UNIVERSITY OF SOUTHAMPTON

FACULTY OF SOCIAL, HUMAN AND MATHEMATICAL SCIENCES

Mathematical Sciences

Using Simulation and Survival Analysis to Forecast Outcomes and Economic Costs of the Antiretroviral Therapy Programme in Zambia

by

Mushota Evans Kabaso

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ABSTRACT

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USING SIMULATION AND SURVIVAL ANALYSIS TO FORECAST OUTCOMES AND ECONOMIC COSTS OF THE ANTIRETROVIRAL THERAPY PROGRAMME IN ZAMBIA

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Of the approximately 35 million people living with HIV in sub-Saharan Africa in 2013, over 1.9 million were in Zambia. The country is among the hardest hit by what is described as a generalised HIV epidemic with a prevalence of 14.3 percent of the sexually active population living with the virus. Limited information on the long–term survival and related economic costs of providing Antiretroviral Therapy (ART) to the needy population is a challenge to planners and others interested in mitigating the effect of this problem.

A two-pronged study has been undertaken to address this paucity of information whose objectives are: 1) To provide better estimates of long term survival estimates of people on ART; and 2) Estimate the number of people on ART in the future and the related economic cost of providing them with ART over the next decade. Survival analysis techniques were employed to estimate distributions of time each patient spent on ART before exiting the system for one reason or the other. These distributions served as input parameters in the Discrete Event Simulation (DES) model which was used to model the number of people on ART in Zambia and provide projections for the cost of providing ART in the future. HIV-infected patients enter the model when they commence ART and then change their health states stochastically until they exit the system due to death or stopping treatment. Economic costs are calculated from the public sector perspective and we anticipate the tool being used for planning purposes in Zambia. The development of the model was with extensive consultation of different staff involved in the running of the ART program in Zambia from clinicians and support staff managing the patients at the clinics to provincial and national ART coordination staff who are involved in managing and planning of the interventions at the macro level.

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DECLARATION OF AUTHORSHIP

I, Mushota Evans Kabaso

declare that the thesis entitled

Using Simulation and Survival Analysis to Forecast Outcomes and Economic Costs of the Antiretroviral Therapy Programme in Zambia

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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- none of this work has been published before submission

Signed: ……..

Date: ……

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This PhD thesis I dedicate to the memory of my parents Matherine Nshinka Kabaso and Victor Mambwe Kabaso without whose determination to send me to school it would not have been possible.

Above all I give thanks and praises to God for the guidance and blessings to enable me complete this work.

1 Introduction

Like many countries in sub-Saharan Africa which are affected by the human immunodeficiency virus (HIV) epidemic, Zambia faces the growing challenge of providing the various clinical care and other services for people infected with the HIV virus. With a 14.3 percent HIV prevalence in the general population, more than 1.9 million out of the country's 13 million people at the last population count in 2010 live with the virus. Zambia is classified as a lower middle income country (LMIC) (World Bank, 2011) by the World Bank.

1.1 Statement of the problem

As the HIV infection matures into acquired immune deficiency syndrome (AIDS) in each of the infected individuals, treatment with antiretroviral therapy (ART) is the only known and acceptable mitigation which can be provided to these people in order to enable them lead close to normal lives while remaining economically productive in society. The number of these HIV-infected citizens who need ART (referred to as the disease burden of AIDS) is large. It has been growing year on year in Zambia over the last decade and planning how to meet this disease burden is a national challenge. A critical aspect of this challenge is estimating the disease burden and its economic cost in the long term from the public sector standpoint since over 90 percent of infected patients receive treatment from public health facilities which are government funded.

1.2 Research objectives and questions

The aim of the study is to provide a planning tool and reference for health intervention planners and financiers on the long term ART outcomes and economic costs. The two objectives to achieve this are:

1. To develop a simulation model of the time intervals from ART initiation to exiting the ART program in Zambia
2. To generate long term program level estimates of the economic cost of providing ART from patient initiation to exit in Zambia

The research questions in the study are:

1. What is the survival estimate of the time intervals from initiation to drop out among patients who commence ART in a LMIC such as Zambia?
2. What is the total economic cost of the provision of ART in Zambia from enrolment to drop out?

1.3 Ethical approval

In order to conduct the research, ethical approval was obtained from necessary institutions even though there was no contact with any of the people on ART during or after the study. The use of patient-level data for this research made it obligatory to obtain necessary ethical clearance. Ethical approval for this research was therefore obtained from the SSEGM Ethics Sub-committee in the Faculty of Social and Human Sciences at the University of Southampton and the ERES Converge Ethics Committee in Zambia. In addition, permission to conduct the research in Zambia was obtained from the Ministry of Health, Zambia as per relevant statutory requirements. This ensured that no violations or infringements on individuals' privacy or rights were committed during the research undertaking according to both the laws of the Republic of Zambia and the United Kingdom.

1.4 Chapter summary

This chapter has provided the following:

- An introduction of the HIV/AIDS situation in Zambia followed by a statement of the problem investigated in this thesis
- An outline of the research objectives and questions

2 Background

2.1 Human Immunodeficiency Virus

First reported in the USA in 1981 (Centers for Disease Control and Prevention, 1981), Human immunodeficiency virus (HIV) is a virus which attacks the human immune system by impairing or destroying CD4 cells which make up key components of the cellular immune system (UNAIDS, 2008). CD4 cells (also known as CD4+ cells) are a type of white blood cells (lymphocytes) which lead the fight against HIV. HIV can be transmitted from an infected person to an uninfected person through a number of ways including unprotected heterosexual or homosexual sex; sharing contaminated syringes or needles; from mother to child during pregnancy, childbirth or breastfeeding and through blood transfusion (FPA, 2008; UNAIDS, 2009).

Globally, the transmission patterns of HIV are categorized in two groups which also roughly define the pandemic geographically (Kilmarx, 2009). Sub-Saharan Africa, which accounted for approximately 71% of the 35 million people living with the virus at the end of 2013, mainly has a generalized epidemic driven by unprotected heterosexual intercourse as well as vertical transmission from mother to child (UNAIDS, 2011, 2012, 2013, 2014). In addition, the Caribbean can also be classified in the same category as Sub-Saharan Africa in terms of the drivers for transmission although the prevalence and number of people living with the virus is significantly smaller. The remainder of the world has concentrated epidemics chiefly made up of Injection Drug Users (IDU) and men who have sex with men (MSM). Paid sex work is also a driver to a lesser extent in this category (UNAIDS, 2012).

Figure 1 shows the trends of the number of people living with HIV and new infections globally from 2001 to 2011. The number of people living with the HIV virus increased consistently from 2001 to 2011 at an average rate of about 1.5 percent per year. This growth rate is much more favourable than the rate at which this number was growing in the decade before (1990 to 2000) when it averaged over 10 percent per annum (data not in the graph). Much of this decline is attributable to a mixture of factors; behaviour change (mainly the reduction of the number of sexual partners, condom use and delayed age of first sex), expanded coverage of

antiretroviral therapy and the natural trend of the epidemic has been reached (Bongaarts, Pelletier, & Gerland, 2009; UNAIDS, 2011; WHO UNAIDS UNICEF, 2011).

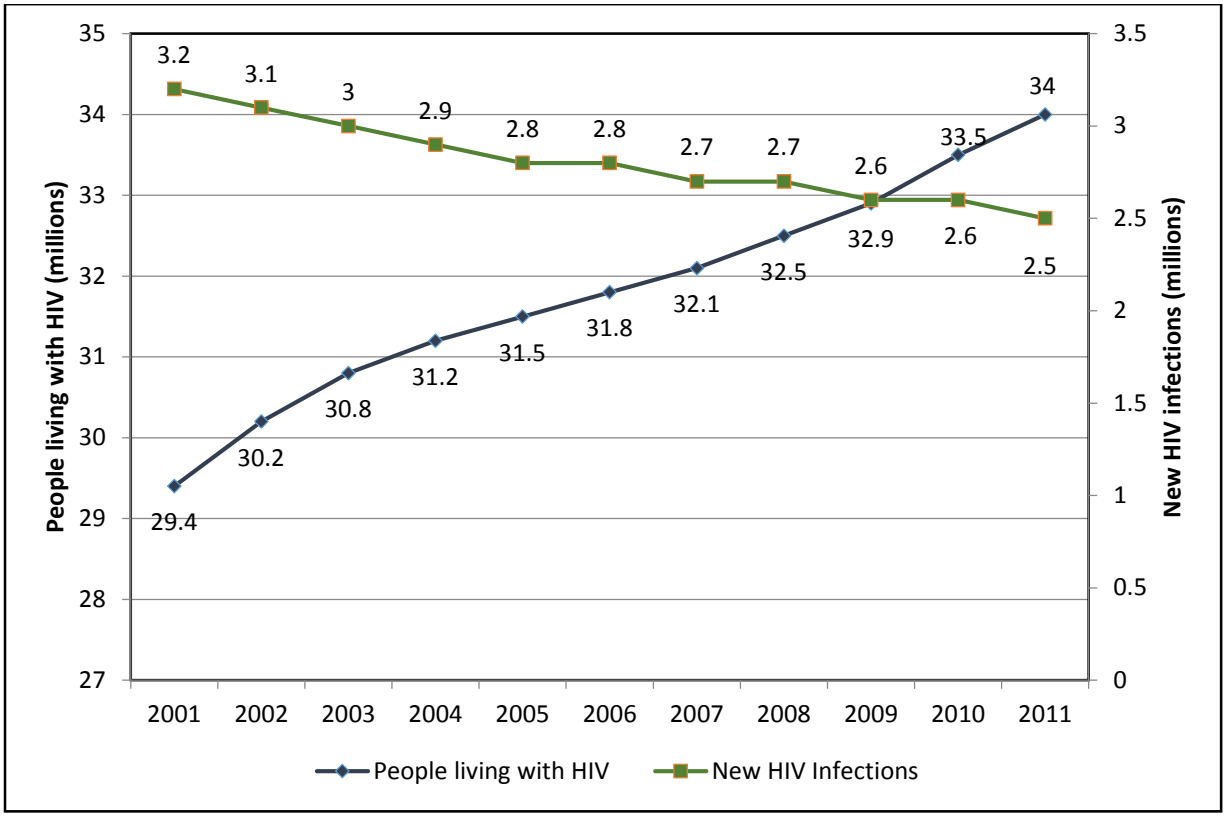


Figure 2.1: People living with HIV and New HIV infections, worldwide, 1990 to 2011 (Source: UNAIDS)

The UNAIDS World AIDS Day report for 2010 (UNAIDS, 2011) reports that 50% of the global number of people living with HIV are female, recording a reduction of 2 percentage points compared to 2009. However, in Sub-Saharan Africa, 59 percent of the HIV cases are female followed by the Caribbean at 53 percent. By contrast, out of all the HIV+ cases in Europe during the same year, 29 percent were women versus 71 percent in men (European Centre for Disease Prevention and Control, 2011; UNAIDS, 2010) During 2010, the UNAIDS estimated the number of children living with HV to be about 3.4 million representing 10% of the world total. Of the estimated 2.7 million new HIV infections for the year 2010, about 390,000 were children (WHO UNAIDS UNICEF, 2011).

2.1.1 Acquired Immunodeficiency Syndrome

Persons infected with HIV are said to have developed Acquired Immunodeficiency Syndrome (AIDS) if their immune systems become compromised by the virus to the extent that the body's immune system fails to fight off diseases. The term AIDS refers to advanced levels of HIV infection (and therefore immune suppression) in which a number of otherwise easy to fight off diseases manifest in the infected person. These diseases are known as opportunistic infections since they take the weakened immunity of the person as an opportunity to manifest (American Cancer Society, 2012).

Formally, the United States government's Centers for Disease Control and Prevention (CDC), defines AIDS as having a positive HIV blood test coupled with the occurrence of any one of more than 20 opportunistic infections including certain infections, cancers, and syndromes that are AIDS-related. Additionally, an HIV positive test result and a CD4 counts of less than 200 cells per micro-liter (µL) of blood is also applied to indicate that a person has AIDS. A normal CD4 count is between 500 and 1,500 cells per micro litre of blood in adults and can reach 2,500 cells in children below 15 years (Centers for Disease Control and Prevention, 1992; UNAIDS, 2008)

2.1.2 AIDS-related Opportunistic Infections

As a result of HIV infection, a person's immune system is suppressed making it susceptible to infections which it would have otherwise fought off naturally. Such intercurrent infections are known as Opportunistic Infections (OI) since they take the immune suppression as an opportunity to infect a person. Opportunistic infections are caused by a wide range of pathogens (Ioannidis & Wilkinson, 2003). Some of the common OIs include tuberculosis (both pulmonary and extra-pulmonary), oral candidiasis, herpes zoster, cryptococcal meningitis and pneumonia (Egger et al., 2002; Ghate et al., 2009; Gona et al., 2006).

2.1.3 AIDS-related mortality

As many as 24 million people had been estimated to have died from AIDS worldwide by the United Nations Population Division between 1980 and 2007 (Bongaarts et al., 2009). The Population Division based these estimates on data collected by UNAIDS on prevalence of HIV in the population for persons aged between 15 and 49 years. Projections of both prevalence

of HIV and AIDS mortality were generated by using a model developed by UNAIDS for the period through to 2030. By the year 2030, the pandemic is projected to have claimed 75 million lives. The World Health Organization (WHO), UNAIDS and UNICEF estimate that 1.8 million and 10.7 million people died from AIDS in 2010 and 2011 respectively. This trend indicates a consistent reduction in mortality from a peak 2.0 million AIDS deaths in 2008 (UNAIDS, 2012; WHO UNAIDS UNICEF, 2011). Figure below shows the distribution of AIDS deaths by region for 2011. Africa continues to bear the largest burden of AIDS-related deaths accounting for 70 percent of the global total. The regions experiencing AIDS mortality the most after Africa are South East Asia as well as Eastern Europe and Central Asia accounting for 15 percent and 5 percent of the reported global mortality respectively.

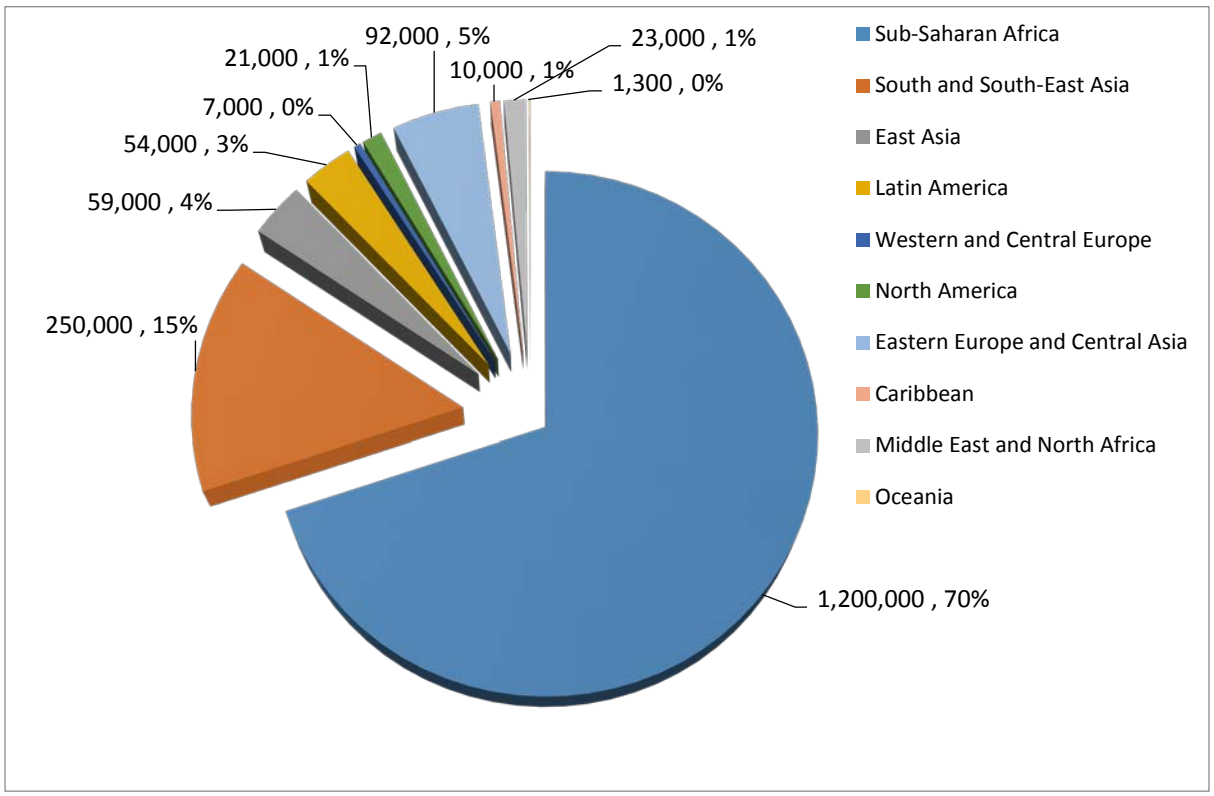


Figure 2.2: AIDS-related deaths by region, 2011 (Source: WHO UNAIDS)

2.2 The HIV and AIDS epidemic in Zambia

The first documented case of HIV infection in Zambia was in 1984. Monitoring HIV prevalence thereafter was by use of HIV prevalence rates among pregnant women attending a sample of 21 clinics in a routine survey known as the Antenatal Clinic Sentinel Surveillance Surveys (ANCSS). Using ANCSS data, population level estimates of HIV prevalence were extrapolated.

The ANCSS provided estimates for the years 1994, 1998, 2002 and 2006 (Fylkesnes, Ndhlovu, Kasumba, Mubanga Musonda, & Sichone, 1998; Ministry of Health Zambia (MOH), 2007). This was not perfect but was a good indicator of the situation in the general population. From 2002, however, nationally-representative population-level estimates of HIV have been obtained from Demographic and Health Surveys (Central Statistical Office (CSO) & Ministry of Health Zambia (MOH), 2003, 2009).

From those early years, HIV infections have spread throughout the country to epidemic levels. Nationally, the HIV prevalence in 2007 was 14.3 percent of adults aged 15 to 49 years (Central Statistical Office (CSO) & Ministry of Health Zambia (MOH), 2009). This prevalence level is considered a stable level at which the epidemic has reached after what epidemiologists contend was a peak prevalence of about 16 percent during the mid-1990s. HIV incidence (new infections) in the population aged 15 – 49 has been reported to stabilize at about 1.6 percent although the absolute number of new infections increases year on year as a result of consistent population growth in the country.

2.3 Demographic and AIDS profile of Zambia

2.3.1 Demographic characteristics of the population

According to the 2010 Zambia census of population and housing, there were 13 million people in the country during that year with 51 percent of them being females (Central Statistical Office (CSO), 2012a). The age distribution of the Zambian population revealed a very young population with about 45.5 percent of the country's inhabitants aged below 15 years. The age group 15 – 64 years was 52 percent of the total population and only 2.6 percent of the population was recorded as aged 65 years or over. In terms of residence, 60 percent of the Zambian population lived in rural areas in 2010 compared with 40 percent in urban areas.

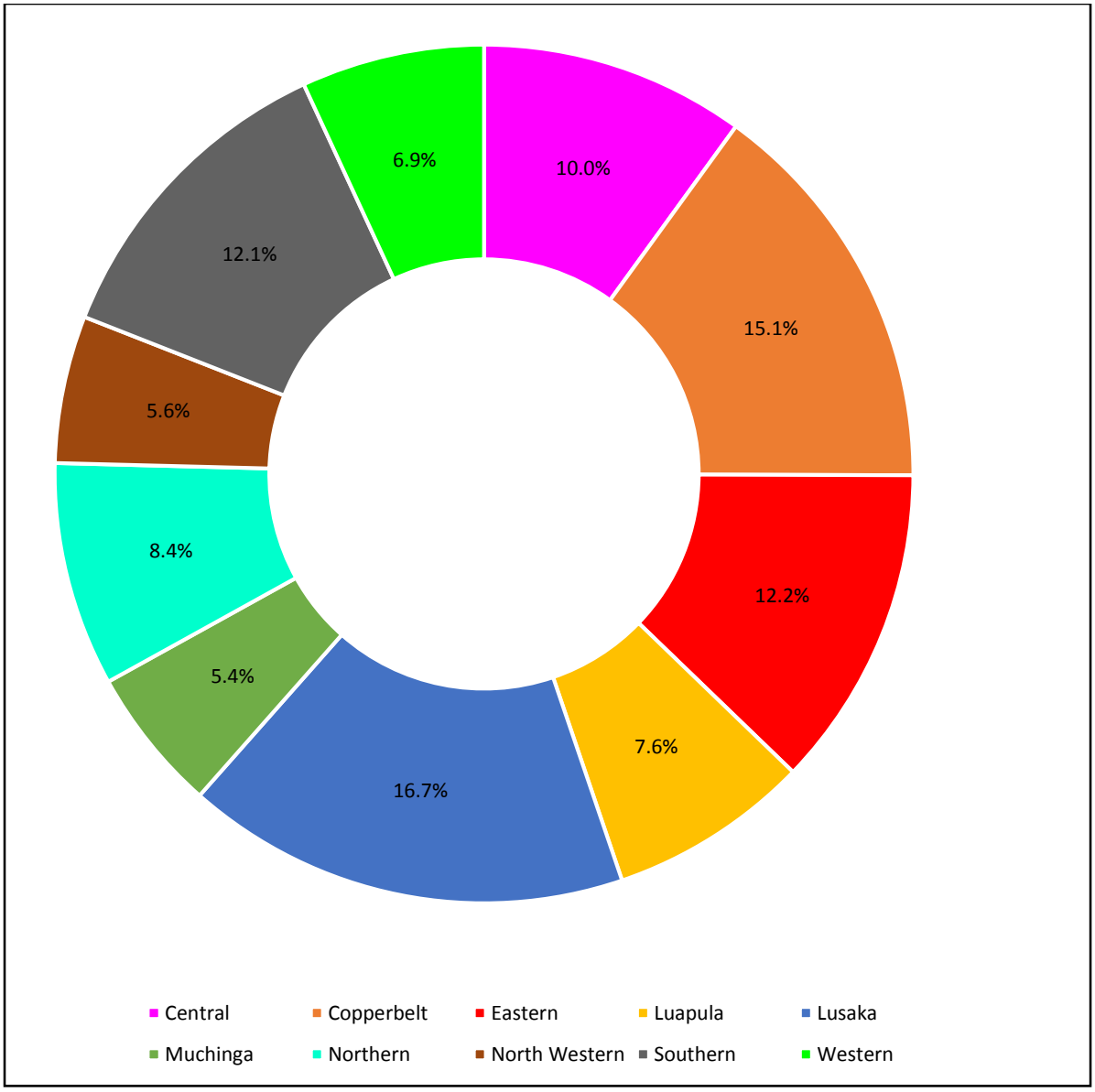


Figure 2.3: Distribution of population by province in Zambia, 2010 (Source: Zambia Census of Population and Housing, CSO)

The country is divided into ten provinces for administrative purposes and the distribution of the population in these regions varies widely with the more urbanized provinces being home to most people. Lusaka province (host of the nation's capital, largest commercial city and seat of government) has the largest share of the Zambian population at 16.7 percent, followed by the Copperbelt province (home of the copper mines, the country's economic mainstay) at 15.1 percent. This is shown in Figure 2.3. The smallest share of the population is in Muchinga, a new province created in October 2011 which has only 5.4 percent of the national total. The urbanized provinces have population densities many times more than the national average of 17.4 persons per square kilometer (45 persons per square mile). This is as a result of people

migrating to these areas in search of work and other social amenities not readily available in the rural areas. Lusaka province has a population density of 100.1 persons per square km, followed by Copperbelt province, which has a density of 63 persons per square km. By contrast, some of the more rural provinces have population densities of less than 10 persons per square km (Muchinga and Western provinces have densities of 8.1 and 7.1 persons per square km respectively)

2.3.2 State of the HIV epidemic in Zambia

Zambia has a mature and generalized HIV hyper epidemic (or pandemic) according to the country's National HIV/AIDS Council. The epidemic is primarily driven by heterosexual contact which accounts for approximately 78 percent of new infections (Ministry of Health Zambia (MOH) & National HIV/AIDS/STI/TB Council Zambia, 2009; National HIV/AIDS/STI/TB Council Zambia, 2015). Vertical transmission from mother to child during pregnancy, at birth or during breastfeeding is the next most important transmission route of HIV in Zambia, accounting for 10 percent of new infections. Other modes of transmission are unsafe medical injections (0.2 percent) and blood transfusions (0.02 percent) of all new infections. The other vehicles of infection such as IDU and MSM are not documented because IDU is only practiced on a small scale in the Zambia and homosexual activity is taboo and illegal therefore not well understood or documented.

