encouraged because patients are on both Non ARVs and ARVs. Measures are put in place to trace defaulters using locater maps and their phone numbers.
Quality of Life	Patients are assessed according to WHO clinical staging (I, II, III and IV). This staging helps to assess the patients' mobility, self-care, performing usual activities such as work, study/leisure. Their emotional status is assessed to know if they are anxious, depressed or in pain. Patients in stage I are usually healthy.	In addition to that patients' status is assessed on every return visit if they are healthy, able to work, /sick, able to work, sick, unable to work. Bedridden, or deceased, This helps to determine their quality of life according to WHO clinical staging. Patients in stage I are healthy and able to work but in stage II, III, IV are usually sick.	Patients in WHO clinical stage I and II responds quickly to ARVs drugs and relatively remain health, able to work. Others in stage II with an increase in CD4 count (>350 cells/ μ l) move to stage I and stay in this health state for a number of health cycles. Stage III and IV, the severe stages may slowly respond or deteriorate to stage V.
In -patient Utilization	This has reduced greatly with low morbidity and mortality rates. The OIs, Cryptococcal meningitis is very rare. TB incidences are reducing and hence fewer patients in the medical wards.	Most patients tend to have fewer and minor OIs which do not require in-patient utilization, especially those patients with good adherence to the drugs (No ARVs and ARVs).	There are fewer admissions with reasonable number of patients in the wards because of use of ART intervention. A lot more patients are health, able to work and maintain their clinical visits.

The matrix shows convergent views of clinicians about the No – ART and ART period. The key informants discussed and analyzed the OIs, use of Non – ARVs and ARVs drugs, quality of life and in-patient utilization in both interventions. The clinicians stated that the common OIs in Zambia are oral candidiasis, mycobacterium tuberculosis, rash, cryptococcal meningitis, pneumocystis carinii pneumonia.

They discussed drugs used for curative of the mentioned OIs according to types: antibiotics, antifungal, ant TB, antiviral, simple analgesics and multivitamin supplements. However, they said in the ART utilization, Non ARV drugs are used along with ARVs to minimize the reoccurrences of OIs. They further said that the quality of life in the pre-ART period was assessed by their ability to perform activities of daily living whilst in the ART period this assessed according to WHO staging and CD4 count. In comparison of No-ART to ART utilization, the clinicians outlined the benefits of ART intervention with emphasis on reduced morbidity and mortality and their quality of life.

CHAPTER FIVE

5. DISCUSSION OF RESULTS

This study, employing methods used in similar studies done in industrialized countries and South Africa, provides a unique contemporaneous composition of the use, cost and outcome of No-ART and ART for HIV-infected people. The key finding in this study is the relative effectiveness of ART compared to No-ART in a district setting. The research gives a better indication of the costs of providing ART over a patient's lifetime and also a solid indication of the current costs of treating opportunistic and HIV-related infections for patients who are on No-ART. These findings are essential for budgeting for HAART intervention to the provider, Ministry of Health.

5.1 Challenges and Constraints to the Study

One of the difficulties in comparing patients who receive ART to those who do not is the potential incomparability of cohorts. The study design for the costing undertaken was to use patients as their own control, i.e. observing them in their pre-ART period and ART time-observation; this was partly facilitated by the delay in initiation of ART in the cohort members. This design does however introduce a bias in that there is a survivor effect; the patients who ended up on treatment did not experience the period of increased morbidity prior to ART time-observation.

The study was restricted to one ART center in Choma district, unlike in other studies done were the control group is taken from another facility. Besides that, anticipating the survival benefits of ART has been one of the key uncertainties to date in analyses that have considered the cost-effectiveness of HAART intervention. The main reason for this uncertainty is that the intervention has not existed in a standardized manner for long enough to ascertain what the survival benefit will be.

5.2 Transition Probabilities of the Cohort

The study reveals that transition probabilities of the cohort on ART stage 1 had less transition probabilities to the most severe states. They stayed longer in their relatively health states as compared to those patients on No-ART whose probability from I – IV was 0.24917 whilst in ART it was 0.1239. The study further reveals that patients on ART stage1 had a lower transition probability of 0.0125 to death and in No-ART it was higher, 0.0678.