2.3.3 HIV prevalence in Zambia: trends and patterns

Geography, age and gender define some of the most important factors that characterise the heterogeneity of HIV prevalence in Zambia. Figure 3 shows that women in the sexually active population (15 – 49 years) generally show a higher HIV prevalence than do their male counterparts. Specifically, 5.7 percent females versus 3.6 percent males (aged 15 – 19 years) are HIV positive. This trend increases to a peak of 26 percent prevalence for females aged 30 – 34 years compared with 17.1 percent among the males of the same age group. However, this pattern is reversed for age groups between 40 and 49 years where men have a higher HIV prevalence. This trend, it is proposed, is as a result of younger females preferring older male sexual partners and vice versa (Central Statistical Office (CSO), Ministry of Health Zambia (MOH), National HIV/AIDS/STI/TB Council National HIV, & MEASURE Evaluation, 2010; Ministry of Health Zambia (MOH) & National HIV/AIDS/STI/TB Council Zambia, 2012). The

total prevalence in all age groups is still higher in women compared to men of reproductive age with women recorded at 16.1 percent versus 12.3 percent in men (against a national prevalence rate of 14.3 percent for both sexes).

The same report indicates that the HIV prevalence in urban areas is twice that in the rural parts of the country, 19.7 percent versus 10.3 percent respectively. This trend is also true within the sexes disaggregated by residence, 23 percent for urban women compared with 11 percent among rural women and 15.9 percent prevalence for urban men versus 9.4 percent for their rural counterparts. Furthermore, the HIV prevalence is distributed with a similar pattern between provinces with the more predominantly rural provinces having lower rates than the urbanised provinces.

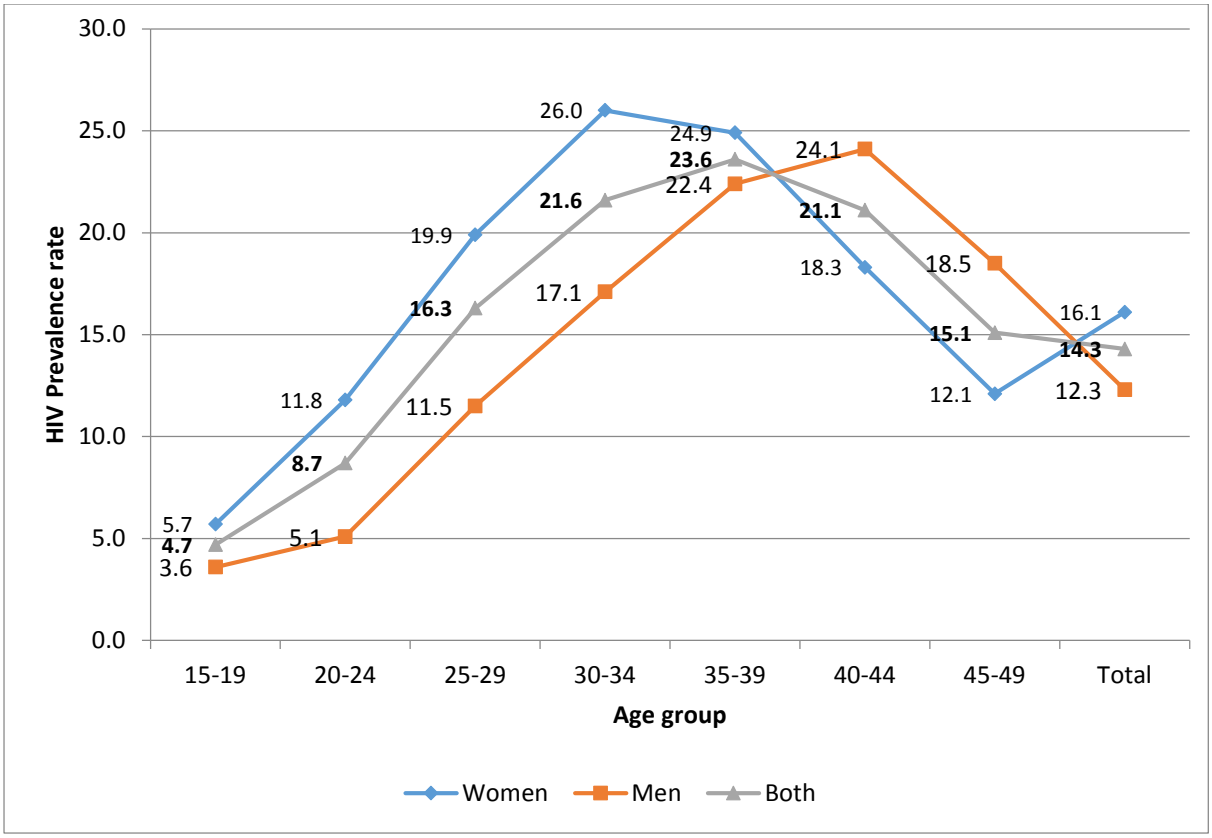


Figure 2.4: HIV prevalence rate by age and gender, 2007 (Source: ZDHS 2007)

According to the Zambia Demographic and Health Surveys (ZDHS) conducted by the Ministry of Health in 2001 (Central Statistical Office (CSO) & Ministry of Health Zambia (MOH), 2003) and 2007 (Central Statistical Office (CSO) & Ministry of Health Zambia (MOH), 2009), the

province with the highest HIV prevalence rate in Zambia remains Lusaka province. The 2007 survey reported a provincial prevalence rate of 20.8 percent with the next highest being 17 percent in the copper producing province (the Copperbelt) while the other commercialized provinces (Central and Southern) also had prevalence rates of about 15 percent or higher. The lowest reported prevalence rate at provincial level in 2007, as was the case in 2001-2002, was in the Northern province at 6.8 percent versus the earlier rate of 8.3 percent. The more rural and less commercialized provinces of the country have continued to show lower HIV prevalence rates over the periods covered by the two surveys ranging from 8.3 to 13.7 percent in 2001 and 6.8 to 15.2 percent in 2007.

Other socio-economic characteristics of the HIV epidemic in Zambia do not show very significant differences in the distribution of people infected with the virus. In 2007, HIV prevalence among people in Zambia with no education was reported to be 10 percent compared with 13.7, 15.1 and 19.3 percent for those whose highest level of education was primary, secondary and tertiary respectively. There was a variation in the HIV prevalence rates by employment status with 15.6 percent of employed individuals testing positive while only 11.7 percent of the unemployed tested HIV positive in 2007. Zambians falling in the fourth wealth quintile exhibited the highest HIV prevalence (20.6 percent) relative to the other quintiles, followed closely by the highest (fifth) quintile which had 17.8 percent of individuals testing HIV positive. People in the lowest wealth quintile had the lowest prevalence rate of 7.8 percent. The wealth quintiles tie in well with the higher prevalence rates discussed above in the more urban commercialized provinces.

2.3.4 National response to the HIV/AIDS epidemic

The Zambian political leadership, along with other global leaders, pledged to do all it can within its powers to reverse the spread of HIV at the United Nations General Assembly Special Session on HIV and AIDS (UNGASS) of 2001. Zambia's development blueprint known as the National Development Plan, currently in its sixth phase (hence known as the Sixth National Development Plan, SNDP), incorporates HIV/AIDS related issues in all its programs, cutting across all sectors of national development.

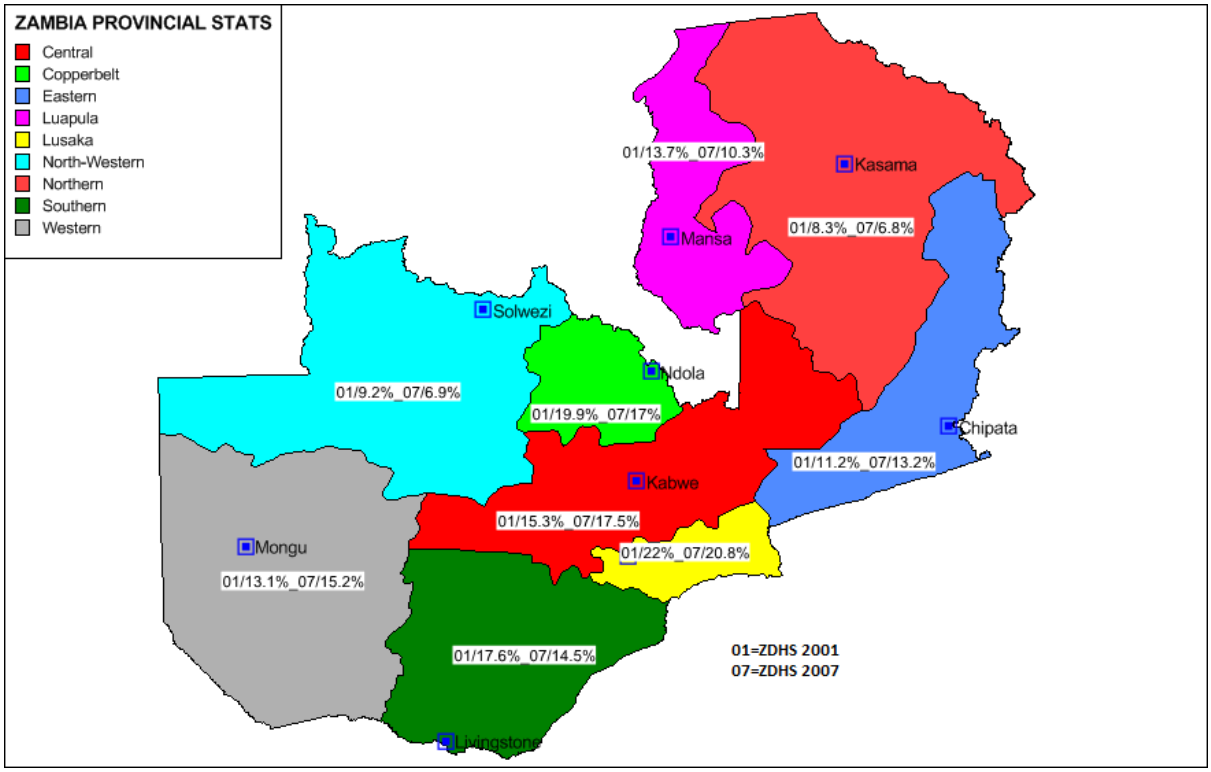


Figure 2.5: HIV prevalence rate by province and year, 2001-2007 (ZDHS 2001 & 2007)

The national response to the HIV/AIDS epidemic is in turn implemented according to plans set out in the 2011-2015 National AIDS Strategic Framework (NASF) which follows on from earlier strategic plans 2002-2005 and 2006-2010. The NASF sets out as its priorities to accelerate and intensify HIV prevention; accelerate the provision of quality treatment care and support for PLWHA; to mitigate the social-economic impacts of HIV/AIDS on the most vulnerable groups such as orphans and vulnerable children; and to strengthen the capacity for a well-coordinated and sustainably managed HIV/AIDS program in the country.

To achieve these objectives, the Government of the Republic of Zambia (GRZ) has scaled up the different HIV-related services over the last 10 years to reach as many people in the country as possible. Counselling and testing (CT) services were being offered in 1,784 health facilities countrywide in 2011 with nearly 2.04 million people receiving CT services. This represents 94 percent of all health facilities in Zambia and is a substantial increase from only 1,083 health facilities offering the service in 2007. During the same year, 560,000 pregnant women were tested for HIV in a direct effort to institute prevention strategies for the unborn children where the need would arise. In addition, 32,293 infants born to HIV-infected women were tested for HIV within 12 months of birth to determine their HIV status. This number

increased from 23,713 infants tested in the previous year. A recently added national prevention strategy for HIV in Zambia is male circumcision (MC) (National HIV/AIDS/STI/TB Council Zambia, 2010). With only 13 percent of Zambian males circumcised, the opportunity to further mitigate the spread of the HIV virus is high with increased circumcision of males aged over one year. The MC services are being provided as part of a comprehensive package of CT and Sexually Transmitted Infections (STI) testing and treatment.

Antiretroviral therapy services and general care services for PLWHA are offered in both public and private health facilities in the country alongside CT and PMTCT. In 2011, there were 509 health facilities providing ART services in all the provinces and nearly all districts of the country (up from 373 facilities in 2009). Further details of the ART services are outlined in the next section.

2.3.5 The antiretroviral therapy program in Zambia

While counselling and testing, as an entry point, is the most vital initial step in combating the HIV epidemic, providing treatment and care services to those individuals who test HIV positive is critical when their infection reaches advanced stages. Antiretroviral therapy (ART) service provision has seen a very rapid growth in Zambia over the last decade. During what could be described as the pilot phase in 2002, there were only 143 patients on ART in Zambia at the country's 2 national referral hospitals (one located in the nation's capital and the second located in a town in the Copperbelt province). Antiretroviral therapy was offered at these sites because at the time, these were the only facilities in the country at which both specialist personnel and equipment required to monitor the patients were available. A trend of the number of people in need of treatment and the corresponding number who were receiving the treatment in presented in figure 5 below. The 142 people on ART in Zambia in 2002 were against an estimated disease burden of 236,000 patients representing an unmet need for ART services of over 99 percent. During the development and expansion phases of the national ART response (2004 – 2005), capacity building and increases in the number of health facilities providing ART was put in place. This ensured that Health care workers were trained, laboratory equipment, logistics and information systems developed and put in place and more patients put on treatment from an array of additional entry points such as PMTCT, TB clinics, STI clinics and provider initiated testing for HIV. By the end of 2005, more than 51,700

people were on ART against a disease burden of over 256,000 (the unmet need had been reduced to 80 percent from over 99 percent in 2002).

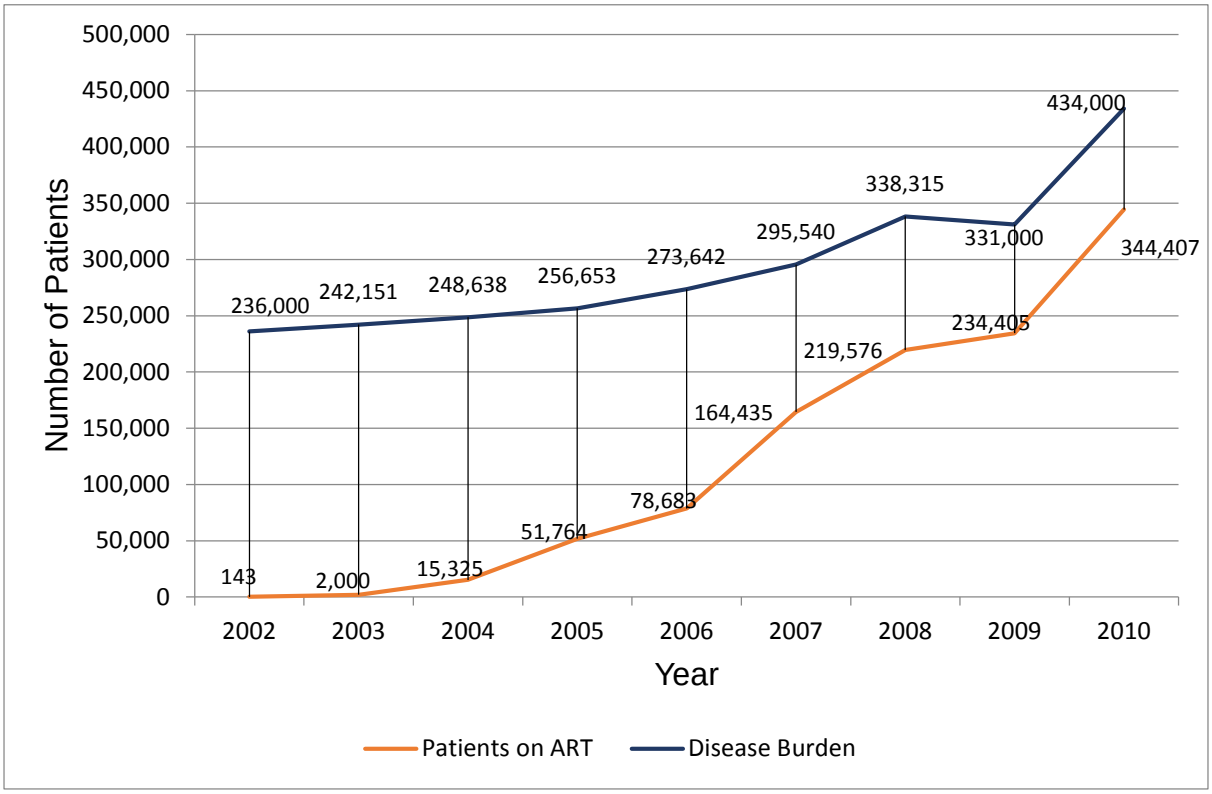


Figure 2.6: Antiretroviral therapy and disease burden in Zambia, 2002 – 2007 (HMIS, Ministry of Health)

Further expansion of ART services aimed at reaching rural and other remote communities was embarked on between 2006 and 2010. In 2010, patients on ART in rural areas increased to 34 percent compared with only 11 percent in 2008. The gap between people needing ART services and those actually receiving ART was consistently reduced over the years with only a 22 percent unmet need in 2011 (414,517 on ART vs. 535,685 requiring ART). ART services were being offered at 450 sites in 2011.

An integral component of the ART program during the years has been the release of ART protocols which are used by different practitioners to provide the care and treatment services to patients. These protocols describe which antiretroviral drugs should be given to PLWHAs in different categories and circumstances such as pregnant women, people presenting with advanced clinical symptoms, people presenting with important co-infections such as TB and so on. Contained herein is the all-important CD4 cut-off point at which ART is to be initiated

for any patient. In Zambia, prior to 2007, ART was commenced for all individuals whose CD4 count was less than 200 cells/µL of blood. This was in line with WHO recommendations for LMICs for the management of PLWHAs (World Health Organization, 2004, 2006). However, after sufficient research showed the benefits of commencing ART at higher CD4 count levels than 200 cells/µL of blood, the Zambian government adopted the new WHO guidelines. In 2007, the new cut-off point of 350 cells/µL of blood was the adopted as the criteria for initiating ART in both adults and paediatric patients and new guidelines were formally published in 2010 (Ministry of Health Zambia (MOH), 2010).

2.4 Chapter summary

This chapter has achieved the following:

- Provided a description of HIV and how it affects HIV-infected persons Provided a profile of the HIV epidemic in Zambia outlining its salient characteristics in the country
- Discussed the trends and patterns of HIV prevalence in Zambia and the national response to the epidemic

3 Literature Review

3.1 Introduction

In this chapter, healthcare modelling literature is introduced in order to provide a general sense of the utilisation and application of OR techniques in the field. Examples are presented in which different aspects and problems in healthcare are modelled before focusing on applications to HIV/AIDS. To illustrate these various research concerns, the remainder of the chapter is arranged into three broad categories labeled HIV/AIDS modelling, Survival Analysis and Economic Analysis in Healthcare. The first part is a discussion of studies outlining the OR techniques applied to the various aspects of the HIV/AIDS epidemic. Some of the different characteristics of the epidemic to which the reviewed literature relates include applications in prevention of HIV, the care and treatment of PLWHA, HIV transmission dynamics and other epidemiological considerations

The second part deals with the survival estimation of HIV-positive persons. Research is reviewed outlining the evolution of the research area from purely observational cohort studies in the early years of the epidemic to more sophisticated mathematical and other models developed after several years of observations. This section of the literature review ends with a synopsis of the different methodologies employed in survival analysis and how the current work is proposed to fit into this picture. Using a similar structure as above, a separate section of the chapter is dedicated to a review of literature on economic evaluation and related models. HIV/AIDS-related economic analyses are presented in four broad commonly used methodologies applied to a similar spectrum of the aspects of the epidemic (transmission, prevention, care and treatment) as discussed in the survival analysis part of the literature review.

3.2 Operational Research methods in healthcare

The application of Operational Research (OR) in healthcare has been practiced for over 40 years (Brailsford, 2005; Flagle, 2002) and extensive documentation now exists in the literature of these practices (Katsaliaki & Mustafee, 2010). Decision making in diverse areas of healthcare have been aided by operational research including (but not limited to) hospital capacity planning and management, supply chain management in blood banks, evaluation of

hospital efficiency, national drug control policy, decision making for bioterror preparedness, and analysis of asthma treatments (Brandeau, Sainfort, & Pierskalla, 2004). Rais and Viana (2011) conducted a survey of OR in healthcare with a focus on optimization methods employed in healthcare planning in problems such as demand forecasting, location selection for health centers and emergency vehicles as well as capacity planning (Koch & Weigl, 2003; D. B. Smith & Aaronson, 2003; H. K. Smith, Harper, Potts, & Thyle, 2009; White, Smith, & Currie, 2011). A broad spectrum of research has been conducted using optimization in diverse aspects of healthcare including disease diagnosis and treatment planning (Censor, 2003; Olafsson, Jeraj, & Wright, 2005; Trofimov, Vrancic, Chan, Sharp, & Bortfeld, 2008), prevention of diseases (Kresel et al., 1987; Welte et al., 2004), scheduling of patients, doctors operating rooms (Vermeulen et al., 2009) and so on. Specialized health delivery aspects such as organ transplant or donation equally benefits from optimization methods in OR.

Davies and Davies (1995) proposed discrete event simulation (DES) to be one of the methods in OR most suited to modelling health systems because of its ability to model individual entities (patients in this case). Furthermore, the authors argue that DES allows for incorporation of resource constraints in the system while also accounting for as much detail as the real life system has since it does not have to meet restrictive assumptions typical of analytic models. This position is supported by another researcher (Caro, 2005) who holds that the method of DES allows for a disease to be modelled naturally without much restriction but with the added advantage of providing the flexibility of conducting sensitivity analysis which can be very useful in studies where different costing policies are necessary to be studied to inform decision making. DES has also used to evaluate different disease treatment policies as in the case where it was used to test the effectiveness of a new treatment for osteoarthritis pain (Ward et al., 2007).

Various simulation methods have been used in healthcare modelling to investigate or evaluate problems in a wide range of categories such as 1) Healthcare system and design; 2) Management of healthcare planning; and 3) Medical management (Pierskalla & Brailer, 1994). Simulation as an operational research method has been employed in other specific areas such as the improvement of healthcare systems in hospitals where various studies have concentrated efforts in the different aspects of hospital service delivery (inpatient,

outpatient, laboratory, pharmacies, etc) (Gunal & Pidd, 2009). Simulation has also been used in the study of the transmission dynamics of tuberculosis (TB) against the background of TB-HIV co-infection (Mellor, Currie, & Corbett, 2011; Roeger, Feng, & Castillo-Chavez, 2009).

Over the last several decades, healthcare expenditure has increased substantially and with it has come the need to evaluate the cause and effects of various aspects of healthcare in relation to the money spent in the sector (Noelle, Jaskulla, & Sawicki, 2006). As a result of this, OR methods have been extensively applied to the area of economic evaluation of healthcare ranging from the cost of different treatment policies to the lifetime costs of certain diseases (Barton, Bryan, & Robinson, 2004; Jackson, Sharples, & Thompson, 2010). Others apply OR to the problem of resource allocation for preventive HIV activities in the case where resources may be allocated at multiple levels (Lasry, Zaric, & Carter, 2007). Other research in resource allocation includes areas such as in improving the efficiency of hospital operations (Aktas, Ulengin, & Onselsahin, 2007), the location of trauma systems relative to the needs of the communities they serve (Branas, MacKenzie, & ReVelle, 2000). Decision trees are used in health economics as tools to aid decision making at the aggregate level and are well understood as modelling methods (Brennan, Chick, & Davies, 2006).

With the above overview of different OR strategies applied in general healthcare, the following section focuses on HIV/AIDS modelling by discussing the different OR techniques and which situations they have been applied to, as reported in the literature.

3.3 HIV/AIDS modelling

Modelling HIV/AIDS has been practiced and reported in research work since the 1980s when the disease became a public health concern (Roberts & Dangerfield 1990). Like any other epidemic, the HIV/AIDS epidemic has been studied and modelled by scientists in a variety of fields including epidemiologists, statisticians, mathematicians, operational research specialists and other applied disciplines (Fusaro et al., 1989). Furthermore, different aspects of the pandemic have been of interest including, but not limited to, transmission dynamics, magnitude of the epidemic, infectivity and infection distribution, survival analysis, disease progression and clinical trials. Aside from the above epidemiological realm, substantial

research into the various aspects of planning, financing and related prevention and treatment options has been published.