Patients in stage II, in No-ART moved to severe stage IV more rapidly with the probability of 0.1874 than those in ART with less probability of 0.0714. The same patients in stage II, in No-ART move to stage V with the probability of 0.15613, higher than those in ART whose probability was 0.00001 which

is negligible. In stage III – IV, the transition probability of No-ART was 0.1169 more than in ART which is 0.0906. In stage IV – V, the most severe stage, in No- ART, the probability was 0.1874 and in ART it was 0.0801. Their cycle length which defined the speed at which they moved between the states in this study was 12 months.

These findings concur with the study done by Badri, et al. (2006) in Cape Town, South Africa on when to initiate HAART in sub-Saharan Africa, cost-effectiveness study. The cost-effectiveness analysis was conducted from a public health perspective using primary treatment outcomes and healthcare utilization.

A Markov state-transition model was developed to determine cost-effectiveness of initiating HAART at three CD4 cell count thresholds ($<200/\mu\text{l}$, $200-350/\mu\text{l}$ and $>350/\mu\text{l}$). The results were that patients in stage 1 with CD4 count $>350/\mu\text{l}$, on No-ART had the transition probability to death of 0.001262 with No-AIDS whilst those with AIDS, the transition probability were 0.002225. Patients on HAART with No-AIDS, their transition probability from stage 1 to death were 0.00024 and those with AIDS, the transition probability were 0.00155. This revealed the cost-effectiveness of HAART.

Cleary, et al. (2006) conducted a study on cost-effectiveness of HAART in Khayelitsha town, South Africa based on Markov modeling to determine the cohort transition probabilities in Markov states. The study revealed that transition probability of patients on HAART to death was 0.006 and patients on No-ART were 0.022, higher than ART group. This study also concluded that HAART intervention was cost-effective. The findings of the study on transition probabilities for ART and No-ART cohort are similar to this research study's results shown in table 3.

5.3 Rating of Quality of Life using EQ – 5D

The results on the health-related quality of life assessed based on the utility values between 0 (death) and 1 (full health) in table 4 show that the utility values decline consistently as the disease progresses to severe stages. The most severe stage 4 with AIDS symptoms, the utility value is as low as 0.28. Patients in stage 1 had a higher utility value of 0.85.

Mathews and May (2007) conducted a retrospective analysis study on HIV clinic based cohort (1996 – 2000) in USA. The study analyzed three dependent variables (survival, emergency department visits and hospital discharges of HIV infected patients). The analysis was divided into six month intervals and the aim of the study was to estimate the prognostic value of EQ - 5D for the three dependent variables.

The modeling approach was used for each of the three dependent variables. The CD4 count and viral load were examined jointly to assess adjusted effects of each EQ - 5D health dimension (mobility, self-care,

usual activities, pain/discomfort and anxiety/depression). EQ - 5D instrument was combined with a global rating of current health using a visual analog scale (VAS).

The study results were that the median EQ - 5D VAS scores were 64.5, 70, and 75 for CD4 <50, 50 – 199 and ≥ 200 . For hospital discharge rate outcome the adjusted scores were 0.85 and 0.79. The study concluded that EQ - 5D contributed meaningfully to prognostic information for three important health care outcomes for adults with HIV infection and further concluded that EQ – 5D is a relevant and quantifiable outcome of care.

Jelsma and Maclean (2003) conducted an investigation into the health related quality of life of individuals living with HIV who were receiving HAART. In this study, the utility values were combined with life expectancy estimates to calculate QALYs. The results revealed that at baseline the overall health state value for the cohort was 0.7 and after 12 months on HAART improved to 0.84 utility values. The conclusion was that HAART intervention was cost-effective. The results are similar to this study where the cohort has the highest utility value of 0.85 in their healthiest Markov states.