Owing to the lack of empirical information about the dynamics of the disease in the early years of the epidemic, deterministic models were initially much more sensible to use than stochastic models (R. M. Anderson, May, & McLean, 1988; R. Anderson, Medley, May, & Johnson, 1986). Deterministic models have been used extensively to model spread of the HIV and other similar viruses successfully (Perelson, 2002). Further areas of application in HIV are in public health policy evaluation and the evaluation of different intervention strategies in prevention, care and treatment of the disease. Economic evaluation of various aspects of HIV have benefited from different operational research modelling exercises over the last several years. The following sections present an evaluation of the different forms of models applied to healthcare and HIV.

3.3.1 HIV/AIDS modelling in developing countries

In order to put the work in this thesis into context, HIV/AIDS modelling in developing countries is highlighted followed by a discussion of the different methods used in HIV/AIDS modelling. Since the majority of people living with HIV/AIDS are resident in sub-Saharan Africa, there has been a substantial amount of research effort to model the pandemic in this geographic region which represents the developing countries as opposed to the developed western countries of the northern hemisphere. A number of methods have been used in modelling HIV/AIDS in different settings described by Salomon et al. (1999) as ranging in complexity from “simple extrapolations of past curves to complex transmission models.” Based on an epidemiological model in sub-Saharan Africa and South East Asia, Hogan et. al. (2005) developed a model to assess the costs and health effects of a range of interventions for preventing the spread of HIV and for treating people with HIV/AIDS in the context of the millennium development goal for combating HIV/AIDS. A model to study the cost effectiveness of a community-based intervention for reducing the transmission of Schistosoma haematobium and HIV in Africa was developed using data from Rural Zimbabwe (Ndeffo Mbah et al., 2013). In a paper to investigate the impact of mathematical modelling of HIV/AIDS on policies and programs in the developing world, Stover (1999) conducted a literature review and summarized those findings supported by more than one group of researchers. Evidence gathered showed that

simulation has contributed significantly to understanding important issues to do with the epidemic including the benefits of early intervention, the need for combined intervention, demographic impact of HIV/AIDS and so on. The paper further proposes that simulation modelling can play an important role in helping establish monitoring, evaluation and research priorities and systems. Evaluation of interventions would be one of the beneficiaries of mathematical modelling.

HIV/AIDS modelling in developing countries has also been used to model the effects of the pandemic on the African economy as well as aspects of the cost effectiveness of prevention and treatment programs (Dixon, 2002). Other research in the developing world include the estimation of the HIV/AIDS in sub-Saharan Africa using seroprevalence data from antenatal clinics.

3.3.2 Compartmental Models

Widely used in medicine, general healthcare and elsewhere (Jacquez, 1972), compartmental models are founded on the principle that an entity (or a group of entities) will occupy one state (compartment) of a system at any given time and move on to the next compartment governed by appropriate mathematical equations. The compartmental models built can either be deterministic or stochastic depending on assumptions made (i.e. whether chance is taken into consideration or not) which govern the movement of the entities between states (Garnett, 2002; Mishra, Fisman, & Boily, 2011).

In HIV/AIDS research, compartmental models have been used in a wide variety of problems and situations ranging from studying the effect of male circumcision on female-to-male transmission of HIV in Botswana and Kenya (Nagelkerke, Moses, De Vlas, & Bailey, 2007) to the comparison of heterosexual and unsafe injections as modes of HIV transmission in Africa (French, Riley, & Garnett, 2006). Other applications have been the exploration of the HIV/AIDS epidemic among IDU in Thailand in order to see long term effects on the population (Bogard & Kuntz, 2002) and others. A sample of relevant HIV/AIDS studies employing this modelling technique is described below.

Abu-Raddad et al. (2008) explore the role of the Herpes Simplex Virus 2 (HSV-2) in the prevalence of HIV in Africa by constructing a compartmental model that took into

consideration both the transmission and acquisition dynamics and their interaction between the two viruses. From this study, it was estimated that HIV was not a significant driver for HSV-2 prevalence in the population while up to 35% of the prevalence of HIV in Africa was attributable to the HSV-2 virus.

In another study, Malunguza et al. (2010) use a compartmental model to show that the use of a single strategy approach (either condom use alone or ART) can have a desirable impact on HIV prevention among homosexual, heterosexual or bisexual people. They show that in the case of Zimbabwe, where like most of Africa, homosexual activities are taboo and illegal, such approaches may be the only way to implement HIV prevention policies among these high risk groups of people who would not otherwise come out to seek HIV prevention services on account of their sexual orientation.

A deterministic compartmental model was used to assess the potential effectiveness of a three-pronged intervention aimed at reducing HIV prevalence among male and female commercial sex workers (CSW) and their clients in southern India (Williams et al., 2006). The three components evaluated were condom use, sexually transmitted infections (STI) management and periodic presumption of treatment of STI. Results showed that condom use accounted for up to 20% averted infections out of the total estimate of up to 30% infections expected to be prevented by the combination of all the components.

Granich et al. (2009) used both a deterministic and stochastic model to investigate a theoretical strategy in which yearly universal counselling and testing for HIV was implemented and followed up with immediate antiretroviral therapy as a way to eliminate the HIV pandemic. Using empirical data from South Africa, the study shows that the commencement of ART as soon as HIV is diagnosed in the general population leads to substantial reduction in mortality rapidly and resulting in a near concentrated epidemic which is undoubtedly easier to manage.

Modelling healthcare related problems using compartmental models is usually an easy decision to make considering that the health of an individual is representative of one state

and one state only until the person moves on to the health state. The transition probabilities from state to state need to be computed in order to run the models.

3.3.3 Markov models

Markov models are a family of models built to assist with decision problems which involve exposure to risks or events over time, on-going exposures or situations where the specific timing of an event is considered important or uncertain(Stahl, 2008). The fundamental assumption in Markov models is that the distribution of the entities or elements in the model at all future states at time (t_{n+1}) is solely determined by the status of the entity at time (t_n). In healthcare, a patient for example may exist in one and only one of a finite number of health states which change at intervals of time referred to as Markov cycles. In this section, literature is reviewed in which different problems around HIV/AIDS are studied by use of Markov models. The first issue reviewed here is on the incidence and prevalence of HIV followed by disease progression. Other issues are HIV transmission and the status of the body's immune system in the face of HIV infection.

In an early publication, Bongaarts (1989) attempted to predict long-term incidence and prevalence of HIV and AIDS as a Markov system. He further proceeded to hypothesise the long-term impact of the epidemic on the demographic profiles of the population. To achieve this, he analysed the resulting survival patterns against the age, marital status and sex of the patients along with behavioural factors such as sexual behaviour and others. Another group of researchers used a Markov model to predict AIDS incidence and prevalence in a population of homosexuals in England and Wales (Aalen, Farewell, De Angelis, Day, & Gill, 1997). Further impacts of sexual contact patterns between men and women on the spread of HIV in urban centres of selected African countries using mathematical methods employing aspects of Markov processes is also reported by others (R. M. Anderson, May, Boily, Garnett, & Rowley, 1991; Garnett & Anderson, 1993).

In the area of disease progression in HIV/AIDS, Binquet at al. (2009) used data based on HIV+ patients seen between 1996 and 2004 in north-eastern France to model the effect of the different drivers of HIV disease progression. The identified stages of the disease were based on 4 ranges of CD4 counts in increasing order such that when a patient moved from one stage

to a higher one, this was recorded as clinical progression of the disease. The researchers employ a multi-stage Markov model to investigate prognostic factors that have an impact HIV evolution. Using five different categories of CD4 counts as markers of immunological evolution and clinical progression of the disease, the impact of different prognostic factors on the transition through the different HIV disease stages was modelled.

In related disease progression research, in order to study how the HIV virus invades its human host, Yuan and Allen (2011) built a combination of deterministic and stochastic models (including Markov Models) to characterise the distinct viral release strategies known as bursting and budding. The virus, they hold, either reproduces within the host cell and then releases itself into the blood (burst) or it continuously releases itself into the blood as replications are made (budding). For this task, the researchers employed the use of Continuous Time Markov Chain models (CTMC) and stochastic differential equations. The application of Markov models in studying similar aspects of HIV disease progression is well researched (Guihenneuc-Jouyaux, Richardson, & Longini, 2000; Jackson, Sharples, Thompson, Duffy, & Couto, 2003; Kanekar, 2010; Satten & Longini Ira M, 1996; Titman & Sharples, 2009; Vaughan, Drummond, & Drummond, 2012).

To understand the status of the body's immune system in the face of HIV infection a model was developed by Mathieu et al. (2005) in which they used both CD4 and Viral Load (VL) to model the status of the immune system and the state of the infection respectively. They employed a series of methodological combinations including a continuous time homogeneous Markov process (HM), the HM-covariate model (by introducing covariates into the HM model), an extension of the HM to a piecewise homogeneous model (PHM) and a combo of the HM-cov and the PHM models.

Palombi et al. (2012) explored the prospects of the elimination of the HIV/AIDS epidemic by using a Markov prediction model. This was achieved by parameterising the model (i.e. CD4, VL, ART use or not) using empirical data from Malawi and Mozambique. Several health states were formulated and the model was then used to simulate the epidemic in a hypothetical population of a rural district in southern Africa of 3,000 inhabitants. The results indicated that

the treatment of all infected individuals could result in a very significant reduction in incidence of HIV which could theoretically lead to a sterilisation of the epidemic.

In contrast, the long term implications of ART are reported (Tebas et al., 2001) in the scenario where treatment is initiated immediately or staggered over a period of time. The Markov model developed analysed together with a set of decision trees to gain an in-depth understanding of the different initiation policies, reveals that the initiation of ART immediately would result in a 57% undetectable infected population with a large (38%) proportion of the population with a drug-resistant virus compared with 64% undetectable (with only 24% drug resistant) population if initiation of ART was provided to 10% of the population annually from the time of detection.

Other uses of Markov models in HIV/AIDS modelling include the estimation of the size of the epidemic in the general population and in subgroups of the general population such as IDU of homosexual men (Amundsen et al., 2000; Lieb et al., 2010), estimation of HIV population dynamics (Sloot, Ivanov, Boukhanovsky, Van De Vijver, & Boucher, 2008). The application of Markov models to economic aspects of HIV is discussed in detail below. Markov models are well understood and are among the most widely used in HIV/AIDS research, as seen above, as well as in general healthcare. In the case of long term survival, estimation of a Markov model requires a significantly large amount of computations in order to generate all the transition probabilities. This is a requirement because all health states in the model ought to be computed. Other methods such as Discrete Event Simulation handle this issue of transitions differently as outlined below.

3.3.4 Decision Trees

Decision trees are used to aid the process of choosing the best strategy which enables a decision maker reach their goal by representing the problem in a treelike structure. The separate branches of the tree represent the different choices and their outcomes. In healthcare, the choices at each decision node often correspond to different ways of managing a medical condition, while the random nodes represent the possible outcomes for a patient in terms of morbidity, incapacitation, life expectancy or mortality Using a time-homogenous Markov model to generate transition probabilities, Piroth et al. (2005) constructed a model

using a decision tree designed to represent the possible stages at which antiretroviral therapy could be initiated for PLWHA based on a 10-year follow-up period. Conclusions from the study indicate that there would be desirable benefits on the outcome of interest, namely maintaining a CD4 count of at least 500 cells/µL blood, if treatment were commenced immediately for individuals who had advanced infection (i.e. viral load over 100,000 copies of HIV per milliliter of blood [100,000 copies/mL]) and delay the administration of the protease inhibitor-based ART if the viral load was less than 3,162 copies/mL and CD4≥350 cells/µL of blood. Using data from 17 Sub-Saharan African countries, Aledort (2006) used a decision tree to investigate diagnostic screening strategies being used up to the year 2005 in comparison with potential new strategies which could deliver the HIV sero status of infants from as early at 6 months after the birth (from an HIV-infected mother). This model, whose population was infants <12 months in the sub-region, yielded as its outcome a number of health benefits such as Disability adjusted life years (DALY) saved and proportion of disease burden averted as a result of more efficient HIV diagnosis and therefore timely treatment. Furthermore, the early infant diagnosis (EID) proposed showed potentially improved outcomes because both eligibility and availability of ART was projected to increase.

The use of decision trees as described above in HIV research has not been applied successfully to survival estimation as the method is more suited to treatment policies and similar decision-related healthcare practices which involve choosing one route over the other. For survival analysis and estimation, more appropriate tree-structured methods such as Survival Trees are used and these are discussed in the survival analysis section of this work.

3.3.5 System dynamics

Developed in the 1960s as a set of methods to be used in the application of feedback concepts to social systems and later to complex feedback loops in business (Forrester, 1968), System Dynamics (SD) has evolved as a method of choice in various aspects of healthcare (Taylor & Lane, 1998) including HIV modelling (Atun, Lebcir, McKee, Habicht, & Coker, 2007; Lebcir, Atun, & Coker, 2010). The main feature of SD is that stocks of people, materials or other entities of interest accumulate in compartments and leave to enter other compartments governed by systems of algebraic relationships and differential equations. Brennan et al. sum it up by stating that the rate of change of the system is a function of the systems' state itself

(i.e feedback). The method is appropriate for studying large and complex phenomena such as spread of disease (Bagni, Berchi, & Cariello, 2002), estimating the impact of diseases on the public (Nyabadza & Mukandavire, 2011) and the evaluation of economic aspects of the health service delivery (P. C. Smith & van Ackere, 2002) among others.

In 1990, a comprehensive SD model of the transmission dynamics of AIDS among homosexuals in the UK was developed (Roberts & Dangerfield, 1990). The model was designed to account for the complex virological and behavioral facets of the epidemic such as infection rates, the incubation period of the disease and the heterogeneity of sexual mixing (partner change rates and high sexual risk practices). Heidenburger and Flessa (1993) also developed a system dynamics model in the early 1990s to provide helpful understanding of both the dynamics of the epidemic and policy implications using data from Tanzania. The model was able to illustrate possible medical or economic characteristics of the epidemic while taking into consideration the behavioral and virological profiles of the population. Needle sharing as the mode of transmission of HIV was reported by Homer and St Clair (1991) in a study of a population of IDUs in California, United States in which the sub focus was also estimating HIV-related deaths . The SD model used was built on a structure consisting of three IDU-needle sharer population stocks and related flows. The IDU population flowed from the uninfected sharers stock to infected sharers then on to the Infected Former Sharers stock. The model accounted for additional losses of the population from each stock level by either death or standard loss (defined as out-migration or non-HIV death) besides the flow described above.

More recently, Lebcir et al. (2010) conducted an SD study to investigate the interplay between TB, Multi Drug Resistant TB (MDRTB) and HIV/AIDS transmissions for a population of Injection Drug Users (IDU) in the region of Samara in Russia. The model was designed to allow for the MDRTB cure rates to be varied by between 5% and 80% while ART coverage was allowed to be anywhere from 0 to 100 %. This variation allowed the researchers to explore the resulting dynamics at the population level and make conclusions. Comparable results were reported in an earlier paper for a different IDU population in which MDRTB and HIV interact in the same way in Estonia (Atun et al., 2007).

One of very few early SD models developed to investigate the effect of ART in the treatment of HIV/AIDS was reported in 2001 (Dangerfield, Fang, & Roberts, 2001). The model developed by these researchers utilised a homosexual database among UK HIV+ patients as their base data. The study explored treatment outcomes of triple ART therapy as it was being introduced to replace mono and dual therapy to treat AIDS. Some of the scenarios explored include the effects of ART on both the survival time and infectivity of the patient, the impact of ART during the time when it was at its most efficacious on new infections and effects of risky sexual behaviour by patients on ART. The findings of the research showed that triple therapy showed impressive results in reducing new infections owing to the suppression of the virus but that risky sexual behaviour could slow down the benefits of triple therapy with regard to new infections.

As seen above, the application of system dynamics in HIV has been mainly in understanding the transmission dynamics of the virus on its own or in the case of co-morbidity with diseases such as TB. Mortality due to HIV has also been incorporated in some studies. All research conducted using SD, as the method demands, has been at the population level and lacks the ability to replicate the individual behaviours of the PLWHA.

3.3.6 Discrete Event Simulation models

A discrete event simulation (DES) model is a mathematical structure in which the state of the system changes only at those discrete points in time at which events occur and not at fixed time intervals. In essence, the system is modelled as a series of events, that is, instances in time when a state-change occurs (Robinson, 2004). The series of state to state changes mimic a queuing system in which the attainment of a new state is modelled as a discrete event which is a function of time. Although DES has been used extensively to model queuing scenarios in healthcare, it has also been used to simulate complex diseases such as chronic illnesses including HIV/AIDS. A DES model has the ability to use stochastic processes to simulate outcomes for a theoretical cohort of patients which replicate the statistical characteristics of real life patients as specified in the model by Simpson et al (2009). To model the course of a disease more naturally, DES is more flexible than Markov modelling because here, patients can compete for resources in the system such as health care workers, drugs or space and then change their health state as a result of the outcome of such interactions. These models are

considered complex networks. The literature discussed below is focused on available research in HIV/AIDS using DES. Areas of application include PMTCT, HIV transmission, HIV vaccine trials and HIV co-infection with TB.

The method of DES is employed in the prevention of mother to child transmission (PMTCT) set up to evaluate the benefits of ART at childbirth and/or different bottle-feeding strategies in a developing country setup (Rauner, Brailsford, & Flessa, 2004). Data from Tanzania and a variety of sources including the WHO was used to populate the model, creating a population of individuals who have the attributes of the typical developing country population under study. This stochastic model investigated the outcomes for a treatment only and treatment and bottle-feeding scenario by producing estimates of the prevalence of the virus in adults as well as the Cost-effectiveness of the two policies. A similar model was developed to evaluate intervention strategies in the area of PMTCT by Vieira et al. (2009) with use of data from Botswana, a Sub-Saharan African country with one of the highest HIV infection rates in the world.

In the area of HIV transmission, DES has been used to model social interactions and HIV transmission in small world networks (SWN) (Vieira, Cheng, Harper, Senna, & De Senna, 2010). The SWN was assumed to have a population living in a complex network of social, cultural and other interactions. Other characteristics of the population also taken into consideration include the demography, diseases and types or levels of service delivery among others. To evaluate an HIV vaccine trial design known as the Retrospective Partner Trial (RPT), Adams et al. (1998) used DES as the appropriate tool for this purpose. The aim of the research was to quantify the differences between a standard vaccine trial and the RPT HIV vaccine trial design with its associated statistical methods for calculating the vaccine effects. Simulating a closed population of homosexual males, complex transmission system dynamics were modelled incorporating various sexual contact patterns such as length of partnership, differing partnership-seeking propensities, variable rates of sexual activity and belonging to concurrent partnerships. The RPT design's was found to have a better statistical power in comparison with the standard vaccine trial for the case where vaccine had a low susceptibility effect and a strong infectiousness effect.

As with any other virus, the co-infection of HIV with other diseases has been explored by many researchers. Mellor et al (2011) developed a DES model of endemic TB, with HIV co-infection, incorporating household structure in the high HIV-prevalence Sub-Saharan Africa sub region. The model focused on the transmission of TB against an assumed random transmission of HIV. Made up of a sub-model each for HIV and TB, this was to ensure that the accurate progression of each disease was replicated. The major finding from this work was that TB control was effectively tackled if healthcare authorities targeted their TB case finding efforts to those households with HIV-infected individuals.

The co-morbidity of TB and HIV is further examined by predicting the effect of HIV on TB outbreaks by Porco et al. (2001). Their DES model was designed to account for the co-infection at different states of HIV (by WHO stage I, II, III and IV) (World Health Organization, 2010a) and TB (from newly infected through to active infectious TB). This was set up such that the individuals who have active TB are infectious but they are allowed to become non-infections as a result of treatment or death. Results reported indicated that the presence of HIV had the potential to increase both the severity and probability of TB outbreaks although very high TB treatment rates could substantially reduce this amplification. Furthermore, the HIV presence in individuals was hypothesized to cause an even more pronounced effect on TB outbreaks if long-term TB infections were considered in the model (i.e. reactivation of TB). This is against the background that HIV was expected to cause TB to recur in patients more frequently in the developing world where there are higher number of people latently infected with TB coupled with much lower TB treatment rates. The model did not model long-term TB infection. Other work in the comorbidity of TB and HIV have been reported by Getz et al. (2005) and Raimundo et al. (Raimundo, Engel, Yang, & Bassanezi, 2003).

The ability of DES to easily include many conditions or attributes in the models it has been used to study makes it a possible choice in the modelling of chronic diseases such as HIV/AIDS. For example, the co-infection of HIV and TB, the different transmission dynamics of HIV in vaccine trials and a host of other opportunistic infections are all easily incorporated into the model without the need to compute transmission probabilities for each of the additional health states the inclusion demands.

3.3.7 Agent-based Simulation models

Agent Based Simulation (ABS) is a modelling approach in which the 'agents' or entities in the model are assigned individual characteristics which influence their behaviours and determines how they interact with other agents. All the agents in turn interact with the environment in which they exist resulting in models of very complex systems. Distinctly different from other modelling techniques by this salient feature of developing the model from bottom-up, ABS is a powerful computational tool which allows the modelling of simultaneous interactions of agents with each other and the environment in which they operate be they social, structural or otherwise. The effect of this interaction gives rise to changes in the state of the system under study providing a basis to recreate and analyse the conditions of complex real-life phenomena. Here, a sample of ABS models looking at questions in HIV/AIDS are discussed with a further focus on HIV prevention and transmission.

Richardson and Grund (Richardson & Grund, 2012) argue that a more detailed understanding of the macro level HIV transmission among IDU is better understood by use of ABS. They demonstrate this by constructing a set of four calibrated ABS models with increasing complexity of the interactions of the agents and the networks they belonged to and by adding the dimension of additionally belonging to an IDU injection gallery. Results show that as the model complexity is increased, then so do the levels of HIV seroconversion making the point that studying the dynamics of diffusion patterns at the aggregate (macro) level may not be as beneficial as accounting for the complexities of the IDU interactions with each other and the environment in which they operate.

In a recent publication on HIV transmission, Beyrer et al. (2012) built an Agent-based simulation (ABS) model to incorporate several key drivers of HIV transmission among MSM. The drivers of the transmission accounted for in the model include the existence of a high number of partners in a population, the higher transmission rate of HIV relative to vaginal sex and others. Parameterised with data from urban USA and Peru (high income and middle income countries respectively), the model was used to estimate developing countries' transmission patterns and other underlying characteristics by adjusting access to health care to as low as one-third of the levels in the richer countries.

To further explore other aspects of HIV transmission, recent research has been conducted. The existence of concentrated HIV epidemics outside Sub-Saharan Africa is well documented in the literature (WHO UNAIDS UNICEF, 2011). An inevitable aspect of the presence of these populations, in addition to HIV among heterosexual partners, is the possibility of the epidemic spreading across the groups or populations. One effort to quantify the magnitude of the extent to which HIV-1 moves between these high risk groups is reported by Graw et al. (2012) using ABS alongside phylogenetic analyses. In their model, a distinction is made on the type of individual or agent by viewing infected and uninfected (or susceptible) individuals. The infected individuals are characterised by demographic, virological behavioural and social properties and belonging to the IDU, MSM, heterosexual contact or sex worker high risk categories. Uninfected individuals are only assigned to any one of the four high risk groups above. The model tracks three events in the epidemic namely infection, development of AIDS and death. The results of the model using data from Latvia show that the heterosexual epidemic in that country is being sustained by IDU who act as the bridge for the epidemic to cross from one group to the other. The researchers point out that although there is a very low chance that IDU may trigger a generalised epidemic in Latvia, future policy implementations and other interventions in prevention, care and treatment of HIV should be targeted at this population.

In the HIV prevention sphere, the prevention of HIV transmission among MSM was studied by Sullivan et al. (2012) who use the same model developed by Beyrer et al (2012). The team adds data from Kenya representing a generalised epidemic with some MSM infection and data from India which has a mixed epidemic with MSM, IDU and heterosexual infections. Using similar setting-specific characteristics as in the Beyrer model, the model explores, as prevention methods, condom use, oral pre exposure prophylaxis (PrEP), improved ARV initiation and a combination of these. Results indicate that the combination of all the interventions has a realistic potential to reduce incidence and that the increased coverage of efficacious interventions is critical for the reduction in incidence to be achieved. Furthermore, it is evident that additional aspects such as adherence to the prevention strategies will also have significant positive effects on the epidemic.