5.4 Cost-Effectiveness Analysis (CEA) Results

As shown in table 5, the CEA results reveal that the costs of No-ART are \$10,166,199, less than for ART which are \$12,226,813. The health effects in ART are more than in No-ART which are 6,073 and 3,381 respectively. The incremental costs of ART and No-ART were \$2,060,614 and that of QALYs were 2,692. The change in effects and costs gave the incremental cost-effectiveness ratio of \$765.46. The results suggest that ART for treatment of HIV disease offers good value for the resources spent as compared to No-ART.

Badri et al., 2006, conducted a study on AIDS cohort in Cape Town, South Africa. The study aimed at estimating utilization and cost of HIV healthcare and to assess the cost-effectiveness of initiating HAART at different CD4 cell count thresholds (< 200 μ l, 200 – 350 μ l and > 350 μ l) and a No-ART therapy. The incremental cost effectiveness ratio for CD4 count > 350 μ l was 1,148 per life year gained and 1,236 per QALYs gained. The ICER is higher compared to the ICER of this study; probably due to the higher number of the cohort and more in-puts. The study concluded that use of HAART was associated with decreased disease progression, AIDS and death and therefore, it is cost-effective.

In the study done in Khayelitsha, South Africa by Cleary et al. (2006), the results showed incremental cost-effectiveness ratio of US\$1,102 per QALY and US\$984 per life year gained. The ICER of this study is almost within the range of studies undertaken considering that this study had a small sample size.

Rosen and Long (2006) assessed about 15 various studies done in sub-Saharan Africa countries on how much it cost to provide HAART for HIV/AIDS infected people. They stated that so far, the average cost was about US\$850 per patient per year in countries other than in South Africa. In South Africa the cost per patient is US\$1,700 per patient per year. Apparently, this higher cost in South Africa is due to higher in-put prices and more complete in-put costs.

5.5 Life-time Costs of ART versus No – ART

In the Markov simulated cohort of 1000 patients, the estimated total cost of treating the cohort for a period of over 10-years with No-ART was \$10,166,199 and for ART the costs were \$12,226,813 as lifetime costs. This meant that the cost of treating one patient with No-ART per year was \$ 1,166 and with ART was \$1,223. The costs per QALYs gained with No-ART were \$272 and \$38 with ART which was less expensive. This was due to decrease of ART utilization after initiation of the therapy since patients had remarkable reduced incidences of opportunistic infections (Yazdanpanah, 2005).

A study done by Hellinger (1993) in a survey from 10 cities in the US on AIDS's cost and service utilization, comprising a cohort of 1,164 HIV patients, revealed that the estimate life-time costs of treating HIV patients in four stages were about \$119,000 per patient per year. These results are within the range of the study under-taken.

In the study done by Cleary, et al. (2006) on cost-effectiveness of ART in Khayelitsha town, South Africa, the lifetime costs with ART were \$13,694.33 and \$3,307.53 for No-ART. Costs per life year gained with ART were \$1,644.35 and with No-ART were \$1,457.06. The lifetime costs of ART are favorably compared to this study ART lifetime costs although for No-ART they are far less from the study undertaken. Costs per life year gained are relatively higher as compared in this study. The researcher alludes to higher in-puts in the study of the Khayelitsha cohort.

Furthermore, in this study, the mean life years gained with No-ART was 3.25 and 8.50 years with ART. These results are similar to the study done by Clearly, et al. (2006), which revealed that the mean survival for all patients from the time of initiating ART to the time of death was 8.33 and for patients on No-ART was 2.27 years.

5.6 Qualitative Findings from Key Informants

The findings from the clinicians in comparing No-ART to ART reveal the cost-effectiveness of HAART intervention as compared to treating HIV- infected persons with non ARVs drugs. The clinicians' views show that HIV-infected persons on No-ART repeatedly OIs such as TB, oral candidiasis, rash etc. In sub-

Saharan Africa the spectrum of OIs differs from those in industrialized countries. Bacterial diseases are common and can occur at early stages of immune suppression. Cryptococcal disease is a common cause of death and tuberculosis, the most frequent opportunistic infection, is associated with accelerated course of HIV infection (Maartens and Cleary, 2002).

However, HAART intervention has been associated with reduced incidence of tuberculosis and cryptococcal diseases leading to reduced in-patient utilization. A study done by Badri et al. (2006) revealed that the HAART group used fewer in-patient services than the No-ART group. The reduction in use of in-patient services was also observed in studies done in industrialized countries. The researchers concluded that HAART was a more cost-effective way for South African hospitals to treat HIV-related diseases.

The clinicians added on to say that they continue prescribing non ARVs drugs for patients on ART utilization whenever they had OIs such as antibiotics, antifungal, anti-TB drugs. They further stated that all patients with CD4 count $<650\mu\text{l}$ receive prophylaxis of co-trimoxazole on daily basis which help to reduce OIs especially PCP, until their CD4 count is above $650\mu\text{l}$.

Yazdanpanah et al. (2005) conducted a study in Cote d'Ivoire to assess the cost-effectiveness of alternative strategies for initiation of co - trimoxazole in adults with HIV-infection. The study findings were that co – trimoxazole is reasonably cost-effective when initiated in a patient of WHO stage ≥ 2 . Early co – trimoxazole prophylaxis prevents complications prior to ART initiation and should be considered as an essential component of care for early HIV in sub-Saharan.

Lawn et al. (2006) in a study of determinants of mortality and non death losses from an antiretroviral treatment service in South Africa: Implications for program evaluation where patients with CD4 counts <200 cells μl received prophylaxis with daily co-trimoxazole or dapson; the findings were that patients had less disease progression to severity.

In conclusion, the findings from the key informants in comparing No-ART to ART, explicitly shows that HAART intervention is cost-effective and offers better quality of life with the dysfunction of HIV-infection. The intervention reduces in-patient care utilization as evidenced during the time of the study that there was no member of the cohort for in-patient utilization.

5.7 Strengths and Limitations of Study

The study is a valuable contribution to existing work on the lifetime cost of ART and No-ART done in other countries, such as South Africa. The study's interest was incremental cost effectiveness ratio in

comparing the two interventions (ART vs. No-ART) and therefore, presents the first cost-effectiveness derived from a public sector setting; ART center in Choma rural district.

The person-time observation of five year duration on ART was sufficient to capture the full benefit of ART with respect to service costs. The researcher used real data for the five year period study to estimate health service utilization, and applied these estimates to Markov health states of the cohort.

However, a general limitation of this study was that the analysis did not include the utilization of specialized forms of in-patient services at the hospice since there was no in-patient utilization at the general hospital. Data for the hospice admissions were insufficient for their inclusion. A further omission was the failure to adequately capture out-patient visits at the hospital. After all costs and health effects were calculated, the researcher was unable to discount the future costs and health effects to the present value due to time limitation. These omissions are likely to have biased the study against the cost-effectiveness of HAART.

5.8 Sensitivity and Generalizability of the Study

The study is sensitive to the one done in Khayelitsha, South Africa which used Markov modeling on the cohort for a five year person time observation. The findings are similar to this study including transition probabilities and ICER. The study can be generalized to other studies in South Africa other than the Khayelitsha which have used similar parameters.

5.9 Exchange Rates

In order to facilitate a more meaningful comparison across regions, costs were expressed in local units which were calculated to international US dollars at a particular exchange rate in Zambia for each year of the period of study (2004 – 2008). Information on the average annual exchange rate for the period of study was derived from CSO monthly bulletin, i.e. 2003 – 2009.

5.10 Suggestions for further Research

This study was based on a small sample at an ART centre in a rural district. It is recommended that a bigger sample size is conducted to determine whether the findings from this study can be validated.

Some data for this study were collected; the treatment policy and drug regimen for ART has been revised. It is therefore, recommended that a revised study be done.