One of the noted differences therefore between the research situations and problems conducted between DES and ABS is that the latter predicts the state of the system taking into consideration the interaction of the entities with each other or the environment beyond just carrying individual-level attributes. This interaction between entities (HIV+ patients in this case) is not of interest because the objective of this current work which is survival of a patient on ART is assumed to be independent of the interaction the patient may have with other patients on the same treatment. It may be argued that re-infection of an HIV positive person is possible and could affect survival. In this study, such effect is assumed to be zero. Further discussion on choice of method for this work is discussed at the end of the chapter.

3.4 Survival analysis

With its origins in the 17th century as either weekly bills of mortality in London and as lifetables, survival analysis was until the second World War used by actuaries, biomedical researchers and statisticians as lifetables (Lee & Go, 1997). More formal techniques were published after the war with notable papers being those by Kaplan and Meir (1958) and Cox (1972). The death of a biological organism or failure of a machine (or machine part) in engineering is the core interest in survival analysis. Survival analysis techniques are used in many areas of science and beyond. In human resource management the retention or loss of staff may be modelled as a survival problem (Kaminski & Geisler, 2012), in genetics the identification and quantification of protein in genes is studied by using survival methodology to carry out differential expression analysis of proteins (Tekwe, Carroll, & Dabney, 2012). In the engineering sciences, the times to failure of machine parts or the lifetime of a bridge across a river and so on are all modelled as survival problems (Chevalier, Smith, & Dean, 2012; Okasha, Frangopol, & Orcesi, 2012; Tao & Tam, 2012).

Other applications of survival analysis are in as diverse and different disciplines as marine biology and wildlife (Fletcher et al., 2012; McGarvey, Linnane, Feenstra, Punt, & Matthews, 2010), perishable food management and planning (Cruz et al., 2010; Libertino, Osornio, & Hough, 2011), cancer research and cancer medical practice (Abdollah et al., 2012; Vercelli, Lillini, Capocaccia, & Quaglia, 2012), ocean engineering (Long, Lee, & Kim, 2010), actuarial science (Lopez, 2012), economics (Chen, Fan, Pouzo, & Ying, 2010), energy (Niu, Zhang, Zhao,

& Niu, 2012) and so on. In the sections that follow, applications of survival analysis to HIV and specifically ART are discussed.

Some general applications of long-term survival in the context of healthcare include the case where median survival time and long-term survival probabilities of surgery patients in ICU at a large western Australian hospital were fitted to a Cox proportional hazard regression model. The model results indicated that important predictors of long term survival of such patients (between 6 and 60 months) included age, gender, co-morbidities, severity of illness and duration in ICU or organ failure (Ho, Knuiman, Finn, & Webb, 2008). Related work in estimating the survival of critically ill patients is well researched and documented (Bagshaw et al., 2005; Golestanian, Liou, & Smith, 2009; Hartl, Wolf, Schneider, Küchenhoff, & Jauch, 2007). Given the general introduction and examples of survival analysis above, the next section delves into the specific area of survival analysis for people on ART.

3.4.1 Antiretroviral therapy (ART) Survival estimation

Some of the early work in survival estimation of people with HIV/AIDS was published by Lemp et al. (1990) based on patients enrolled between 1981 and 1987 in San Francisco, California. The reported mean survival was 12.5 months in this study with only a 3.4% chance of survival to 5 years after diagnosis of HIV. Similar work reported during this early phase of the epidemic was by Marasca and McEvoy (1986) and Harris (1990). There have been further studies undertaken during the last decade to estimate the survival (and life expectancy) of HIV-infected people on ART (Grover & Shakeri, 2007; Henriques et al., 2012; Kuhn, Thomas, Singh, & Tsai, 1998; May et al., 2007). Different methodologies have been employed in the estimation ranging from Mathematical models (Dasbach, Elbasha, & Insinga, 2006; Hallett, Gregson, Dube, & Garnett, 2008; Yiannoutsos, 2009) to a series of different simulation models (Walensky et al., 2006).

Survival estimates for HIV-infected people presented in research findings are based on a number of different assumptions mainly to do with the attributes attached to the entities (PLWHA) at the beginning of the simulation. There is consensus on some of the critical attributes which most influence the survival patterns, rates and other aspects of HIV/AIDS treatment outcomes. Of these CD4 and Viral load stand out as being some of the most

important (Egger et al., 2002; Mathieu et al., 2005). The CD4 counts have been used in the developing world mainly on account of the lower cost of the tests (Phillips et al., 2008) compared to viral load. Other studies have used CD4 cell counts, Viral Load, the development of opportunistic infections (OIs) and adverse drug reactions to estimate the clinical benefits and cost-effectiveness of ART (Freedberg et al., 2001).

The following three sections of the literature review forms three broad groups of methods used in survival analysis for PLWHA. These are cohort analysis, mathematical and statistical models as well as computer-based simulation models. As is explained below, this grouping is not strict as some models have more than one method used.

3.4.2 Cohort analysis

Cohort analysis is a general strategy which is used to analyse data relating to a group of people who have in common a certain event during a specified period of time. The event could be year of birth (birth cohort), people who joined (or left) the labour force during the same month (labour force cohort), women who had a first child in the same year (first-parity cohort) and so on. The literature reviewed in this section refers to the survival estimation of cohorts of HIV infected patients who were either infected during the same period of time or who commenced ART during the same time period.

The improved survival among HIV+ people after ART initiation is demonstrated by the study of the mortality patterns in an early cohort of HIV+ people in British Columbia, Canada for persons initiated on ART between 1992 and 1996 (Hogg et al., 1998). With a sample of just over one thousand, patients were observed from start of therapy until either death or the development of AIDS. Kaplan-Meier and other statistical methods were used to analyse the outcomes of interest. At 15 months after initiation on ART, there was an observed survival of about 98% beyond this point in the cohort indicating the efficacy of the ART administered to the patients. A population-based cohort study to estimate survival and age-specific mortality in HIV-infected people in Denmark for the period 1997 to 2005 was undertaken by Lohse et al. (2007). They compared survival and age-specific mortality between HIV-infected people and non-infected people from the general population and reported survival from the age of 25 for all subjects. Among HIV-infected people, the median survival was 19.9 years while this

was as high as 51.1 in the general population. Data analysed for survival in the new millennium however (2000 to 2005) showed a survival of 32.5 years. The study provided relatively robust estimates as it included all stages of HIV disease stage, co-morbidities and variable times of commencement of ART.

The Antiretroviral Therapy Cohort Collaboration (ART-CC), a multi-national cohort study of people on ART in 10 countries in North America and Europe, compared changes in mortality and life expectancy at age 20 and 35 years among people on ART (Antiretroviral Therapy Cohort Collaboration, 2008). The study was targeted at persons aged 16 years and above at ART initiation during three periods: 1996-99, 2000-02 and 2003-05. The analysis of the results was disaggregated by baseline CD4 count, sex and IDU history for each patient. The results showed that life expectancy at the age of 20 years was 36.1 years in the period 1996-99 compared with a higher life expectancy of 49.4 years in 2003-05. Women were found to have a higher life expectancy than men and people with a history of injection drug use had a lower life expectancy than the rest of the population who did not have drug use history. The life expectancy of those patients who started ART with baseline CD4 count higher than 200 cells/µL was more than those whose CD4 count was lower than 200 cells/µL.

In South Africa , long-term outcomes (virologic, immunologic, clinical) of ART at a large HIV/AIDS health facility were evaluated and reported by a Sanne et al. (2009). Based on patients initiating ART at the facility between April 2004 and March 2007, patient censoring was effected at the event of death, loss to follow up (LTFU) or study end date (March 2008). Using Kaplan-Meier and Cox proportional hazard models, the researchers analysed the effect of baseline CD4 count on mortality and LTFU among other relationships. The observed mortality rate was 5.1% after a follow-up period of 21 months with more than a third of the deaths occurring within the first 90 days of initiation. Furthermore, the risk of death was nearly 5 times more in patients whose baseline CD4 was less than 50 copies/µL of blood compared to those for whom it was 200 copies/µL or more. The overall crude death rate of 2.9 deaths per 100 person years observed was comparable to other sub-Saharan countries' rates. Excellent virological responses were observed such as viral suppression by month 6 of treatment.

A retrospective cohort analysis of HIV-infected patients presenting at a central HIV/AIDS facility in Serbia was undertaken with the objective of establishing factors influencing the response to treatment and survival (Jevtovic et al., 2010). The observational data gleaned from the over 560 patient record files was found to suggest that patients who commenced ART while less than 40 years of age, were not IDU and initiated the treatment while CD4≥100 copies/µL had a significantly better prognosis of survival than otherwise. Overall estimated survival was 13 years from initiation of ART. The study also revealed that the achievement of undetected viral load was an independent predictor of survival.

The studies reviewed above were conducted as retrospective cohort analyses to either estimate survival of PLWHA or to determine the best predictors of survival. The number of the years patients were predicted to survive has been shown to mainly depend on CD4 count or viral load although there are other predictors such as age at initiation of ART and sex. The current research will attempt to use similar variables to be applied to a much larger dataset of PLWHA in Zambia

3.4.3 Mathematical and statistical models

Mathematical or statistical models in survival estimation are models which use different techniques within general mathematics or in statistics (or a combination of both) to formulate a representation of the real life survival patterns of a population being studied. The use of such techniques is extensive and the following section is a review of a part of the appropriate literature for antiretroviral therapy. Hallett et al. (2008) developed a mathematical model to explore different ART initiation strategies and patient management policies on the impact of ART programs in sub-Saharan Africa. The survival of the people put on ART is a primary subject and outcome of this work. The model assigns characteristics to each individual infected with HIV ranging from time and mode of HIV diagnosis to frequency of clinical monitoring to initiation basis (CD4 counts or syndromic). The stochastic cohort model developed employs various functions among them a constant rate of CD4 decline to mimic disease progression sensitive to age of the client. Initiation into ART was determined by an initiation rule which was a combination of 9 scenarios combining CD4 counts and symptomatic presentations. Survival was modelled based on a three-part set of categories comprising the assumptions that the hazard of death was: 1) constant from that observed in the first three years of ART;

2) increased gradually; 3) increased sharply. The model predicted that the survival of HIV-infected individuals on ART could be increased from 10 years to a range of 17 to 27 years from the time of infection.

In a prognostic model, Egger et al. (2002) analysed over 12,500 patients who started ART with a combination of at least 3 ARVs. The model, based on 13 cohorts of people on ART across a number of countries in Europe and North America, considered the probability of developing an AIDS-defining event and death or death only as outcomes. The survival was modelled based on a number of variables observed at commencement of ART including CD4 count, viral load, age, sex, transmission group (male homosexual, heterosexual, Injection drug use or IDU and other), year of starting ART and others. The resulting survival models were essentially based on Weilbull, logistic and lognormal distributions. The probability of the outcomes was enumerated after 1, 2 or 3 years. The probability of death after three years of ART was reported to range between 0.8% (for individuals who started treatment with CD4 counts greater than 350 cells/µL and not IDU) and 48% (for CD4<50 cells/µL among IDU). Other transmission groups fell anywhere between these two extremes. The research did not document the survival of the patients beyond the 3 years.

Work was undertaken by Mills et al (2011) who calculate life expectancy of people on ART in a resource constrained country (Uganda). At age 20, a person initiating ART was estimated to live an additional 26.1 years compared to 36.1 years for a person in the developed economies (Antiretroviral Therapy Cohort Collaboration, 2008). The life expectancy rates reported in Uganda compared very well with the richer countries, in reference to life expectancy of the respective general populations, making them useful inputs into survival modelling.

Like the cohort-based models discussed in the previous section, the basis of survival estimation in mathematical and statistical models reported in the literature is primarily CD4 counts, a proxy for disease status. Evidence in the research therefore shows that survival of people on ART is sensitive to the timing of initiation of treatment. The underlying mathematical structures built into these models assumed that the distributions of the attributes possessed by the patients were stochastic.

3.4.4 Computer simulation models

While most models discussed above are essentially run on computers, this section puts together relevant models built specifically for this purpose often using some form of specialised or purpose-built software. In this section, a collection of different OR methods employed in survival estimation and executed as computer simulations are reviewed. Using data from an observational cohort, a computer simulation model of the expected survival of people on ART accounting for baseline CD4 cell count is built (King, Justice, Roberts, Chang, & Fusco, 2003). Attributes accounted for in this model included ART treatment failure, risk of ART on-treatment mortality and age-related mortality obtained from either the study, published literature, actuarial tables or expert opinion. Designed as a Markov model, patients were allowed to transition to other health states from the assigned initial health state mimicking the real-life progression of a patient on ART (i.e. experiencing any number of the events listed above). The patients were allowed to undergo these transitions any time during month-long cycles. The health states which could be transitioned to by a patient at any time in their treatment life were ARV treatment round *n*, post-ART grace period and death. Results demonstrate that median long-term survival for people on ART is dependent on CD4 count levels at initiation ranging from 15.4 years to 5.5 years (CD4 > 200 cells/µL vs. CD4 ≤ 50 cells/µL). Patients initiated on ART with a baseline CD4 count of less than or equal 20 200 cells/µL were estimated to live for up to 8.5 years.

In the year 2008, estimates of the time from HIV seroconversion to ART eligibility and from ART eligibility to death were published by Wandel (2008) in a 3-country collaboration known as the eligibility for ART in lower income countries (eART-linc) collaboration. Using a model parameterised from 5 cohorts in the collaboration (2 in Uganda and Thailand and 1 in Ivory Coast), Weibull survival models were used to estimate the duration from HIV-seroconversion to ART eligibility and from ART eligibility to death. The cohorts used to parameterise the models were representative of Low and middle income countries according to the World Bank. Similarly, a model was developed for the entire time between seroconversion and death. Analyses were performed for three CD4 count categories (CD<200 cells/µL, CD4<275 cells/µL, CD4<350 cells/µL) with an additional category of patients initiated with CD4<350 and WHO Stage 3 or 4. Gender and age were also included as further analysis variables for survival and seroconversion respectively. Markov Chain Monte Carlo simulation was used to generate

sample patients for posterior distributions in the model. The researchers reported that the duration from ART initiation at CD4<200 cells/μL to death was estimated at a mean of 3.9 years (median 2.1 years) while the mean time from seroconversion to death was 11.5 years. Across all analysis categories, the mean survival from seroconversion was estimated at 11.3 to 11.7 years.

Basing their evidence of the best ART treatment strategies on an extensive review of published literature, Johansson et al. (2010) constructed a Markov cycle model to estimate the survival of patients on presenting for HIV care in low income countries. The model was designed to produce estimates for both the case where ART was initiated and when it was not initiated for a patient presenting for first HIV care. Strata for baseline CD4 count were set at CD4<50, 50-199 and 200-350 cells/μL. These three strata are a fair representation of the stages of disease progression. The model was run for 100 years (Markov cycle length was 1 year) representing 100 Markov cycles during which patients moved from stratum to stratum till death. Survival estimates of 14.5 years were realised for patients starting ART early (CD4 200-350 cells/μL), 7.6 and 7.3 life years for CD4 50-199 and <50 cells/μL. If patients were not put on ART, their remaining life years reduced to 4.2, 2.0 and 0.7 years for CD4 200-350, 50-199 and <50 cells/μL respectively clearly demonstrating the benefits of ART in general and early initiation in particular.

To estimate the life expectancy of MSM in developed countries with extensive access to ART healthcare Nakagawa et al. (2011), used a previously published computer simulation model (known as the HIV synthesis). Using this model, a 30 year old MSM infected with HIV was considered and their life was modelled until 2090 (i.e. for 80 years) or until death. The men in the model were assumed to have a 40% chance of being a smoker with no hepatitis co-infection and would not be lost to follow up. The estimated life expectancy for such an MSM was found to be 75 years provided diagnosis levels were high (such that CD4 count at diagnosis was at least 432 cells/μL). When low diagnosis levels were assumed (CD4 = 140 cells/μL), the life expectancy fell to 71.5 years.

In the published literature in the category we have labelled ‘Computer simulation models’, the models were built using specialist computer software. The actual simulation methods

used included some of the previously discussed methods. Here data gleaned from large cohorts were used to populate the models and scenarios of various initiation strategies for ART were explored providing a wide-range of outcomes.

The literature reviewed in the area of survival estimation of persons on ART shows that the use of the ARV drugs prolongs the lives of HIV-infected people as long as the initiation of the treatment is early. All reviewed studies above, irrespective of methods used, hold the view that the timing of when to initiate treatment is crucial for longer survival of PLWHA. The timing of when to commence the treatment in turn is most easily and reliably represented by the patient's CD4 count. Other attributes have also been found to further have an effect on survival and these include sex, age at ART initiation, sexual behaviour, IDU and so on.

In the current work, survival analysis techniques will be applied to the large database of PLWHA in Zambia and the resulting survival profiles will be used to develop a simulation model in order to study different scenarios and outcomes thereof to make the case for Zambia.

3.5 Economic analysis in healthcare delivery

This section of the literature review focusses on the economic side of the current research undertaking which is to offer an economic perspective to the provision of ART to PLWHA in Zambia and generally in the developing world. The section also explains and reviews the general literature in healthcare followed by a more focused look at the economic evaluation literature in HIV/AIDS research. Four categories of economic evaluation are discussed in this latter part.

In health economics, the process of 'economic evaluation', generally aims to compare the consequences of healthcare programs with their costs. Here, 'healthcare programs' is used to imply any aspect of healthcare introduced to an existing health system in the hope of better outcomes or performance. Drummond et al (2005) describe four forms of economic evaluations commonly used as follows. *Cost analysis* – dealing only with the cost of an intervention or program; *Cost-effectiveness analysis* – measuring the consequences of programs/interventions in the most appropriate natural effects or physical units such as life

years gained; *Cost-utility analysis* – the evaluation of a program or intervention in terms of an adjusted state of preferred health outcomes such as Quality Adjusted Life Years (QALY); and *Cost-benefit analysis* – the value of consequences of programs and interventions are measured in monetary terms with the aim of making them commensurate with costs.

In practice, most economic evaluations employ more than one of these methods sometimes making the distinction between them quite academic. The following section deals with published literature on the use of some forms of economic evaluations in general healthcare with an emphasis on those related to HIV. Considerable research has been conducted employing simulation in health economic models. In terms of HIV, the last two decades have seen an extensive body of research work focussed on the economic analysis of various aspects of the epidemic from prevention to care and treatment. Different OR modelling techniques incorporating economic analysis have been used for this purpose ranging from system dynamics to mathematical models and Markov models. An array of healthcare aspects have thus been explored including diseases (e.g. diabetes, hepatitis, coronary diseases, tuberculosis), paediatric medicine, influenza and other vaccines, Post-exposure prophylaxis (PEP) and so on (Katsaliaki & Mustafee, 2010). Discrete Event Simulation, note Katsaliaki and Mustafee, has been more extensively used to estimate the cost and cost-effectiveness of providing healthcare, alternative interventions and screening strategies.

3.5.1 Economic analysis in HIV/AIDS

In Africa, various health and other developmental needs compete for scarce resources and among the important challenges being faced on the continent is the HIV/AIDS pandemic. Making decisions on which sectors of the local economies get these resources is of significant importance. Furthermore, deciding which programs within a sector such as healthcare to fund is also an important undertaking. Some basic approaches include making the call on whether the economic benefits of HIV programs outweigh their costs, which HIV programs are the most cost-effective and generally whether HIV programs are more cost-effective than other health programs faced by different nations. Cost-effectiveness of the interventions to mitigate the effect of the epidemic, though not the only method used, is a popular tool used to make the decision on how and on what intervention these scarce resources must be spent. Models have been presented, some of which for example, specifically examine the cost-

effectiveness of additional ARVs added to a regimen, the choice of eligibility criteria for ART and so on (Meyer-Rath & Over, 2012). The three sections below outline four broad forms of economic evaluations as applied to HIV/AIDS research during the last decade.

3.5.2 Cost analysis

There has been a new strategy in HIV prevention called Treatment as Prevention (TasP). This is a strategy that has evolved over the last few years as a result of the successful HTPN 052 trial reported by Cohen et. al (2011) that ART in serodiscordant couples can reduce transmission of HIV by as much as 96%. In order for TasP to succeed in the general population, it is necessary that members of communities frequently test for HIV and commence ART as soon as they test positive instead of waiting for the disease to progress before initiating the therapy. This added dimension of HIV prevention interventions will likely require additional community mobilisation beyond that present in current ART programming. It is also possible that TasP could affect the course of the disease, quality of life and the economic productivity of PLWHA. Estimates of the economic costs of TasP strategies are currently estimated from ART costing studies and data (Meyer-Rath & Over, 2012). Barnighausen et al. (2012) argue that in view of the foregoing additional components, there is need to collect empirical data alongside the many TasP strategies being evaluated in order to more accurately determine the true economic costs of these programs. In South Africa, increasing the provision of ART to all people with CD4<350 copies/μL (current guidelines recommend initiating ART at CD4<200 copies/μL) is projected by Granich et al. (2012) to significantly reduce cost of service delivery while lessening the HIV disease burden. The researchers further report that this could result in a reduction of about 265,000 new HIV infections and over 200,000 deaths.

HIV-related health care costs of long-term ART are presented by Keiser et al (2001) in a study conducted on a comprehensive HIV service within a Veterans Affairs Medical Centre in the Unites States. The analysis of data from this facility is undertaken using mathematical and statistical methods and results indicate a reduction in the mean hospitalisation of HIV-infected persons on ART during 2 years. Total costs of caring for the HIV-infected clients decreased from $1,905 to $1,391 over the 44-month period under study.

In order to estimate the clinical benefits and cost-effectiveness of 3-drug ART, Freedberg et al. (2001) used a computer-based simulation model and compared alternative antiretroviral (ARV) drug combinations. Using chronic illness, acute illness and death as categories of the status of each HIV-infected person outcomes of the model were, among others, life expectancy and lifetime costs of ARV treatment.

An early estimate of the lifetime cost of ART in France during the era of Highly Active Antiretroviral Therapy (HAART) was reported by Yazdanpanah et al. (2002). Their primary objective was to estimate the lifetime direct medical costs of HIV infection and this was achieved by adopting the micro-costing approach in which the unit cost of four stages of disease progression are defined and costs at each of these are individually computed. The sum of costs across all these stages is then summed up to generate a monthly stage-specific cost estimate. A computer simulation was then run to generate the survival times of patients in each stage. Using these survival times and stage-specific cost estimates, the lifetime costs of HIV for patients on ART was computed by multiplying the duration spent in each stage by the corresponding unit cost for that stage. Both in-patient and out-patient care costs were included in the analysis providing a realistic picture. Results showed that the lifetime cost for an HIV patient in France ranged from €156,000 to €253,000 if clinical management of the patient was commenced when the CD4 count was at least 378 copies/μL (the undiscounted cost was estimated at €212,000 to €378,000).

Other research reporting the cost of HIV service provision has been reported including the estimation of unit costs and annual costs of ART service delivery in Zambia (Bratt, Torpey, Kabaso, & Gondwe, 2011), the lifetime costs of treating a person with HIV from infection to death (Hellinger, 1993; Jebakumar, Woolley, & Curless, 1993) and the cost of rapid HIV testing (Pinkerton et al., 2010)

3.5.3 Cost-effectiveness and Cost-utility analysis

A review of 24 studies containing information on both cost and effectiveness of HIV/AIDS interventions on the African continent was conducted by Creese et al. (2002). Results indicate that HIV infection prevention was more cost-effective than each disability adjusted life year (DALY) gained from provision of ART. There are however, very large variances between

interventions partly attributed to the inconsistent collection of cost-effectiveness data during program implementation. The clinical impact and cost-effectiveness of routine, voluntary HIV testing in South Africa was reported by Walensky et al. (2011) in a study that considered the testing annually, every five years or once only. The simulation showed that annual testing of HIV was highly cost-effective in terms of the increase in HIV-infected quality-adjusted life expectancy which would be at 197.2 months compared with 180.6 months from the test date. The study revealed though that the benefit of the intervention would even be more if there was a linkage between ART and the HIV screening and that ultimately, the driver of the cost-effectiveness was the ART.

A cost-effectiveness analysis in drug abuse and HIV testing was conducted to compare three HIV testing strategies offered at a community-based substance abuse treatment program (Schackman et al., 2012). These were, off-site HIV testing by referral, on-site rapid HIV testing with only test results given and on-site HIV testing with risk reduction counselling (sexual risks, injection risks, or reducing substance use) provided to drug users attending the community-based program. Using life expectancy, lifetime costs and Quality Adjusted Life Years (QALY) computed from the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) computer simulation model, the study concluded that on-site testing with information but without the extra risk reduction counselling was the most cost-effective strategy with a cost-effectiveness ratio of US$60,300/QALY.