A societal Cost-Effectiveness Analysis (CEA) perspective could be conducted to determine the costs and benefits that accrue to society, beyond the providers

CHAPTER SIX

6. CONCLUSION

As more effective HIV therapies have become available in particular HAART, resource constraints and cost-effectiveness have increasingly been at the centre of the debate on HIV care globally. The key question has been whether HAART is value for money. Cost-effectiveness analyses have been conducted mostly in industrialized countries and only a few in some countries in sub-Saharan Africa. The analyses have shown that antiretroviral therapeutic regimens offer good value for the resources spent as compared to many other accepted health care interventions.

This was an exploratory study of HAART in Zambia based on rural setting. The objectives of this study were to estimate the costs and effects when ARVs are used in treatment of HIV infected persons. The study describes the costs of prophylaxis and treating of opportunistic infections in HIV infected adults and to determine the incremental cost effectiveness ratio of ARVs at Choma district ART center. To achieve these objectives, a retrospective study was conducted on a cohort using a pre-ART and ART patient-time observation for a five year period. Economic analysis methodological approach was used in the study to compare the two interventions and establish the cost-effectiveness of HAART.

Cost-effectiveness analyses use widely accepted methodology to establish which of two or more competing interventions can give the maximum output i.e. health effects (e.g. QALYs) for a given level of input (health system resources valued in terms of their economic cost). When compared to other interventions in the health sector, it can also establish allocative efficiency – doing the right thing. HAART intervention reduce the cost of medical care of HIV disease because it reduces the incidence of opportunistic infections and leads to a corresponding reduction in in-patient healthcare use after initiation of the therapy.

The analysis from this study shows that HAART is highly cost-effective. This implies that the programme yields more health gains (QALYs) from the same levels of spending with HAART.

6.1 RECOMMENDATIONS

HAART intervention has been shown to be cheaper per QALY and to lead to enhanced life expectancy. Therefore, more refined cost-effectiveness analyses are needed to evaluate available HIV/AIDS prevention, treatment and care and to identify the interventions that provide the best value of money.

Policy-makers should place more emphasis on the current focus of reducing the cost of antiretroviral drugs particularly those drugs that are relatively expensive such as Efavirenz, ddI and Kaletra since ARVs account for nearly 50% of the lifetime cost per patient.

This research study undertook the provider's perspective (public healthcare system) in comparing ART to No-ART. Guidelines recommend that costing should also be undertaken from a societal perspective in order to include direct non-healthcare costs such as transport and time costs incurred by patients. Therefore, an additional research should be undertaken into the full range of non-health care costs imposed on patients in order to inform policy-makers on further interpretation of cost-effectiveness results in terms of allocative efficiency. Besides that, societal perspective would capture added benefits associated with HAART, such as productivity gains and opportunity costs associated with seeking care, which could potentially further improve the cost-effectiveness of HAART.

In Zambia, at the university level, particularly Masters in Public Health (MPH) program, students as future policy-makers for the country, should be encouraged to undertake research of cost-effectiveness analyses in public healthcare systems in order to contribute to the current state of knowledge in this area.

The School of Medicine should motivate the students further to undertake such economic analyses by acquiring the Decision Analysis by TreeAge (DATATM) software version 4.0 and WHO CostIt Intervention Software Template.

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APPENDICES

A: FILE CHECK LIST

Instructions:

- Check the file number
- Review the patient's file using the check list.
- Record the appropriate information.
- When you have finished, return the file to the record room for filing.
- Thank the filing officer.

1. Physical examination

- a. Weight (kg) ----- b. BP----- c. Temperature ----- d. Heart rate----- e. Resp rate-----
f. Patient's complaints-----
g. Abnormal findings -----

2. WHO staging

- a. 1 - Opportunistic infections -----
b. 2 - Opportunistic infections -----
c. 3 - Opportunistic infections -----
d. 4 - Opportunistic infections -----

3. Prescription of prophylaxis drugs

- a. Septrin 960mg od ---- days b. Fluconazole 200mg od ---- days
c. Isoniazid ---- tabs od ---- month d. Rifampicin ---- tabs od x ---- days
e. Amphotericin B. ---- mg ---- x---- days.