A simulation model to study the cost-effectiveness of variants of PMTCT post-partum strategies using ARV interventions for the mother and the infant in sub-Saharan Africa employed Markov modelling (Maclean & Stringer, 2005). This model, based on Zambia data, showed the cost-effectiveness of exclusive breastfeeding for 6 months at a cost of $806,995 generating a total of 446, 208 Quality Adjusted Life Years (QALYs). An additional daily dose of the ARV Nevirapine (NVP) given to the infant is reported to have cost $93,638 and although it generated 1,183 additional QALYs was not feasible as it exceeded the standard willingness to pay ($64/QALY) for most resource-poor settings. A more recent effort in establishing the cost-effectiveness of PMTCT strategies was reported by Robberstad and Evjen-Olsen (2010) in a study that utilised data from Tanzania. Using a decision tree, the costs and outcomes of single-dose nevirapine (sd-NVP) and ART-based PMTCT Plus regimen as different strategies to

prevent MTCT were computed. Cost-effectiveness was calculated as the cost per DALYs averted. The final results showed that though more expensive to implement by up to 40%, the ART-based PMTCT plus strategy yielded at least 5 times better health benefits at US$162/DALY averted with an incremental cost effectiveness ratio of US$4,062 USD per child infection averted.

In order to assess the long-term economic and clinical impact of 3-drug ART compared to 2-drug ART, a cost-effectiveness study was conducted designed to track viral load and CD4 count as proxies for the progression of HIV-infected people from asymptotic infection to AIDS-defining illnesses and ultimately death (Cook et al., 2004). The study revealed that triple therapy provided to an asymptotic HIV+ patient yielded a better survival than dual therapy with a total discounted cost over the initial 5 years of treatment being US$5,100 lower than that for dual therapy. The lower discounted costs were mainly attributable to savings as a result of the delayed onset of AIDS. Additionally, the incremental cost per life year gained by adding the third drug to the dual therapy (i.e. adding Indinavir to Lamivudine + Zidovudine to make 'triple' therapy) was estimated at US$13,229 which fell within accepted levels for similar medical interventions at the time of publication.

3.5.4 Cost-benefit analysis

As indicated above, most economic analyses combine one or more methods when measuring the effect of an intervention in relation to costs. In a paper which could serve as a practical guide for conducting cost-benefit analysis (CBA), La Croix and Russo (1996) outlined both the costs and the potential benefits of routine voluntary HIV counseling and testing for hospital patients. Costs associated with the HIV testing included the testing kits with related consumables, the rental cost of the laboratory and the cost of staff time from drawing the blood for the test through to the post test counseling at which results are given to the patient. Benefits considered were primarily in terms of the calculated value of life. Beyond monetary terms, benefits discussed included those to the healthcare worker (HCW) by way of their ability to take precautions thereby reducing their exposure rates to HIV, the possible life-extending antiretroviral therapy the patient could receive and the possible infection of the patient's sexual partners averted as a result of safer sex practices. Cost-benefit ratios ranging from 1:21 (for HIV prevalence of 0.23%) to 1:636 (for prevalence of 10.63%) were derived

from the study showing that HIV testing was far more beneficial to society than the cost of conducting the tests.

With an objective of comparing costs and benefits of providing pregnant women with PMTCT in Mozambique, Peffer et al. (2002) used the UNAIDS cost-effectiveness tool (CET) to develop their model. The costs arm of the study accounted for costs of counseling and testing, antiretroviral therapy provided to mother and infant (nevirapine) as well as the cost of nutritional counseling and provision of infant feeding formula. The results indicated that the intervention would result in savings of over US$5,200 and a negative DALY cost of about US$1.53 for the case without infant formula.

Andresen and Boyd (2010) used a mathematical model to estimate new HIV infections and deaths prevented in a supervised injection facility in Canada. These prevented deaths and infections were viewed as societal benefits and compared with costs which were taken to be the annual operating costs of the facility. It was demonstrated that the intervention would prevent 3 deaths and 35 new HIV infections annually with a benefit-cost ratio of 5.12:1. Other CBA has been conducted in areas such as HIV counseling and testing for women in child-bearing age (Brandeau, Owens, Sox, & Wachter, 1993), needle and syringe exchange (Clark & Corbett, 1993) and partner notification by people who test HIV positive (Judson, 1990).
Significant economic analysis research has been conducted to study different HIV/AIDS interventions with more work found in the literature directed at prevention strategies. Cost effectiveness studies seem to be more preferred along with cost analysis more than are cost benefit and cost utility methods. The work proposed in the current research will utilize only cost analysis.

3.6 Chapter summary

The literature reviewed covers a wide variety of OR methods which have been used to investigate different aspects of HIV. Some aspects of HIV studied include HIV transmission dynamics using system dynamics, agent-based simulation, compartmental models and discrete event simulation. Decision trees have been used in determining the best antiretroviral treatment strategies. In the area of HIV prevention, compartmental and ABS models have been developed to explore different HIV prevention methods alongside STIs; in

PMTCT research as well as the prevention of HIV transmission among MSM. The dynamics of HIV transmission from concentrated populations (IDU, MSM, and CSW) to heterosexual populations has been studied with the aid of ABS models. Agent based simulation and Markov models have been used in determining which prognostic factors have an impact on HIV evolution, general disease progression as well as key drivers of the epidemic among injection drug users. The effect of ART on levels of viral load and CD4 cells counts have also been determined using Markov models. Determining the size of the HIV epidemic and possible strategies to sterilise or eradicate it from the population have been investigated by employing compartmental and Markov models. Various aspects of co-morbidities of HIV and TB, herpes simplex virus and others have been researched using compartmental models and DES.

Different approaches in the estimation of the survival of HIV-positive people have been used by different researchers. A fundamental difference in this work lies in the definition of the event of interest based on which the time intervals are modelled. Typically, the event of interest is the death of the HIV-positive individual. The same techniques have been used to model the time intervals leading to loss to follow up or a combination of death and loss to follow up and so on. In general, HIV-positive people are observed in prospective cohorts or data is reviewed in retrospective cohort analyses. Kaplan-Meier survival curves and Cox proportional hazards models have been used as some of the main statistical techniques to study the survival patterns and other covariates which affect survival. The effect of CD4 counts on survival of people on antiretroviral therapy is a common relationship of interest in most literature. Some researchers have generated age-specific survival rates while others have reported life expectancy instead. Survival of PLWHA has also been of interest against the background of different drug combinations at ART initiation. A number of multi country models of the survival of PLWHA have been constructed to account for possible geographic, economic or other differences in similar categories of PLWHA such as MSM, IDU, heterosexual populations and so on. Furthermore, research work has been published specifically estimating survival of PLWHA from seroconversion or from the first time they present for HIV care to either manifestation of AIDS or death.

Economic analysis literature in the HIV/AIDS sphere revealed substantial work done utilizing different techniques. Cost analyses have been used to test various HIV prevention techniques

including new prevention strategies such as antiretroviral Treatment as Prevention (TasP), the benefits of early initiation on ART, the lifetime direct medical costs of ART in a developed country and others. Cost effectiveness has also been used as an economic evaluation technique in many other areas such as testing different HIV interventions, routine voluntary HIV testing in a population with high HIV prevalence rates and the comparison of different PMTCT strategies in a resource constrained environment. Comparison of 2 or 3 drug ART has also been studied in terms of cost effectiveness in the long-term. The other frequently reported method of economic analysis in HIV/AIDS is cost benefit analysis. Cost-benefit analysis has been used in investigating routine testing and counselling and the different scenarios of PMTCT in resource poor settings in sub-Saharan Africa.

The long-term survival of PLWHA exiting the ART program as a result of death, LTFU and stopping treatment has not been fully explored by using DES as the primary modelling technique. The use of large data sets which have many years of observations has also not been explored extensively to gain further insight into the different outcomes or survival using DES. The effects of treatment policy changes recommended by the WHO for initiation of ART (from 200 to 350 cells/µL of blood) on survival are still being explored. Prognosis of drop out (survival) for PLWHA on ART is still to be well understood if treatment is commenced at earlier stages of the disease (than the now recommended WHO cut-off of 350 cells/µL of blood), say at 500 CD4 cells/µL of blood, in resource constrained settings. The proposed work seeks to help fill some of these gaps by using a patient-level electronic database of people on ART with records of up to 10 years. Discrete event simulation is the method of choice for this project and it is envisaged that this simulation will provide a tool to be used to answer the different questions on dropout outcomes of ART at different levels of disease progression. The model will also provide an opportunity to alter any of the treatment policies to other desired levels of CD4 count and other attributes. Furthermore, questions that may be answered by this research will include the study of possible variations in drop out patterns based on different treatment regimens which are provided to patients at initiation of treatment. The different covariates which affect survival of PLWHA on ART will also be explored to determine what factors to significantly affect survival.

There has previously been research on long-term economic costs of the provision of ART to PLWHA from initiation on ART to drop out or exit from the program (Resch et al., 2008), but more up to date estimates are needed. There is need to analyse the costs associated with different treatment strategies for treatment considering that HIV is currently a chronic illness and not a disease which always results in very early mortality. The proposed research will also provide an insight into the various costs associated with the commencement of treatment at different stages of disease progression as described above. In general, the proposed model combining survival and economic costs of ART in resource limited settings will present an opportunity to understand the implications of long-term ART on the PLWHA and also act as an important tool in healthcare planning.

In summary, the chapter has provided:

- An overview of OR methods in healthcare followed by an introduction of the developments of OR output in HIV/AIDS
- A chronicle of different OR methods which have been used to model HIV/AIDS-related problems
- A discussion of survival analysis techniques and how they have been applied to HIV/AIDS survival estimation
- An introduction of common economic analysis techniques used in healthcare modelling with specific references to HIV/AIDS applications

The next chapter outlines how these modelling opportunities have been explored using appropriate methodologies

4 Data

4.1 Introduction

This chapter describes the data used in the research and where it is obtained from within the Zambian health system. Descriptions of the type of data and what kind of database the data is stored in are given as well as other data sources from where additional data was obtained from for the research. A description of the data collection process is given along with the status of the data when it was collected. The challenges faced during data collection are outlined to provide the reader with an understanding of the process and duration of data collection. A discussion on the missing data in the dataset is presented in this chapter. Efforts to address these missing data are clearly stated supported by the results of the effort to mitigate the problem. The chapter also provides a description of the ART program in Zambia by presenting a series of descriptive accounts of the statistics from the dataset such as the gender distribution, patient flow, patient outcome, etc. To conclude the chapter, a discussion on the choice of covariates subjected to statistical analysis and subsequently simulation modelling is given.

4.2 The electronic medical record system for HIV in Zambia

Following a policy statement issued by the Ministry of Health of Zambia on 23rd November 2007, the official medical records system for HIV-positive patient management and reporting in Zambia is SmartCare. SmartCare is an electronic medical record (EMR) system designed to store individual medical records for HIV-positive individuals in Zambia who enrol into any of the dozens of health facilities countrywide (http://www.smartcare.org.zm/). The system is made up of two main components namely the pre-coded paper forms used by the clinicians to manage patients and the computerised database. Clinicians use the paper forms during clinical consultation and other interactions with patients which are then entered into the electronic database by dedicated data entry clerks located at the health facility.

4.3 Database description

While multiple computers in the same facility are usually set up in a network ensuring that only one database is updated at all times, the SmartCare system is not connected by virtual networks between any two separate ART facilities. On a monthly basis, the databases are

backed up and physically sent to a central repository in the district or city (District medical Office) where a district-level merged database is generated. The district databases are in turn merged at the Provincial Medical Office and finally the provincial medical office databases are merged into a national database housed at the Ministry of Health headquarters.

4.4 Data collection

The SmartCare national database was the primary data source for this doctoral research project. The data for the research was provided to the researcher by the Zambian Ministry of Health (MOH) in the form of Microsoft Excel spreadsheets and Microsoft Access databases. These were collected from the ministry headquarters and represent all the ten provinces of Zambia. The MOH did not have dedicated database programmers of SQL or Structured Query Language who could extract the detail needed for the research from the database. This in turn led to challenges in obtaining the data at the time it was required.

4.5 Challenges in data collection

The absence of an SQL programmer at MOH prompted the ministry to seek the services of a programmer from the software development team. Delays in securing the time for this programmer to extract the data at the MOH ensued despite the software developers assuring the MOH of the availability of the programmer. More than two months were spent waiting for this software programmer to put in time into the programming to extract the requested data. As a result, this process of back and forth went on for over 12 months without usable data being made available to the researcher.

When further efforts to get some data from the programmers proved futile, the ministry decided to allow the researcher to appoint an independent SQL programmer to work with other IT personnel at MOH to extract the data. Progress was speeded up after this decision and the researcher was able to receive data from the appointed researcher with approval by relevant MOH staff in Zambia after a delay of about 18 months.

4.6 Other data sources

Data to complete the research undertaking was derived from other sources to compliment and validate the some aspects of the SmartCare data. The other data sources include:

- The 2010 Zambia Census of Population and Housing (Central Statistical Office (CSO), 2012b)
- Demographic and Health Surveys 2001 – 2002 (Central Statistical Office (CSO) & Ministry of Health Zambia (MOH), 2003)

  Health Management Information System, HMIS (electronic database and reports)

4.7 Analysis of Missing Data in the Zambia ART data set

Incomplete or missing data occurs in many research settings and the missing data gives rise to complications in data analysis and inference. The challenges brought on by missing data to researchers are profoundly acute for longitudinal research projects where multiple cycles of the same data are collected over extended periods of time (Graham, 2009). Three mechanisms for missing data are frequently discussed namely: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). Data is said to be MCAR when the probability of a variable having a missing value does not depend on any of the observed or unobserved quantities or variables in the dataset. For this case, unbiased estimators are obtainable from the dataset by ignoring the processes which generate the missing values (Kadengye, Cools, Ceulemans, & Van den Noortgate, 2012). When data is considered MAR, it means that a missing value depends on a selected number of observed or unobserved variables in the dataset. For the case where missing values are neither MCAR nor MAR, then they are considered to be MNAR which implies missing data items are dependent on unobserved variables.

Many methods exist for dealing with missing data, so-called imputation methods. The performance of these imputation methods varies in terms of effectiveness and each researcher is expected to make a decision based on the use of the resulting 'complete' data set. Some methods used to impute data are Complete Case Analysis (CCA) where a whole case is ignored in the analysis as long as it has a missing value, Simple Random Imputation (SRI), Multiple Imputation (MI), Regression Imputation (RI), Direct Likelihood (DL) Analysis, etc (Finch, 2008; Kadengye et al., 2012). Besides these methods based on modelling the patterns or characteristics of the missing data, some researchers have employed such basic

methods as list wise deletion in which entire cases or individuals with any missing data are omitted from the study or pairwise deletion and mean substitution. Other imputation methods, specifically used to impute missing values in longitudinal studies, were summarised by Engels (2003) in Table 4.1. The methods were used to illustrate their differences when imputations were performed on different types of data sets such as population data, baseline data, before-data as well as before–and-after-data.

Table 4.1 Definitions of imputation methods and circumstances of their application

Group	Imputation method*	Definition
Population	Column mean	Mean of all persons in the dataset for a particular year
Population	Column median	Median of all persons in the dataset for a particular year
Baseline	Class mean	Mean of other persons in corresponding class
Baseline	Class median	Median of other persons in corresponding class
Baseline	Hot deck	Value of a random person in corresponding class
Baseline	Regression	Predicted value from a regression model
Baseline	Regression with error	Same as Regression with an error term added
Before	Previous row mean	Mean of person's previous known values
Before	Previous row median	Median of person's previous known values
Before	LOCF	Last observation carried forward
B/A	Row mean	Mean of person's values before and after
B/A	Row median	Median of person's values before and after
B/A	NOCB	Next observation carried backward
B/A	Last & next	Average of the last known and next known values

*All missing values are replaced by values obtained by the method in this column

Missing data were found to occur in the Zambia ART data used in this research. Considerations were made based on the nature of the data being used in the research and what the data would be used for to aid the choice of imputation method. The other factor in choosing the imputation method was the large sample size of the data, that is, over 400,000 patients or cases. We consider five different approaches to imputation: i) The *hot deck* method assumes that a person's missing data is a random sample of other people in the same class. A donor (different person) with a value in the same class is selected at random and the missing value is replaced with the sampled value; ii) The *linear trend* at a point approach replaces the

missing value with the linear trend for that point obtained from a regression of the data series. Here, the missing value is replaced with its predicted value; iii) The *series mean* method replaces the all the missing values with the mean of the entire series; The mean of nearby points uses all valid points below and after the missing value to compute a mean which then replaces the missing value; iv) The *median of nearby points* method replaces the missing value with a median computed from all valid values before and after the missing value. Results of the imputation for the Zambia data on baseline CD4 are given in Table 4.2.

Table 4.2: Comparison of different imputation strategies for the Zambia ART data missing values

		Baseline CD4 count	Hot Deck	Linear trend at point	Series Mean	Mean of nearby points	Median of nearby points
N	Valid	400233	547506	548702	548702	548700	548700
	Missing	148469	1196	0	0	2	2
Mean		217.22	217.44	216.952	217.216	217.716	209.840
Std. Error of Mean		.319	.273	.2330	.2329	.2445	.2413
Median		178.00	178.00	207.983	217.216	186.000	179.000
Mode		1500	1500	1500.0	217.2	1500.0	1500.0
Std. Deviation		202.003	202.148	172.6020	172.5226	181.0747	178.7782
Variance		40805.249	40863.797	29791.452	29764.055	32788.047	31961.631
Skewness		2.985	2.977	3.495	3.495	3.094	3.274
Std. Error of Skewness		.004	.003	.003	.003	.003	.003
Kurtosis		13.179	13.107	19.161	19.180	15.433	16.872
Std. Error of Kurtosis		.008	.007	.007	.007	.007	.007
Sum		86936914	119050115	119042032.4	119186720.2	119460807.5	115139441.0
Percentiles	25	92.00	92.00	124.000	124.000	111.000	105.000
	50	178.00	178.00	207.983	217.216	186.000	179.000
	75	281.00	281.00	237.000	237.000	275.000	265.000

Various measures of central tendency and variation are computed to see which method produces results closest to those for the original data. In this case, the Hot Deck method has the closest values to the original data (BaselineCD4 Count). The mean is 217.22 (95% CI: 216.59 to 217.85) for the original data and 217.44 (95% CI: 216.9 to 217.98) for the hot deck while the median is identical; the standard deviation is also close as are the percentiles.

As a method to impute missing data, hot deck imputation is widely used by survey practitioners in different types of surveys including longitudinal trials (Andridge & Little, 2010; Tang, Song, Belin, & Unützer, 2005; Taylor & Lane, 1998; Twisk & De Vente, 2002). It was chosen over other sophisticated methods such as multiple imputation (MI) because of its simplicity and the fact that the results obtained compared very favourably with the non-

missing values in the data set. The strength of the hot deck method is that it imputes real values instead of values based on parametric assumptions, which results in realistic imputed values. The imputed data using the Hot Deck method will be used in the rest of the analysis.

4.8 Characteristics of the Zambia ART program

This section provides a description of the dataset used in this research. General characteristics of the ART program in Zambia are summarized from the data and other aspects of the dataset also discussed to provide the reader with a sound understanding of the nature, size and extent of the dataset. All data discussed in this section is from the Zambia ART dataset. This analysis is based on 487,492 patients eligible for analysis out of over 600,000 enrolled patients on the ART program in Zambia. A high proportion of people put on ART in Zambia were alive after 9 years of being on treatment. The earliest patient considered in this study commenced ART in January 2003, while the most recent started during August 2013. The censorship point for the analysis is 31 March 2014. Different events were then recorded over a period of 95 months.

4.8.1 Geographical distribution of patients enrolled on ART

The geographic distribution of patients enrolled on ART in the Zambia ART program follows patterns of population density and distribution similar to that in the general population with the highest numbers of patients in the urbanized provinces. As can be seen in Figure 4.1, Lusaka and Copperbelt provinces along with Southern and Central provinces together make up 75 percent of all patients enrolled on ART although they collectively hold only 53 percent of the national population. The higher proportion of the patients enrolled on ART in these urban provinces is as a result of the initial concentration of ART clinics in the predominantly urban provinces which had higher population densities and corresponding HIV prevalence before the service was more widely offered in the rural provinces. Muchinga province, which is a new province created in 2011 does not show up in the Zambia ART data because the database was still in the process of being revised to include it as a separate province. The province is made up of parts of northern and eastern provinces.

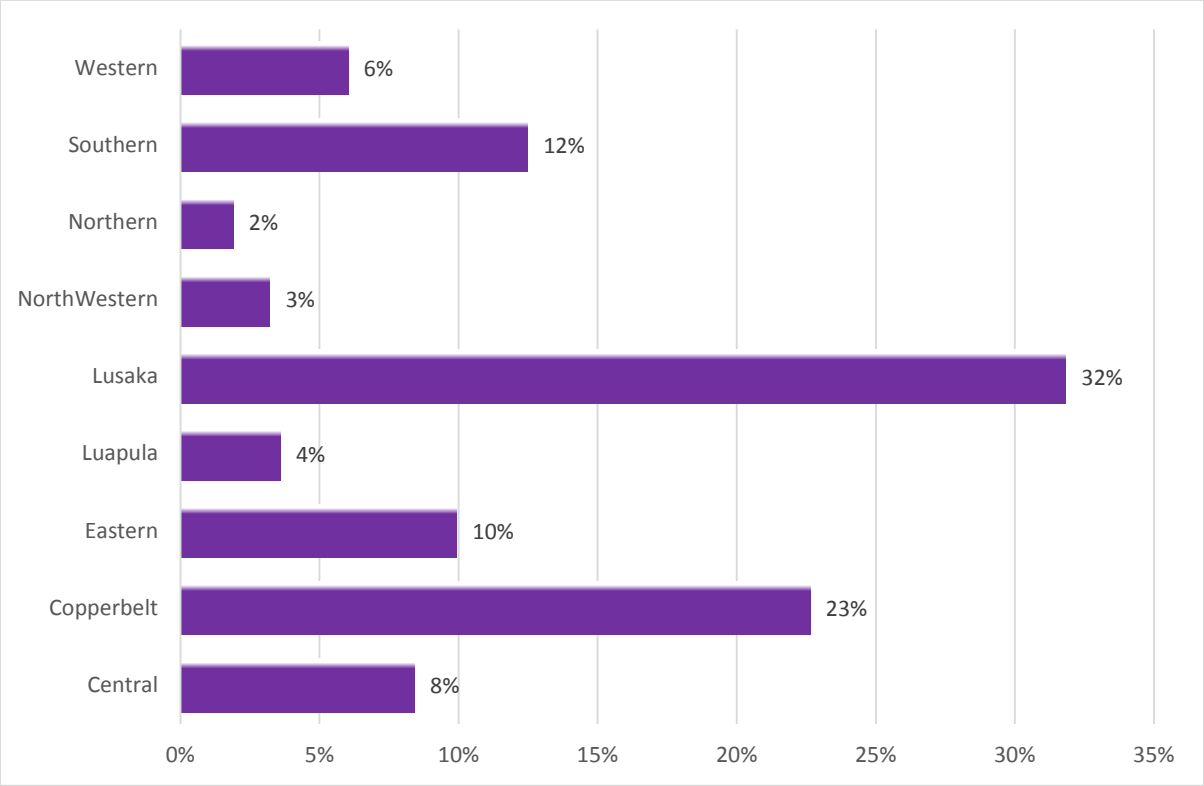


Figure 4.1: Percentage distribution of patients enrolled in the ART programme in Zambia by province of enrolment, 2003 to 2013

Patients registered in rural health facilities (HF) account for 10% of the total while the rest are registered in urban health facilities. The rural/urban variable is used in this case to refer to the location of a health facility where a patient is enrolled and not necessarily the residence or location of the patient under observation. The large disparity in the distribution of the patients does not reflect the true picture of the actual distribution owing to the definition of 'urban' and 'rural' health facilities. The health facilities are defined as urban as long as they are within 'close' proximity (and in the same local authority) to social and commercial amenities such as a post office, bank, market, etc.

4.8.2 **Demographics**

The enrolment of patients into the ART program started with very small numbers in 2003 when ART was offered at only two health facilities which had the requisite specialists and diagnostic equipment for patient monitoring to commence treatment. Thereafter, as shown in Figure 4.2 there was a rapid increase in the number of patients receiving ART following the government's decision to scale up the provision of the service by training service providers

and procuring equipment, drugs and laboratory supplies. Over 1,000 patients were being enrolled per month by 2005 rising to between 5,000 and 7,000 patients per month from 2009. This high inflow continued until the first quarter of 2013.

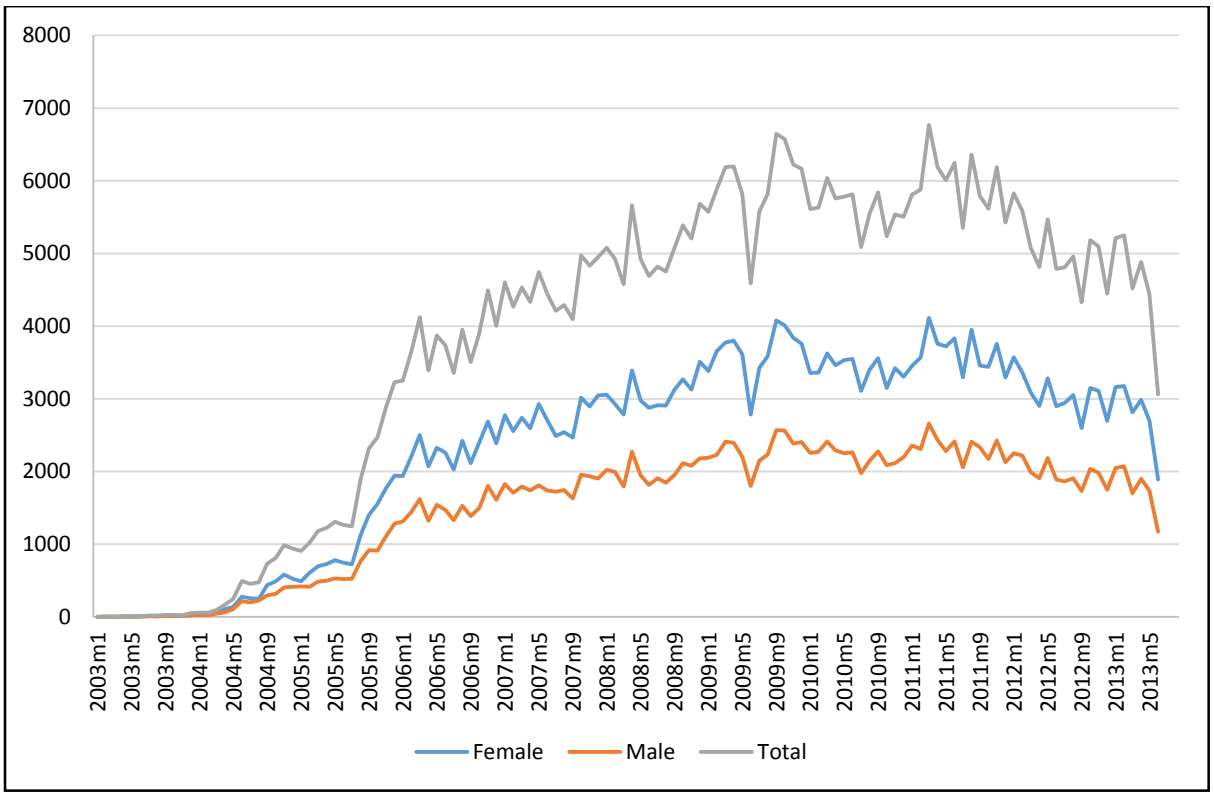


Figure 4.2: Number of new patients enrolled on ART by month, January 2003 - July 2013

The reduction in the last two quarters of the observation period may be attributed to logistical challenges in updating databases from all the districts in the country which have to send databases on physical removable media (CDs or USB flash drives) to the MOH headquarters. By design, these databases should be merged into district databases which are then sent to provincial capitals where ideally a provincial database is created. This is seldom achieved owing to the number of facilities and challenges on the ground. It is therefore a fair assumption that the number of new patients initiated on ART is a steady 5,000+.

The distribution of the new patients enrolled onto ART by gender shows a higher number of female patients enrolled compared to men. This trend has been consistent during the entire period under observation and as at the end of observation, 295,930 female patients had been initiated onto ART compared with 191,562 male patients.

Table 4.3: Patient characteristics

Variable	Gender		Total	
	Female	Male	Number	Percent
Residence				
Rural	30,830	19,581	50,411	10%
Urban	265,100	171,981	437,081	90%
Age Group				
Under 15 yrs	14,541	14,097	28,638	6%
15 yrs +	281,389	177,465	458,854	94%
Baseline CD4 Count				
< 200 copies	156,288	113,824	270,112	55%
≥ 200 copies	139,642	77,738	217,380	45%
< 350 copies	256,084	169,015	425,099	87%
≥ 350 copies	39,846	22,547	62,393	13%
< 500 copies	278,026	180,976	459,002	94%
≥ 500 copies	17,904	10,586	28,490	6%
200 - 349 copies	99,796	55,191	154,987	32%
Baseline WHO Stage				
Stage I	115,670	58,041	173,711	36%
Stage II	56,866	35,019	91,885	19%
Stage III	105,946	83,391	189,337	39%
Stage IV	16,368	14.047	30,415	6%

This represents a consistent 20 percent higher enrolment of female versus male patients onto the program over the last period from 2003 to 2013. Table 5.3 shows that there were 61 percent female and 39% males enrolled on ART with paediatric patients (aged less than 15 years old) accounting for 6%, while adults made up 94 % of this patient population. The median age at ART initiation was 35 years (Interquartile range (IQR): 29 – 41 years)

4.8.3 Disease progression in patients at enrolment

It is a fact that HIV positive patients are enrolled onto ART when the disease is at different stages of advancement. One measure of the extent of advancement of HIV infection is WHO staging which is based on the clinical presentation of the patient (World Health Organization, 2010a). The distribution of ART patients enrolled onto ART at different ART clinics in Zambia by WHO stages is presented in Figure 4.3 below. In terms of WHO staging, the majority of patients who were enrolled on ART in Zambia during the observation period (55%) were in either stage I or II, 39% were in stage II and only 6% were enrolled into ART when they were in stage IV. This is consistent with the recommended practice of enroling patients as early as possible based more on CD4 count than symptomatic presentation or WHO staging.

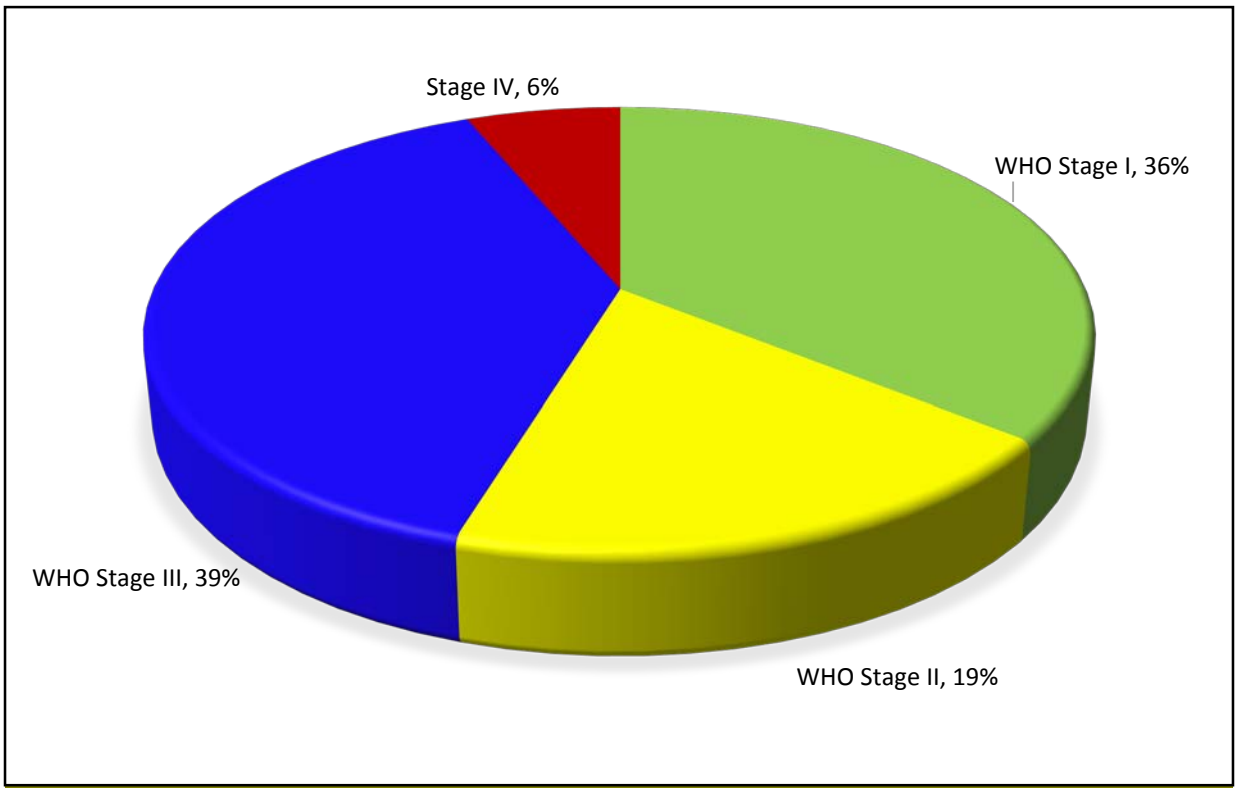


Figure 4.3: Percent distribution of patients by baseline WHO stage at enrolment onto ART (n = 487,492)

About 45 percent of the patients enrolled while in stages III and IV. If the situation had been such that enrolment on ART was based on WHO staging, then the majority of patients would

have been in the WHO Stages III and IV according to existing guidelines (Ministry of Health Zambia (MOH), 2010). In absolute numbers, 190,173 people were enrolled as WHO stage III patients while 174,478 patients presented to the clinic for enrolment onto ART before the disease progressed to the second stage. The WHO stages II and IV accounted for 92,291 and 30,549 patients enrolled during the same period.

The other measure of disease progression in patients with HIV is the count of CD4 cells per micro-liter (µL) of blood. In terms of disease progression, as measured by its proxy the CD4 count, the median CD4 count at enrolment among patients in the Zambia data was estimated at 181 copies/µL (IQR: 97 – 282 copies/µL). About half or 55 % of the patients had CD4 count less than 200 copies/ µL of blood at enrolment into ART. The other cut-offs for baseline CD4 counts were distributed as follows: 87 percent less than 350 copies/ µL of blood; 94 percent had less than 500 copies/µL of blood. In order to compare all groups of people in the categories, the additional category of those patients with CD4 counts between 200 and 349 was also created. This group made up 32 percent of the total number of enrolled patients.

Of the two measures of disease progression, CD4 count is more accurate and reliable. Studies have shown that WHO staging can misclassify patients eligible for ART by as much as 50% meaning that patients who ought to be on treatment could be missed if only WHO staging were used as the initiation criteria (Baveewo et al., 2011; Carter et al., 2010; Kagaayi et al., 2007; Torpey et al., 2009). As a result of this, the WHO staging is not used in further analysis beyond this descriptive account in this research undertaking.

4.8.4 Patient outcome by cohort

In Figure 4.4, a picture of the final status of each patient cohort enrolled between 2003 and 2013 is shown. The graph shows that of the patients who were enrolled onto ART in 2003 and 2004, none were still on ART in 2013 and all had either been lost to follow up, died or had stopped treatment. The proportion of patients whose status was recorded as on ART, as expected, increases from 19 percent in 2005 to 87 percent in 2013 because the patients in the latter years will have only been on treatment for a few years compared to those who enrolled in the earlier years. With similar logic, the percentage share of patients whose status was declared are LTFU reduces from 60 percent in the cohort enrolled on treatment in 2003

to only 9 percent in the 2013 cohort because the earlier patients are bound to be lost. The other such reducing trend is that of the percentage of patients whose status had been recorded as died (27 percent among the 2003 cohort versus 3 percent among the 2013 cohort of patients enrolled onto ART).

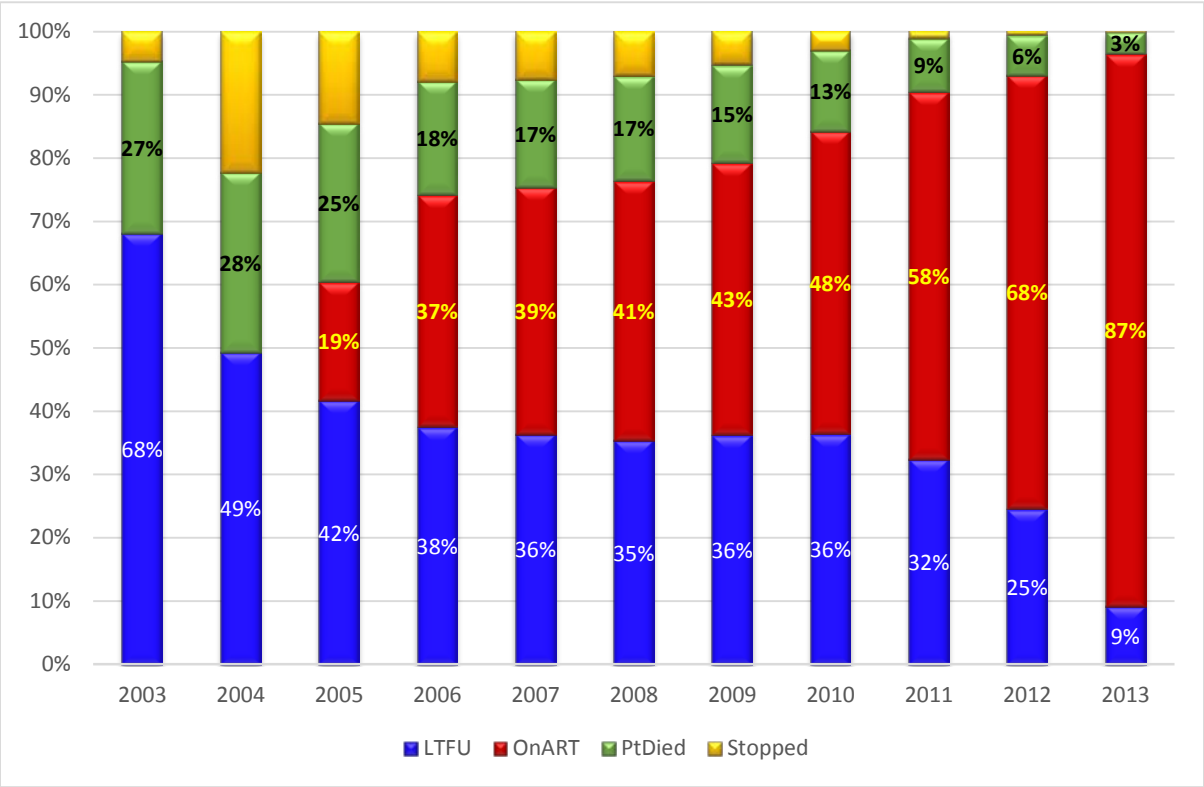


Figure 4.4: Status of patients at censorship point by year of enrolment, 2003 to 2006

Table 4.4 shows of all the people enrolled on ART during the observation period, 49 percent were alive and on ART at the censorship point. The table also shows that 5 percent of the patients were recorded as those who had stopped treatment while 13 percent died during the observation period. The category LTFU (lost to follow up) accounted for about 33 percent of the patients. For purposes of this work, the three categories of patients exiting the treatment program namely those who were LTFU, Died or Stopped treatment were combined to form the category 'Exited ART'. This combined category represented 51 percent of patients enrolled onto ART but exited the treatment program before the end of the observation period.

Table 4.4: Status of patients on ART in Zambia as at May 2014

Status	Gender		Total	
	Female	Male	Number	Percent
On ART	150,926	87,645	238,571	49%
LTFU	93,622	67,243	160,865	33%
Patient Died	37,999	26,921	64,920	13%
Stopped	13,383	9,753	23,136	5%
Combined categories				
Exited ART	145,004	103,917	248,921	51%
Total	**305,943**	**198,130**	**487,492**	**100%**

4.8.5 Covariates analysed: in the dataset, in survival analysis and in simulations

The full dataset for the Zambia ART program has a large number of variables and the variables used in this research project is a subset of the full dataset. The list of variables in the dataset which were considered for analysis is displayed in Table 5.3 with explanation of what the variable represents and a summary of its distribution.

Other variables not explicitly shown in Table 5.3 were derived from the variables on the list by creating categorical variables from continuous variables such as age and CD4 count. These were Age group (created as 5 year age groups, 2 age groups “paediatrics” and “adult”, and others) and CD4 categories (CD4 cut-offs at 200, 350, 500, etc.). The distribution of patients in the program by some of these derived variables is tabulated in Table 4.5. It is expected that although all the variable listed in Table 5.3 were subjected to statistical analysis in the survival analysis chapter, not all variables were used in the simulation model. Further analysis of variables is performed and presented in the survival analysis chapter.

The age structure was also compared with that in the general population and that of the sexually active population in both the national census and specialized surveys such as the Demographic and Health Survey and Sexual Behaviour Survey (Central Statistical Office (CSO) & Ministry of Health Zambia (MOH), 2009; Central Statistical Office (CSO), 2012b).

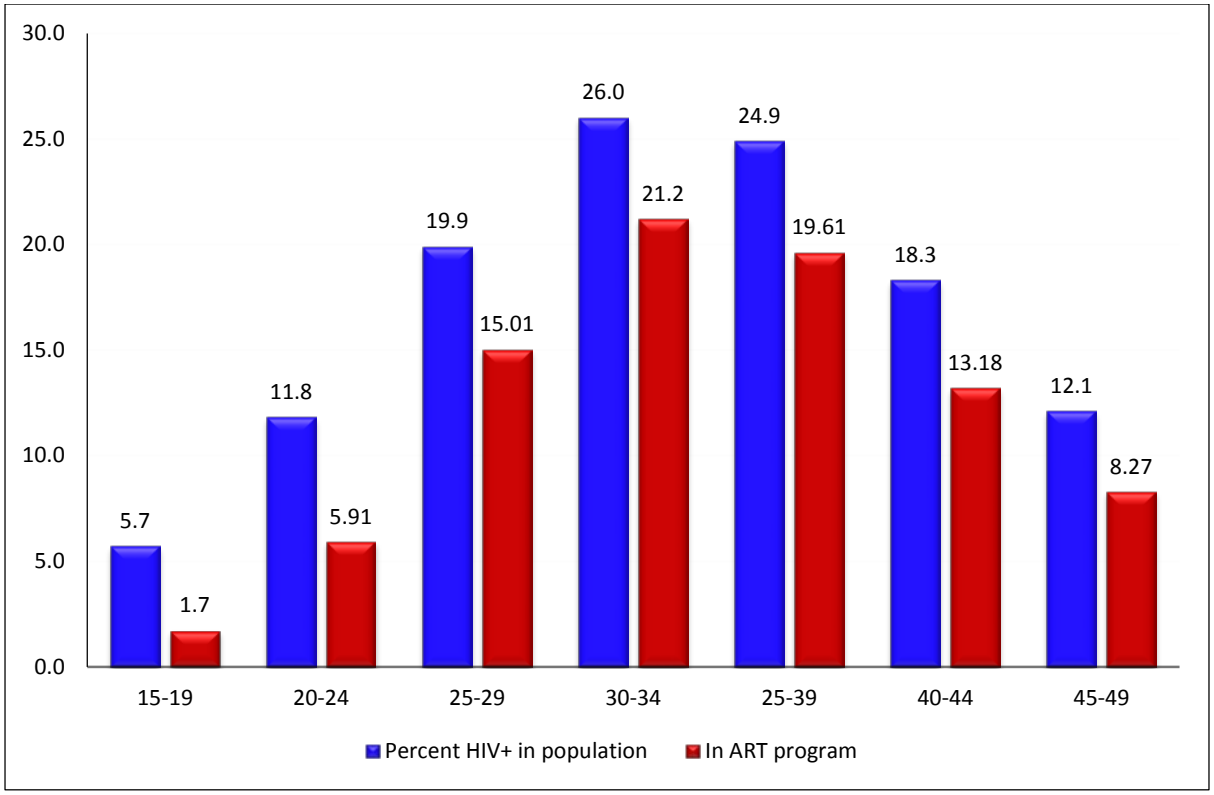


Figure 4.5: Age structure comparison of HIV positive people in the general population vs patients on ART

The results are shown in Figure 4.5 indicating that the general distribution of ages in the Zambia ART program is representative of the HIV positive population as estimated by the demographic and health survey of 2007.

4.9 Chapter summary

This chapter has:

- Provided a description of the nature of the data management system for HIV-positive people in Zambia
- Described the electronic health record system known as SmartCare used in Zambia
- Given an account of the data collection process for the current research
- Outlined problems faced during the data collection
- Provided a list of other data sources used in the study
- Provided general statistics about the ART program in Zambia
- Provided justification why some important variables were not used in simulation modelling later in the thesis

5 Survival Analysis

5.1 Tasks addressed in this chapter

Task 1: What are the main covariates which have an effect on survival of ART patients in Zambia?

Task 2: What measure of effect do the covariates of survival have on ART patients?

Task 3: What is the best combination of covariates predicting survival for patients on ART in Zambia

5.2 Methodology

This section describes the choice of methods and the justification for that. A list of the tasks undertaken to answer the research questions is also provided to make it easier to follow the different stages of the thesis and which objective is being addressed.

5.3 Research tasks

The research questions from Chapter 1 are re-stated here to remind the reader what this research project was designed to achieve. Research tasks for each objective are listed immediately following the question.

Question 1 What is the survival estimate of the time intervals from initiation to exiting ART among patients who commence treatment in a LMIC such as Zambia?

With the understanding that survival was defined as the time intervals between enrolment and exiting the ART program, the tasks undertaken to answer this question are as follows.

Tasks for Question 1

Task 1: What are the main covariates which have an effect on survival of ART patients in Zambia?

Task 2: What measure of effect do the covariates have on survival of ART patients?

Task 3: What is the best combination of covariates predicting survival for patients on ART in Zambia?

Task 4: What is the survival profile of ART patients in Zambia?

Question 2

What is the total economic cost of the provision of ART in Zambia from enrolment to drop out?

Tasks for Question 2

Task 5: What are long-term estimates of the economic costs of ART provision in Zambia?

5.4 Choice and justification of methods

Survival analysis techniques were used to explore the nature of the survival times of the population under study. Differences in the survival patterns of different subgroups of the population were identified statistically and probability distributions were fitted to any such sub-populations. The survival analysis techniques were necessary because the data from the observations are right censored therefore raising the need to model beyond the censoring point into the future. The resulting sub-populations were later exclusively modelled in the DES model in order to generate the desired estimates for the many 'what if' questions stated in the tasks in the previous section. Early studies employing similar survival analysis techniques include Lemp (1990), Marasca and McEvoy (1986) and Harris (1990) while more recent uses of the same methodology have been reported by Sanne et al. (2009), Jevtovic et al. (2010), Mills et al. (2011) and Johnson et al. (2013).

The choice of the simulation method for this research was primarily driven by the nature of the system to be modelled. Discrete event simulation was viewed as an appropriate method to model the survival of persons on antiretroviral therapy because the main characteristics (primarily CD4, age, sex) used to predict the survival of these patients are stochastic. Previous research has employed DES in modelling outcomes of long term diseases (Caro, 2005; Patten, 2007; Simpson et al., 2009). As patients move through the model, they experience events such as change of antiretroviral drug regimen or death at different intervals in time, also stochastically. The occurrence of these events at different times also makes DES a practical choice over methods such as Markov models which are updated at each time cycle rather than at each event. Discrete event simulation is also able to predict the course of a disease more naturally than most other simulation methods among other reasons because DES uses

a random draw from distributions of attributes in the population to predict outcomes of interest. While computationally complex, DES models are easier to sell to stakeholders in this case the planning departments in the Ministries of health, because of the visualization facilities available. We use Simul8 (Simul8 Corporation, 2011) in this project, which has been designed to enable users to see the movements and visualize what happens to each patient as they move through the model.

5.5 Introduction to Survival Analysis

In this chapter, a description of the statistical techniques from Survival Analysis which were applied to the data is given. The work in this chapter answers Tasks 1 to 4 as outlined above and in the previous chapter. Stated generally, survival analysis is a collection of statistical methods for the analysis of data where the outcome variable of interest is the *time to event* (Kleinbaum & Klein, 2005). Survival analysis is used to identify the covariates which drive the survival among people on ART in Zambia. This analysis is limited to the use of variables which are available in the database and are in a usable form. Other variables such as viral load, trends of CD4 count during ART, incidence of opportunistic infections and others which affect survival (World Health Organization, 2010a, 2010b) have not been considered here for the following reasons.