4. Prescription of curative drugs

- a. Septrin ---- mg ---- ---- days b. Fluconazole ----- mg ----- ----days
c. Anti-malaria-----: ----- mg ----- days. d. Anti-biotic ----- mg ----- ---- days
e. Anti-fungal-----: ----- mg ----- days. f. TB drugs -----tabs od ----- mths

5. Investigations

- a. None b. CD4 count ----- c. Hemoglobin/ hematocrit d. Full blood count
 e. ALT/AST f. Creatinine g. Sputum AFB h. Chest X-ray i. Pregnancy
 j. RPR k. TLC l. Amylase/lipase m. Viral load n. Other-----

6. Referrals

- a. Family planning b. Nutritional support c. In-patient care
 d. TB treatment e. Community health worker f. Other

7. HIV care summary sheet

- a. Diagnosed HIV+ date ----- b. Enrollment date ----- c. ARV start date -----
 d. Allergies to medications-----
 e. Opportunistic infections -----

8. Follow-up visits

Date	Weight	Height	WHO Stage	CD4	CD4%	Viral load	Hb	AST	ALT	Cre	Other

9. Antiretroviral medications

Drug	Dose	Freq	Start date	Stop date

10. Patient status

- 3mons** a. Healthy, able to work b. Sick, able to work c. Sick, unable to work
d. Bedridden e. Deceased
- 6mons** a. Healthy, able to work b. Sick, able to work c. Sick, unable to work
d. Bedridden e. Deceased
- 12mons** a. Healthy, able to work b. Sick, able to work c. Sick, unable to work
d. Bedridden e. Deceased
- 24mons** a. Healthy, able to work b. Sick, able to work c. Sick, unable to work
d. Bedridden e. Deceased
- 36mons** a. Healthy, able to work b. Sick, able to work c. Sick, unable to work
d. Bedridden e. Deceased
- 48mons** a. Healthy, able to work b. Sick, able to work c. Sick, unable to work
d. Bedridden e. Deceased.

B: SEMI – STRUCTURED INTERVIEW SCHEDULE ON THE QUALITY OF LIFE.

Instructions:

- a) Introduce yourself to the respondent.
- b) Explain the objectives of the research and the benefits.
- c) Obtain consent from the respondent to proceed with the interview
- d) Check the respondent’s identification card.

Section A: HIV Status and Enrollment

1. How old were you when you had an HIV positive test done?
a. 15 – 24 years b. 25 – 34 years c. 35 – 44 years d. above 45 years
2. Which year did you have the HIV test done? -----
3. How long did it take you to get enrolled at the ART center?
a. Less than a week b. 2 weeks c. More than a month

4. For how long were you in the HIV care programme before starting ARVs?

a. Less than a month b. 3 months c. More than 6 months d. More than a year

5. For how long have you been taking ARVs?

a. Less than a month b. 3 months c. More than 6 months d. More than a year

Section B: Quality of Life with HIV disability

I. Mobility

6. Did you have any problems walking around in the following months:

3 mons a. No problem walking b. Some problem walking about c. Confined to bed

6 mons a. No problem walking b. Some problem walking about c. Confined to bed

12 mons a. No problem walking b. Some problem walking about c. Confined to bed

24 mons a. No problem walking b. Some problem walking about c. Confined to bed

36 mons a. No problem walking b. Some problem walking about c. Confined to bed

48 mons a. No problem walking b. Some problem walking about c. Confined to bed

II. Self-care

7. Did you have any problems in taking care of yourself in the following months:

3mon a. No problems with self-care b. Problems washing/dressing self c. Unable to wash/dress self

6mon a. No problems with self-care b. Problems washing/dressing self c. Unable to wash/dress self

12mon a. No problems with self-care b. Problems washing/dressing self c. Unable to wash/dress self

24mon a. No problems with self-care b. Problems washing/dressing self c. Unable to wash/dress self

36 mon a. No problems with self-care b. Problems washing/dressing self c. Unable to wash/dress self

48 mon a. No problems with self-care b. Problems washing/dressing self c. Unable to wash/dress self

III. Usual activities

8. Did you have any problems in performing your usual activities in the following months:

3 months

- a. No problems with performing usual activities (work, study, housework, family/ leisure activities).
b. Some problems with performing usual activities. c. Unable to perform usual activities.