- Viral load is still expensive in Zambia and is not tracked routinely except in instances where possible drug failure is suspected
- Repeat CD4 count tests are not consistently done because of inadequate laboratory capacity.
- Opportunistic infection data is not consistently recorded by clinicians on the patient files, usually due to heavy patient load, and is therefore not available for analysis.

The identification of the drivers of survival from the Zambia ART database was critical in deciding the extent of detail to account for in the simulation model. The other aspect discussed in this chapter is that of assessing the magnitude of the effect which these covariates or factors have on survival. A combination of these two processes provided a set of factors we can used to disaggregate the population of people on ART into sub-populations

that are homogeneous with respect to their survival times. Probability distributions of the survival times of these sub-populations or risk groups govern the time which persons on ART spend in the various stages of the disease until death or other event. The distributions were estimated from the electronic database and form the model inputs for the simulation model.

5.6 Data layout and analytical considerations

Patients are enrolled onto the database on the day that they commence ART and observed for purposes of the analysis. The patients are typically expected to attend the clinic every month but due to high numbers of people on ART, once stable, the patients are seen by the initiating clinician on a quarterly basis or sometimes less frequently. The antiretroviral drugs (ARVs) are also issued in a similar manner but to ensure that adherence to the medication is more closely monitored, a large number of patients who have long review dates with the doctors are issued their drugs to last shorter periods. This results in patients attending the pharmacy to collect drugs more frequently than they do to see the doctors or other clinicians who initiate the therapy and manage the disease.

For purposes of this research, survival of patients on ART with "Exited ART" being the event of interest is considered. Patients are recorded as "Exited ART" when their status changes from "On ART" (patient is alive and receiving ART) to:

- **Died** – the patient died during the observation period
- **Lost To follow Up (LTFU)** – the patient has missed their appointment by a period greater than 90 days
- **Stopped** – the patient has stopped ART either by order of a clinician or by their own decision during the observation period

Figure 5.1 below shows a graphical picture of the patient flow based on which the survival analysis is performed [adapted from Machin et al. (2006)]. Patients entered the study during a period known as the observation period in which the status of each patient was recorded according to the categories above. The survival analysis is undertaken at a point in time referred to here as the Analysis point taken to be 31st March 2014. The event of interest is

Exit ART and is associated with the parameter *time to event*. The *time to event* is defined as the number of days between the day a patient entered the study and the day the patient exits ART. Not all patients will exit ART during the observation time. Therefore, a classification of the patients relative to the time when they experienced an event (or did not) was made as follows. Those who did not experience any event and were known to be alive and on ART at the end of the observation period are known as right censored patients (represented by white crosses). Their date of exiting ART is not known because it had not happened at the time the observation period ended. Patients who exited ART during the observation period are marked with a black cross.

Although the event of interest is exiting the ART program, we also present results showing the survival of patients on ART until death. These provide a means of verifying the data and the subsequent simulation model. For this part of the results, all other events other than death are considered censored.

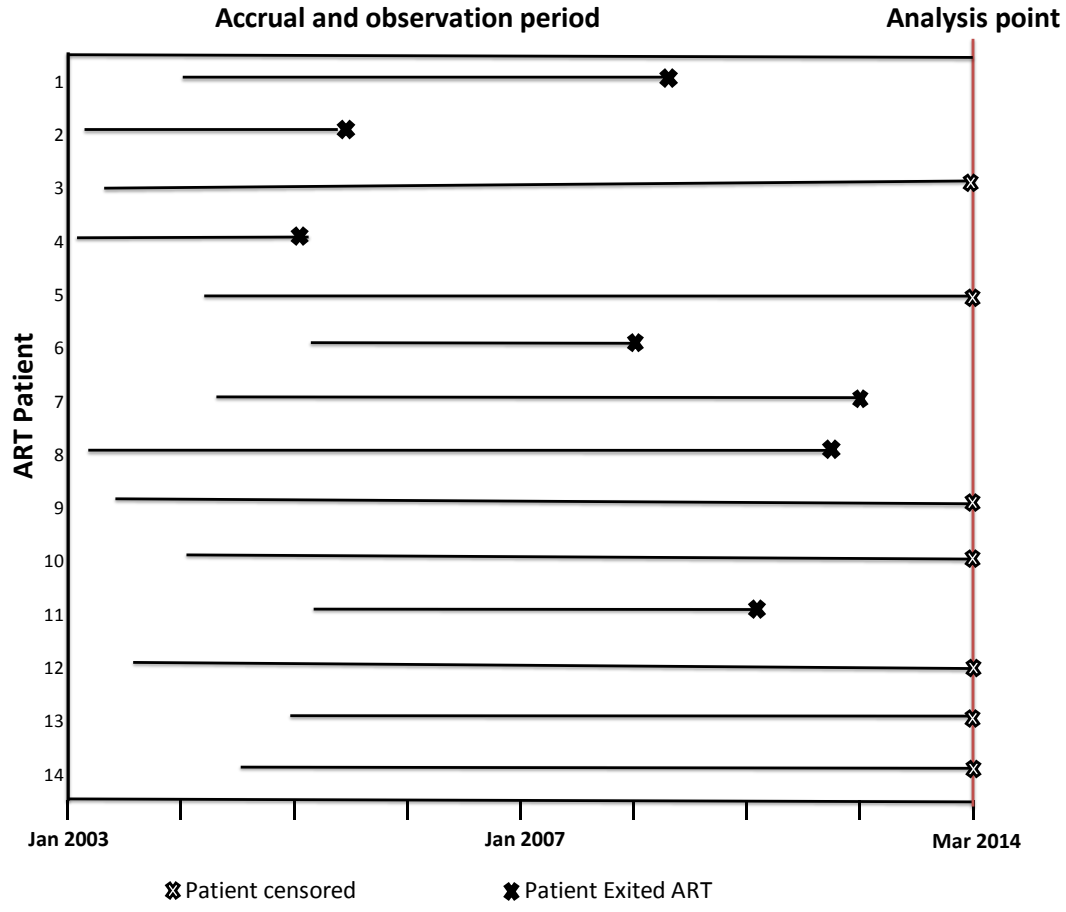


Figure 5.1: Graphical representation of patients on ART included in the study

5.7 The Survival and Hazard functions

The most commonly used functions to describe survival data are the survival function and the hazard function. The two functions are closely related as explained below and thus the estimation of only one of them is usually sufficient followed by a derivation of the other from the estimated function.

Let *T* be a random variable denoting the survival time for a patient and *t* is a specific value of the random variable *T* (*T≥0)*. If T has a probability density function $f(t)$, then the probability that a person survives beyond time t is called the survival function and is given by:

$$S(t) = P(T > t) = 1 - F(t) = 1 - \int_{x=0}^{t} f(x)dx, \quad (5.1)$$

where *F(t)* is the cumulative distribution function of the random variable *T*. The survival function is a non-increasing function which is such that at *t*=0, S(t) is 1 and as *t* goes to infinity, the function S(t) equals 0. These properties are interpreted to mean that at time t = 0, every patient has probability of surviving beyond that time equal to 1. The probability of anyone being alive in the population is equal to zero at infinity.

Related to the survival function, the hazard function denoted by *h(t)* is the instantaneous rate of failure during a time interval given that the patient survived up to the time *t*. It is therefore the conditional probability that the failure (or event of interest) will occur in the time interval between *t* and *t + Δt* , given that *T ≥ t*. That is

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t} \quad (5.2)$$

The hazard function is for this reason sometimes referred to as the conditional failure rate or the conditional density (Allison, 2010; Kleinbaum & Klein, 2005). The relationship between the survival function and the hazard function is well defined. The survival profile of a dataset can therefore be fully understood by estimating only one of these functions and then deriving the other according to the relationships between them. To illustrate this relationship we

define a related function, the cumulative hazard function, which measures the cumulative risk accumulated up to a point t as follows:

$$H(t) = \int_{x=0}^{t} h(x)dx, \tag{5.3}$$

where *h(x)* is the hazard function. The cumulative hazard function (5.3) can be expressed in terms of the survival function *S(t)* by use of the two other basic relationships between the hazard function and the probability density function of *T*:

$$h(t) = \frac{f(t)}{S(t)} \tag{5.4}$$

and

$$f(t) = \frac{dF(t)}{dt} = -\frac{dS(t)}{dt} \tag{5.5}$$

Thus

$$H(t) = \int_{x=0}^{t} \frac{f(x)}{S(x)}dx = -\int_{x=0}^{t} \frac{1}{S(x)}\left\{\frac{d}{dx}S(x)\right\}dx = -ln\{S(t)\} \tag{5.6}$$

This expression allows us to summarise the relationships between the functions as follows:

$$S(t) = e^{-H(t)} \tag{5.7}$$

$$F(t) = 1 - e^{-H(t)} \tag{5.8}$$

$$f(t) = h(t)e^{-H(t)} \tag{5.9}$$

Survival data can therefore be adequately explained by use of any combination of the various forms of the survival and hazard functions. Estimating these functions is achieved by use of non-parametric methods.

5.7.1 Estimating the survival function

In general, the probability of survival up to a time *t* is given by the formula

$$S(t) = p_1 \times p_2 \times p_3 \times \cdots \times p_t \tag{5.10}$$

Where the p_i's are the conditional probabilities of surviving the time interval *i* having survived the preceding interval time *(i-1).*

To estimate the survival function $S(t)$ we employ the Kaplan-Meier (K-M) estimator. This has been one of the most commonly used methods of estimating survival functions ever since Kaplan and Meier (1958) showed that the product-limit estimator was the non-parametric likelihood estimator of the survival function. The method employs the use of survival times for both the (right) censored event times and the uncensored event times (i.e. when the event of interest, death, is observed). The probability of survival at each time point after an event has occurred is evaluated based on the number of patients who have survived up to that point, giving rise to a set of conditional probabilities which, when multiplied by each other, provide an estimate of the survival function (Hosmer, Lemeshow, & May, 2007). Mathematically, the survival function is given by the following representation.

Let the random variable *T* have *m* distinct time events such that $t_1 < t_2 < \ldots < t_m$. If at each time t_i there are exactly n_t patients who are at risk of an event and have survived up to this time, then the probability of experiencing the event (death) at time t is given by:

$$p_t = \frac{n_t - d_t}{n_t} \tag{5.11}$$

or

$$p_t = 1 - \frac{d_t}{n_t}, \tag{5.12}$$

where d_t is the number of patients who experience the event at time *t*.

The Kaplan-Meier estimator is defined as

$$\hat{S}(t) = \prod_t \frac{n_t - d_t}{n_t} \tag{5.13}$$

Here, $\hat{S}(0) = 1$ for all t less than t_1 meaning that the value of the Survival function is equal to 1 at the beginning of the observation. These successive overall probabilities of survival $\hat{S}(1), \hat{S}(2), \hat{S}(3) \cdots \hat{S}(t)$ are known as the Kaplan-Meier or product limit estimators of survival (Machin et al., 2006).

A useful way to view the K-M estimate of the survival function is to plot a graph of $\hat{S}(t)$ against time, t. The graph is equal to 1 at the point *t=0*. The graph is plotted as a step function which declines towards 0 as time increases. If all patients in the observation experience a death during the observation period, the K-M curve is equal to zero at the appropriate time t when the last of the patients was recorded as dead. In most situations, the curve ends with a plateau from the time of the last event to the censorship point. The graph remains horizontal for any period of time between which no deaths are recorded and drops instantaneously whenever a death is recorded.

The accuracy of survival curves is measured by calculated confidence intervals which are computed at the point of interest. Assuming that the K-M estimates are normally distributed, the 95% CI at any point in time t is

$$\hat{S}(t) \pm 1.96 \times SE[\hat{S}(t)] \tag{5.14}$$

The quantity $SE[\hat{S}(t)]$ is obtained by using Greenwood's formula

$$SE\big[\hat{S}(t)\big] = S(t)\sqrt{\sum_{j=0}^{t-1} \frac{d_j}{n_j(n_j - d_j)}}. \tag{5.15}$$

5.7.2 Comparison of survival functions

Survival curves described above can be obtained for different sub-populations (e.g. males versus females) from the same data set and plotted on the same graph to visually see the

relationship between them. The fundamental question which arises is whether the differences between any two (or more) survival functions are statistically significant or not. Consider two hazard functions computed from a population. To answer the question of whether the differences observed graphically between the hazard functions are statistically significantly, we formulate the following hypothesis

$$H_0 : h_1(t) = h_2(t)$$
$$H_1 : h_1(t) \neq h_2. \tag{5.16}$$

This hypothesis is best answered by use of the log-rank non-parametric test (Hosmer et al., 2007; Kleinbaum & Klein, 2005). The test compares the overall K-M curves by making use of the observed and expected cell counts across the categories of the outcomes. The log-rank test is computed as follows:

$$\chi^2_{log-rank} = \frac{(O_1-E_1)^2}{E_1} + \frac{(O_2-E_2)^2}{E_2}, \tag{5.17}$$

where O_i and E_i are the observed events and total number of expected events in each of the two groups (i.e. *i* = 1, 2*)*. At each time event time, the expected number of events is calculated as the number at risk of death in the group at that time, multiplied by the number of patients who are alive in the group at that time, or

$$E_1 = \sum_{i=1}^{2} \frac{d_i}{r_i} r_{1i}. \tag{5.18}$$

Here, d_i is the number of deaths at event time *i* and r_{1i} is the number of patients alive in group 1 at the time of the event. If the total number of deaths in the whole dataset is *n*, then the expected number of deaths in group 2 (E_1) is given by $n - E_1$ [adapted from Bewick et al. (2004) and Machin et.al. (2006)].

The log-rank test for the case where there are more than two groups is computationally complex and is achievable by use of computer packages based on the logic above. If there are

k groups and *m* distinct failure times in all groups and that at failure time t_j we have a total of n_j patients at risk of failure, then if d_j represents the number of deaths observed (implying that $n_j - d_j$ survive that time period), the log-rank test statistic is derived from the combination of *m* contingency tables (each of size $k \times 2$). The resulting test statistic for this case would be a generalized from of (5.17):

$$\chi^2_{log-rank} = \sum_{g=1}^{m} \frac{(O_g - E_g)^2}{E_g} \tag{5.19}$$

The computed values of the test statistics in (5.17) and (5.19) are compared to the $\boldsymbol{\chi}^2$ distribution with $g - 1$ degrees of freedom. For the former, $g = 2$ and therefore the degrees of freedom are $2 - 1 = 1$.

5.8 Survival functions for the Zambia ART data (event = Death)

The mean survival time of people enrolled in ART may be defined as the integral of the survival function from zero to infinity and the non-parametric estimator of this mean is:

$$\widehat{\mu_T} = \int_0^{t_{max}} \widehat{S(t)} dt \tag{5.20}$$

where $\widehat{S(t)}$ is the Kaplan-Meier estimator fitted to the Zambia ART dataset up to the maximum observed failure time t_{max}. Since this mean is calculated by the integral in 5.20 which is restricted to the range [0, t_{max}.], the mean is formally called the restricted mean.

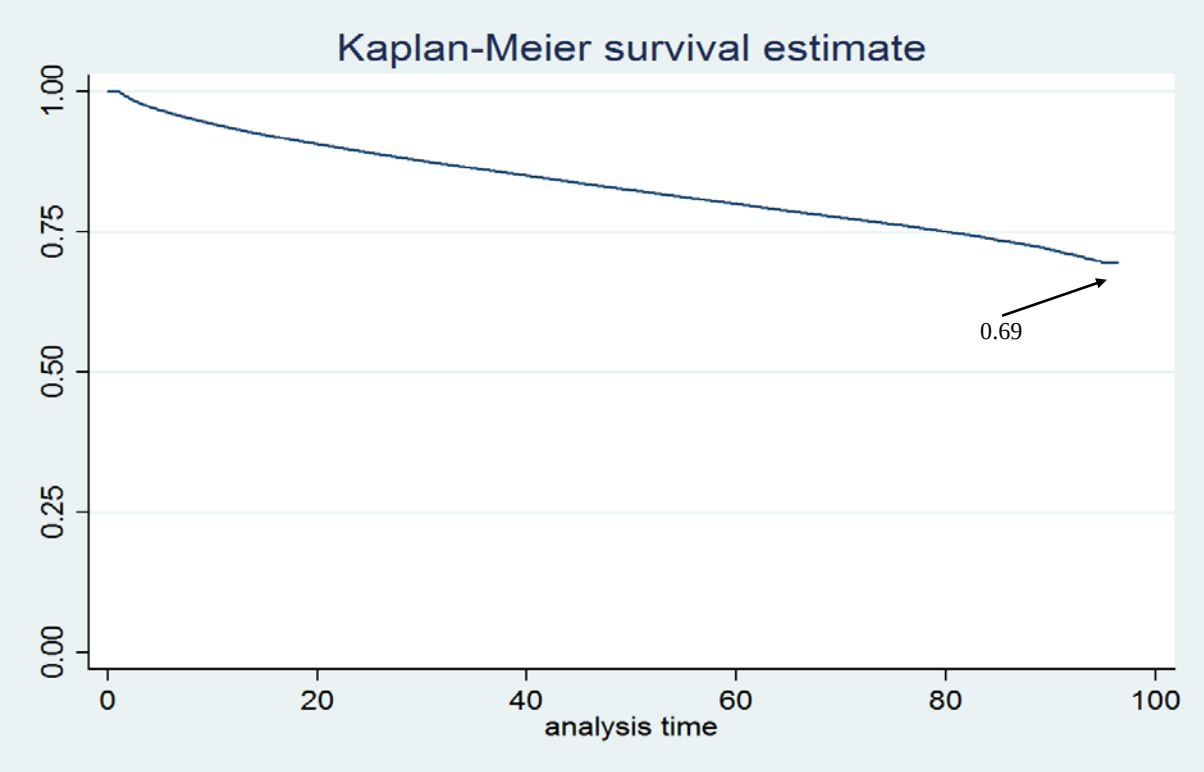


Figure 5.2: Kaplan-Meier survival function for all patients (event = Death)

The estimated mean time between enrolment onto ART and death in the Zambia ART program was 80.3 months (95% CI: 80.2 to 80.4 months). The corresponding Kaplan-Meier graph is shown in Figure 5.2. It is not unusual for the median survival time to be reported in the analysis of time-to-event data. The median survival time is defined as that time beyond which 50% of the subjects are expected to survive. From Figure 6.2 it is clear that the curve terminates at 0.69, a value of the survival function greater than 0.5 which means that at the end of the observation period, more than half the patients were still alive and that the point at which half of the patients will have experienced death was not observed and cannot therefore be computed from the observed data. The cumulative survival probability of 0.69 means that 69 percent of all patients enrolled on ART in the Zambia program were alive and on ART after 94 months. However, for comparison with other studies, the chance of survival at 36 months was considered. A person in the Zambia ART program had an 85 percent chance of surviving beyond 36 months. This compares with an 87 percent chance of being alive and on ART at 36 months in a study of patients at 5 sites in Mozambique, Malawi and Guinea (Fox & Rosen, 2010; Palombi et al., 2009). Another comparable published study which estimates survival at 36 months in the Sub-Saharan setting is based on a public sector HIV/AIDS program

in Uganda by Mills et. al. (2011). In this work, the chance of surviving beyond 36 months was estimated at different age groups: 90.7 percent for the 14 to 19 year olds, 93.4 percent for 20 to 29 years, 93.0 percent for 30 to 39 years, 93.2 percent for 40 to 49 years and 90.9 percent for 50 years and over. There is a paucity of published work on longer term survival such as this research because the epidemic is still evolving hence the comparison at only 36 months.

In order to graphically view the survival patterns of the patients on ART in the Zambian program disaggregated by some background variables, two additional Kaplan-Meier graphs were plotted and are shown below. This first graph shows the survival functions split by gender, Figure 5.3. Female patients have a better survival profile than males because the value of the Kaplan-Meier survival function for the females is higher than that of males. At the end of the observation period, females have a 0.71 chance of surviving beyond 94 months compared to a 0.68 chance of males surviving beyond 94 months. The corresponding mean survival times for males and females enrolled on the program were 81.0 months (95% CI: 80.9 to 81.2 months) and 79.2 months (95% CI: 79.0 to 79.4 months).

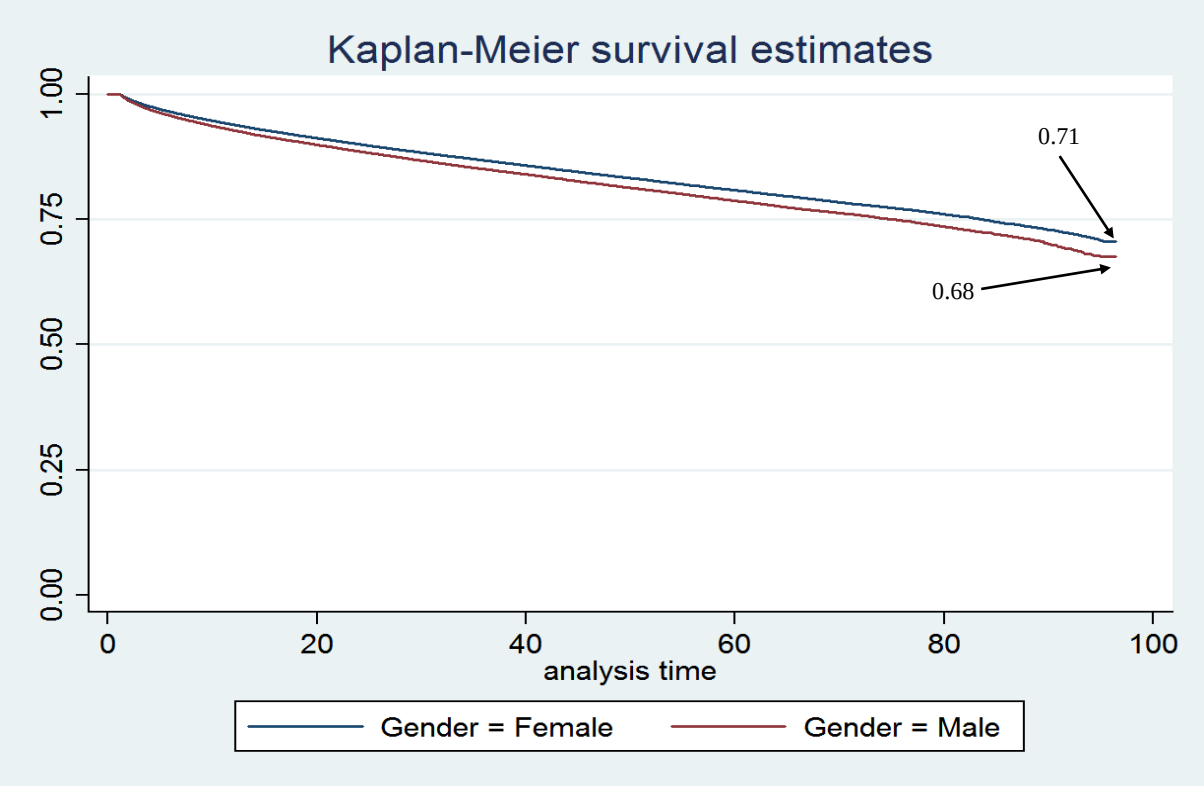


Figure 5.3: Kaplan-Meier survival functions by gender

A comparison of survival profiles for rural versus urban registered patients resulted in Figure 5.4. Patients commenced on ART in urban health facilities had a better survival profile than those enrolled in rural health institutions. For patients in urban facilities, their chance of surviving beyond 94 months was estimated to be 0.70 compared to 0.65 for the rural patients. The mean survival time in rural health facilities for patients enrolled on ART in Zambia between 2003 and 2013 was 76.9 months (95% CI: 76.5 to 77.4 months). By contrast, the mean survival time among urban-enrolled patients was 80.7 months (95% CI: 80.6 to 80.8 months). Survival estimates for patients on ART in very large programs such as Zambia remain debatable because of the unclear extent to deaths among the LTFU patients is verifiable. Some patients recorded as LTFU may be dead while others may have self-transferred to other sites or stopped treatment. This scenario has been compounded by the initial rapid scale up and subsequent decentralisation of ART services (Geng et al., 2011). Zambia, like many countries facing the pandemic initially provided ART services in large urban- based hospitals and clinics.