6months

- a. No problems with performing usual activities (work, study, housework, family/leisure activities).
b. Some problems with performing usual activities. c. Unable to perform usual activities.

12 months

- a. No problems with performing usual activities (work, study, housework, family /leisure activities).
b. Some problems with performing usual activities. c. Unable to perform usual activities.

24 months

- a. No problems with performing usual activities (work, study, housework, family /leisure activities).
b. Some problems with performing usual activities c. Unable to perform usual activities.

36 months

- a. No problems with performing usual activities (work, study, housework, family/leisure activities).
b. Some problems with performing usual activities. c. Unable to perform usual activities.

48 months

- a. No problems with performing usual activities (work, study, housework, family/leisure activities).
b. Some problems with performing usual activities. c. Unable to perform usual activities.

IV. Pain/discomfort

9. Did you experience any pain/discomfort?

3 months a. No pain/discomfort b. Moderate pain/discomfort c. Extreme pain/discomfort

6 months a. No pain/discomfort b. Moderate pain/discomfort c. Extreme pain/discomfort

12 months a. No pain/discomfort b. Moderate pain/discomfort c. Extreme pain/ discomfort

24 months a. No pain/discomfort b. Moderate pain/discomfort c. Extreme pain/discomfort

36 months a. No pain/discomfort **b.** Moderate pain/discomfort **c.** Extreme pain/discomfort

48 months a. No pain/discomfort **b.** Moderate pain/discomfort **c.** Extreme pain/discomfort

V. Anxiety/depression

10. Did you experience any anxiety/depression?

3 mons a. Not anxious/depressed **b.** Moderately anxious/depressed **c.** Extremely anxious/depressed.

6 mons a. Not anxious/depressed **b.** Moderately anxious/depressed **c.** Extremely anxious/depressed.

12 mons a. Not anxious/depressed **b.** Moderately anxious/depressed **c.** Extremely anxious/depressed.

24 mons a. Not anxious/depressed **b.** Moderately anxious/depressed **c.** Extremely anxious/depressed.

36 mons a. Not anxious/depressed **b.** Moderately anxious/depressed **c.** Extremely anxious/depressed.

48 mons a. Not anxious/depressed **b.** Moderately anxious/depressed **c.** Extremely anxious/depressed.

THANK YOU FOR YOUR TIME.

C: INFORMATION SHEET

Purpose

I am a student doing my Masters Degree in Public Health at the University of Zambia, School of Medicine. This course requires us to gain applied experience in designing and conducting research. As such, I have designed a research project in cost –effectiveness of highly active anti – retroviral treatment (HAART) at Choma General Hospital and ART center.

Description

During this study, you will need to answer to a structured schedule interview questionnaire concerning your quality of life with use of non – ARVs drugs from the time you tested HIV positive to the time you were put on ARVs drugs. Your participation will require approximately 30 minutes of your time .The answers you will provide will help us to devise ways and means of helping in provision of ARVs treatment.

Potential Harm

There are no known harms associated with your participation in this research.

Confidentiality

All records of participation will be kept strictly confidential, such that only the researcher and the people that have been treating you and my supervisors will have access to the information. The results from this study will be reported in a written research report and an oral report during a class presentation. Information about the project will not be made public in any way that identifies individual participants.

Participation

Participation is completely voluntary. It may be discontinued at any time for any reason without explanation and without penalty.

Queries: If you have any further queries, please contact: **Biomedical Research Ethics Committee.**

The University of Zambia

E-mail: unzarec@zamtel.zm

Biomedical Research Ethics Committee

Fax: +260 – 1 - 250753

P.O. Box 50110, Lusaka, Zambia

Tel. no. 01 256067

D: CONSENT FORM

I have read the above form and understand the information read. I also understand that I can ask questions or withdraw at any time. I consent to participate in today’s research study.

Participant’s signature/or thumb print: _____ or



Date _____

Name of witness _____

Date _____

Investigator’s signature: _____

Date: _____

E: GUIDING QUESTIONS FOR KEY INFORMANTS.

Instructions:

- Introduce yourself to the informants.
 - Explain the objectives of the research and the benefits.
 - Obtain consent to proceed with the discussion.
1. How did you manage patients whom you suspected to have HIV-related conditions?
 2. What were the commonest conditions patients used to have before use of ARVs?
 3. What was their quality of life?
 4. Discuss the in-patient utilization with non –ARVs to ARVs.
 5. What is the response of patients who are initiated on ART?
 6. Why is the ART intervention used along with No-ARVs?

THANK YOU FOR TAKING PART.

F: WORK PLAN

1. Preparation and submission of proposal
2. Recruitment and training of research assistants
3. Data collection
4. Data entry and analysis
5. Report writing
6. Submit draft report
7. Submit final report

H: GANTT CHART

No.	Activity	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
1.	Preparation and submission of proposal	**	**	**	**	**								
2.	Train research assistants						**							
3.	Data collection						**							
4.	Data entry and analysis							***	***					
5.	Report writing									****	****			
6.	Submit draft report											****	****	
7.	Submit final report													***

I: STUDY BUDGET

No	ITEM	QUANTITY	UNITY COST(K)	TOTAL COST(K)
1.	STATIONERY			
a.	A4 Bond paper (Rim)	10	25,000	250,000
b.	Folders	5	10, 000	50,000
c.	Flash Disc.	1	500,000	500,000
d.	Pens	10	1,000	10,000
e.	Pencils	10	500	5,000
f.	Eraser	10	3,000	30,000
g.	Correction Fluid	4	5,000	20,000
h.	Stapler	1	20,000	20,000
i.	Staples (Box)	1	5,000	5,000
j.	Writing pads	4	5,000	20,000
SUB	TOTAL			1,010,000
2.	SECRETARIAL WORK			
I	Research Proposal			
a.	Typing Proposal	40 pages	1,500	60,000
b.	Printing Proposal	40 pages	2,000	40,000
c.	Photocopying Proposal	200 pages	200	40,000
d.	Binding Proposal	5	10,000	50,000
e.	Submission of Proposal to Ethical Research Committee			500,000
SUB	TOTAL			690,000
II	Pre-testing the questionnaire			
a.	Typing questionnaire	8 pages	1,500	12,000
b.	Printing questionnaire	8 pages	1,000	8,000
c.	Photocopying questionnaire	8 pages x30	200	48,000
SUB	TOTAL			68,000

III	Actual Study			
a.	Typing questionnaire	8 pages	1,500	12,000
b.	Printing questionnaire	8 pages	1,000	8,000
c.	Photocopying Questionnaire	8 pages x 30	200	480,000
SUB	TOTAL			500,000
3.	ALLOWANCES			
a.	Research ass. lunch (training)	2 x 7 days	50,000	700,000
b.	Researcher lunch (training)	1 x 7 days	50,000	350,000
c.	Research ass. lunch (Data collection)	2 x 30 days	50, 000	3,000,000
d.	Research ass. (2) transport	2 x 30 days	10, 000	600,000
e.	Researcher lunch (Data collection)	1 x 30 days	50, 000	1,500,000
f.	Researcher transp. (Data collection)	1 x 30 days	10,000	300,000
SUB	TOTAL			6,450,000
4.	DATA ENTRY AND	ANALYSIS		
a.	Data entry	14 days	50, 000	700,000
b.	Data analysis	14 days	50,000	700,000
c.	Report writing and editing	21 days	50,000	105, 000
d.	Binding report	5 copies	10,000	50,000
SUB	TOTAL			2,500,000
	TOTAL			11,218,000
	CONTIGENCY 10%			1,121,800
	GRAND TOTAL			12,339,800