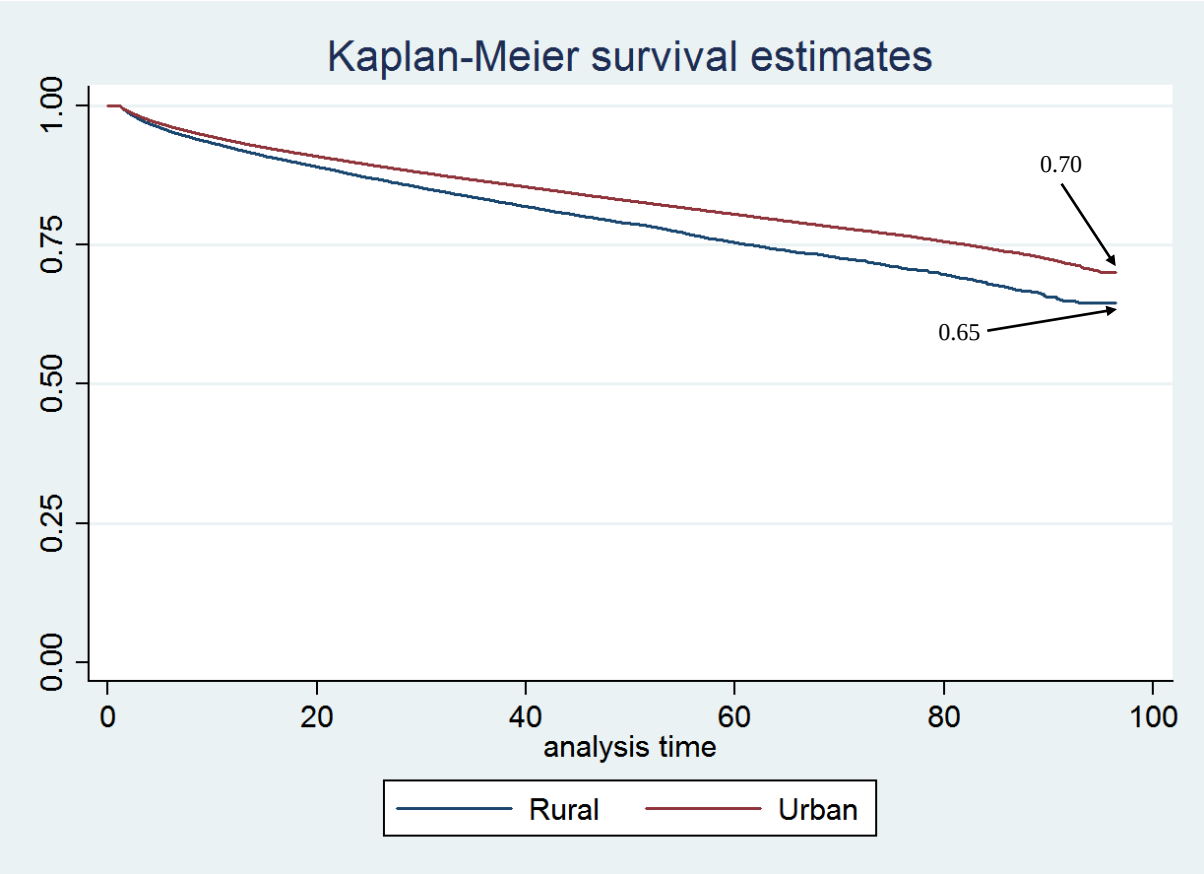


Figure 5.4: Kaplan-Meier survival functions by residence

This was followed by decentralisation to smaller clinics in urban settings and the rural areas of the country. This decentralization, or provision of the HIV/AIDS services closer to the patient's home, provides an opportunity for patients to simply enrol at another facility without officially being transferred from the bigger facilities giving rise to inflated and often difficult numbers to verify which are classified as LTFU. The definition of LTFU is another confounder because it is not uniform between countries and in some cases within the country (Chi et al., 2011). The duration of missing appointments for a patient to be declared LTFU may be 60 days, 90 day, 180 days or other making comparisons especially between countries a challenge

5.9 Survival functions for the Zambia ART data (event = Exited ART)

Overall, the mean survival time (time from enrolment to exiting the system) of people on ART in the Zambia data was calculated to be 48.4 months (95% CI from 48.3 to 48.5 months) during an observation period of 95 months or 7 years 11 months. The estimated cumulative probability of surviving up to 94 months was 0.16. These results are obtained after analysing the Kaplan-Meier estimates of the survival function as shown in Figure 5.5. This compares well with other studies examining patient retention in a similar way at 36 months (Fox & Rosen, 2010; Odafe et al., 2012). A three country study on Retention in ART conducted at sites in Uganda, Zambia and Tanzania also reports comparable results ranging from 32.7 to 90.4 percent at 3 years of observation and 28.5 to 90.4 percent at 4 years of observation (Koole et al., 2014). As explained in the previous section, comparisons with other studies are mainly possible at 36 months of ART provision because the body of literature on the subject is still growing.

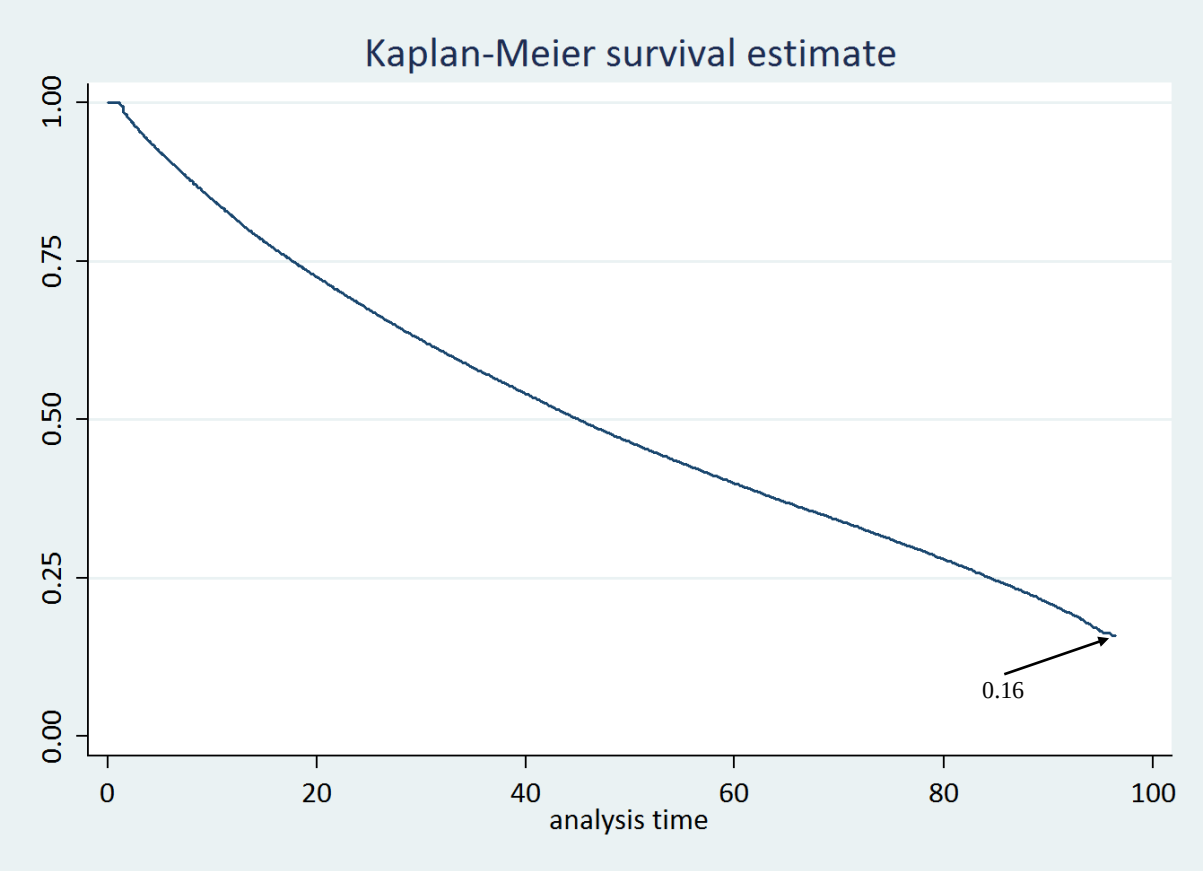


Figure 5.5: Kaplan-Meier survival function for all ART patients

Based on the heterogeneity of the HIV pandemic in Zambia discussed in earlier chapters, the survival of people on ART was examined for the different sub-populations based on different CD4 count cut-offs (at 200, 350 and 500), age group, baseline ART regimen, gender and residence. The resulting survival functions for each category were compared to make a decision on whether the differences seen graphically were statistically significant or not.

The graph below (Figure 5.6) displays the results of the comparison of survival functions based on gender. The graph indicates that that female patients had a better survival probability than men implying that on average, female patients were retained longer than men on the ART program. The mean survival time was estimated at 50 months (95% CI: 49.9 to 50.2) for females patients and 45.9 months (95% CI: 45.7 to 46.0) for male patients. The log-rank test for equality of survival functions shows that these two survival functions have a statistically significant difference ($p < 0.000$). The cumulative probability of survival to 94 months for females was 0.18 (9%% CI: 0.17 to 0.19) while the corresponding probability to survive the same number of months for male patients was estimated as 0.14 (95% CI: 0.13 to 0.15). Comparatively, the chance of survival at 36 months in the current study was estimated at 58.1

percent for females and 53.1 percent for males while the study by Koole et. al. (2014) estimated it to be 68.5 percent and 61.4 percent respectively.

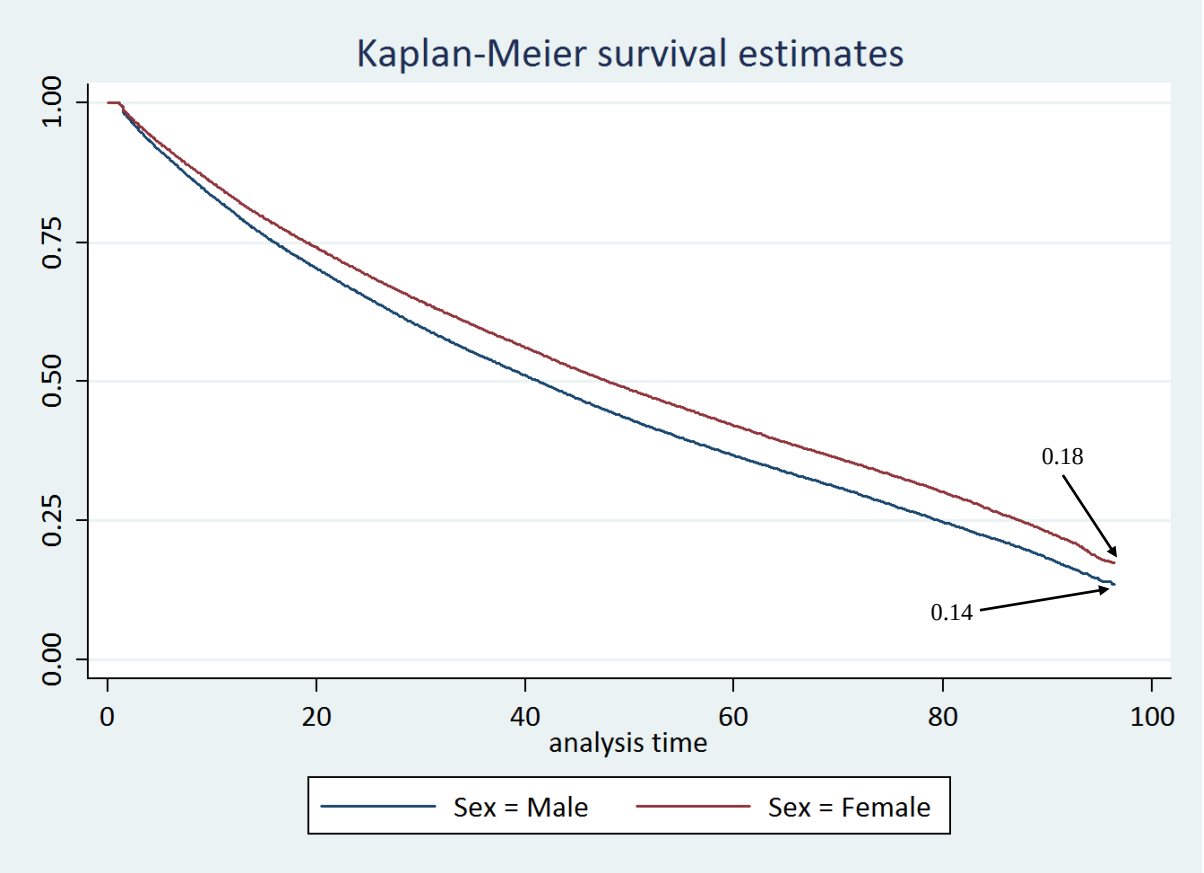


Figure 5.6: Survival function plots for the Sex

The survival functions were estimated and compared for the other covariates and the results are as follows.

- CD4 < 200 versus CD4 ≥ 200: mean survival time was 48.5 months (95% CI: 48.4 to 48.6) versus 48.1 months (95% CI: 47.9 to 48.3) respectively. Cumulative survival probability to 94 months for CD4 < 200 was 0.17 versus 0.15 cumulative survival probability for CD4 ≥ 200. Survival functions were not significantly different at the 5% level (p = 0.075) by log rank test
- CD4 < 350 versus CD4 ≥ 350: the estimated mean survival time for patients enrolled with baseline CD4 < 350 was 48.5 months (95% CI: 48.3 to 48.6) versus 47.9 months (95% CI: 47.6 to 48.2). Cumulative survival probability beyond to 94 months for CD4 <

200 was 0.15 versus 0.16 cumulative survival probability for CD4 ≥ 350. Survival functions were significantly different at the 5% level (p = 0.003) by log rank test

- CD4 < 200 versus 200 ≤ CD4 < 350 versus CD4 ≥ 350: average survival times were estimated at 48.5 months (95% CI: 48.4 to 48.6), 48.2 (95% CI: 47.9 to 48.4) and 48.5 months (95% CI: 48.4 to 48.6) months for the three groups. The cumulative probability of survival to 94 months for the group with CD4 < 200 was 0.17; for the group 200 ≤ CD4 < 350 it was 0.15 and the group with CD4 ≥ 350 was estimated to survive to this time with a probability of 0.15. The three survival functions were different statistically at the 5 % level of significance (p = 0.009)
- CD4 <500 versus CD4 ≥ 500: the estimated mean survival for the former is 48.4 months (95% CI: 48.3 to 48.5) versus 48.6 months (95% CI: 48.1 to 49.1) for the later. Patients with CD4 counts lower than 500 were estimated to have a survival probability of surviving to 94 months of 0.16 and those with CD4 ≥ 500 had a 0.14 chance of surviving to 94 months. The survival distributions of the two groups were not different statistically at the 5% level of significance (p = 0.369)
- Rural versus Urban: persons receiving ART at rural health facilities had a lower mean survival time compared to their counterparts in urban health facilities at 48.1 (95% CI: 47.7 to 48.4) versus 48.5 (95% CI: 48.3 to 48.6) respectively. The comparison of cumulative survival revealed a different scenario with rural clients estimated to survive to 94 months with a probability of 0.22 compared with a probability of 0.16 to survive to 949 months for urban patients. The difference between the two survival curves was statistically significant at the 5% level (p<0.000). This is in comparison with survival chances of 62.7 and 67.8 percent for rural and urban respectively in the three country study in sub-Saharan Africa (Koole et al., 2014)
- Paediatric (less than 15 years) versus Adults (15 years +): survival times estimates for paediatric and adult patients were estimated to be 51.2 months (95% CI: 50.8 to 51.7) and 48.2 months (95% CI: 48.1 to 48.3) respectively. In terms of the cumulative survival probabilities, paediatric patients were estimated to have a survival probability of 0.17 compared with adults at 0.16 of surviving to 94 months. The log rank test revealed that there was evidence of a statistically significant difference between the survival functions of these two sub-populations (p < 0.000)

- ART regimens (Old versus New versus Unclassified): when analysed by the type of ART regimens given to patients at initiation on ART (baseline) based on treatment guidelines in use up to 2007 (old regimen) versus the revised guidelines in use from 2007 (issued in 2010 and referred to as new regimens) versus unclassified regimens, the mean survival time for the old regimens was estimated to be 52.2 months (95% CI: 52.1 to 52.4) while the new regimens was 43.7 months (95% CI: 43.5 to 43.9). The mean survival time for the unclassified regimens was estimated to be 42.6 months (95% CI: 41.7 to 43.5). The corresponding survival probabilities of living up to 94 months were 0.19 and 0.08 for the old and new regimens respectively. Patients initiated on unclassified regimens had a probability of 0.12 of surviving to 94 months. The survival functions were different statistically ($p < 0.000$)
- Other sub-populations compared: Comparisons of survival functions were also performed on the province of residence and on the WHO Stage of the client at initiation on ART. Zambia has 10 provinces (the data only has 9 provinces because the database is yet to be updated with the newest province which was created in 2011) therefore the results are presented in the appendices along with that for WHO staging. The log-rank test showed that survival curves for both the provinces and WHO staging classifications were statistically different at significance levels of 5 percent.

A summary of the comparisons for the survival functions is shown in Table 5.1.

Table 5.1: Survival functions summary

Variable	Mean Survival months (95% CI)	p - value	Cumulative survival probability
Overall	48.4 (48.3 – 48.5)	n/a	0.16
Gender			
Female	50.0 (49.9 – 50.2)	<0.000	0.18
Male	45.9 (45.7 – 46.0)		0.14
Baseline CD4 Count			
< 200 copies	48.5 (48.4 - 48.6)	0.075	0.17
≥ 200 copies	48.1 (47.9 - 48.3)		0.15
< 350 copies	48.5 (48.3 - 48.6)	0.003	0.15
≥ 350 copies	47.9 (47.6 - 48.2)		0.16
< 500 copies	48.4 (48.3 - 48.5)	0.369	0.16
≥ 500 copies	48.6 (48.1 - 49.1)		0.14
200 - 349 copies	48.2 (47.9 - 48.4)	n/a	0.15
Residence			
Rural	48.1 (47.7 - 48.4)	<0.000	0.22
Urban	48.5 (48.3 - 48.6)		0.16
Age group			
Paediatrics	51.2 (50.8 - 51.7)	<0.000	0.17
Adults	48.2 (48.1 - 48.3)		0.16
ART regimen			
Old	52.2 (52.1 - 52.4)		0.19
New	43.7 (43.5 - 43.9)	<0.000	0.08
Unclassified	42.6 (41.7 - 43.5)		0.12

Having shown that some of the survival curves are significantly different at the 5% level using the log-rank test, this forms a basis to consider the inclusion of these sub-populations in the modelling of the survival of persons on ART. The next section explores further considerations on what combinations of the sub-populations to include in the modelling and the extents of their effect on the outcome of interest namely, survival estimates.

5.10 Cox Proportional hazard models

In order to analyse the effects of multiple covariates (both categorical and continuous), methods proposed by Cox (1972) were used. In this paper, he proposed a model which has come to be known as the *proportional hazards model* (PH model). The PH model is a non-parametric model given by (5.21). An explanation of this non-parametric property is presented below. It states that the given any point in time *t* in the study of survival analysis, the hazard at this point

$$h(t) = \lambda_0(t)\exp(\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k) \qquad (5.21)$$

where $\lambda_0(t)$ is the value of the hazard function for the individual under observation when all the *k* covariates are equal to zero (i.e. $x_1 = x_2 = \cdots = x_k = 0$). It is known as the *baseline hazard function*. The covariates (*x*'s) on the other hand are not functions of *t* and are therefore referred to as *time-independent* covariates. The Cox model assumes that the distribution of $\lambda_0(t)$ is unspecified, which implies that the model is a *non-parametric* model. Equations (5.21) and (5.22) are called proportional hazards because the ratio of the hazards of any two individuals *m* and *n* would be

$$\frac{h_m(t)}{h_n(t)} = \exp(\beta_1(x_{m1} - x_{n1}) + \beta_2(x_{m2} - x_{n2}) + \cdots + \beta_k(x_{mk} - x_{nk}), \qquad (5.22)$$

which is a constant over time and the baseline hazard functions cancel out in the numerator and the denominator. This means that the hazard of death in one group is always a constant multiple of the hazard in any other (Bradburn, Clark, Love, & Altman, 2003).

In the same 1972 paper, Cox derives a method to estimate the coefficients in the PH model. In the method he proposes that the estimates of the coefficients in the model, the β_i's, were

to be estimated as maximum likelihood estimates (denoted $\widehat{\beta_i}$'s). Since the likelihood formula used to estimate the $\widehat{\beta_i}$'s considers only probabilities of survival for patients who experience death and does not do this for the censored patients, the method developed by Cox is formally known as *partial maximum likelihood* estimation. The term Cox regression is often used to mean a combination of the Cox PH model and the methods to estimate the coefficients in the model (Allison, 2010). The technical process of the method is not discussed here but the results are easily obtainable with most computer software which handle survival estimation.

5.11 Cox Proportional hazard model for the Zambia ART data

The Cox PH model was fitted to the Zambia data by considering 7 covariates or variables which represent baseline characteristics of the patients enrolled on ART. These are CD4 count cut-offs (at 200, 350 and 500), age group, baseline ART regimen, gender and residence. The covariates used in the model development include the four CD4 count cut off points at 200, 350, 500 and a three group combination of the 200 and 350 cut off point. The convention for the cut off was to code all patients with CD4 count less than the cut off at enrolment on ART as category '1' and the group greater than or equal to the cut off as category '0'. For the Baseline CD4_grp variable, CD4 < 200 = 1, (200 ≤ CD4 < 350) = 2 (recoded as CD4_mid) and CD4 ≥ 350 = 3 to enable the three categories to be compared with each other in turn. The other covariates were gender (female = 1), enrolment age (continuous), Rural/Urban setting (rural = 1) and whether the baseline ARV regimen was the old or new regimen according to guidelines released in 2007 or 2010 (new = 1).

The models were first fitted as univariate models for each variable and then multivariate models were constructed with the necessary parameters to show any benefit of combining the variables. In this case the Log Likelihood values along with the p-values were analysed for inclusion of the individual variables. Hazard ratios were analysed as the direct effect of the variable or covariate on overall survival when all other variables included in the model (in the multivariate case) were zero. The univariate analysis results are shown in Table 5.2 and it can be seen from the respective χ-square p-values that all but two individual covariates (CD4 cut off at 500) resulted in a statistically significant effect on predicting the survival of patients enrolled on ART in Zambia. The hazard ratios in the second column show the hazard of exiting

the ART program for each value of the variable coded '1' versus the value coded '0'. The table indicates that the risk of exiting ART for a person started on the new ARV regimens is 36.5% higher than that of a person who was initiated on the older ARV drug regimens. Alternatively, this may be stated to mean the risk of dropping out in the group on new regimens is 0.732 (1/1.365) times that of the hazard of death for the group CD4 < 200. The other covariates such as cut off points at 350 and 500 can be interpreted in the same way although this is to be done with a lot of caution because of non-significant fit of some of the covariates in predicting exiting ART (e.g. p = 0.479 for CD4 < 500 and p = 0.758 for CD4 200 - 349). Generally, lower CD4 counts at these cut-offs consistently show higher risk of death compared with patients whose CD4 counts at enrolment into ART were higher.

Table 5.2: Hazard ratios from the PH model for the Zambia ART data (univariate analysis)

Covariate	Hazard Ratio	p-value	95% Conf. Interval	Log Likelihood	χ-square (p-value)
CD4 < 200	0.989	0.014	(0.982 – 0.997)	-3,072,821	6 (0.014)
CD4 < 350	0.979	0.001	(0.967 – 0.991)	-3,072,818	11 (0.000)
CD4 < 500	1.006	0.479	(0.989 – 1.024)	-3,072,823	0 (0.479)
Female	0.859	0.000	(0.853 – 0.866)	-3,072,138	1,372 (0.000)
Enrolment Age	0.996	0.000	(0.996 – 0.997)	-3,072,629	388 (0.000)
Rural	1.027	0.000	(1.013 – 1.041)	-3,072,816	15 (0.000)
New ART Regimen	1.365	0.000	(1.354 – 1.376)	-3,023,443	5,337 (0.000)
CD4 200 - 349	1.001	0.758	(0.993 – 1.010)	-3,072,824	0 (0.0758)

For the baseline CD4 group which has 3 categories, the hazard ratio of 1.001 represents the hazard of exiting the ART program when patients whose CD4 count was between 200 and 349 are compared with that of patients whose CD4 count was less than 200. Female patients were estimated to face 0.859 times the hazard of death of men. The effect of enrolment age, rural/urban residence and CD4 < 500 was in favour of older patients, urban dwellers and the CD4 ≥ 500 respectively (0.996, 1.027 and 1.006).

Table 5.3 shows the multivariate analysis involving the same variables as above presented in groups made up of a CD4 cut off variable, gender, enrolment age, rural/urban residence and new/old regimens. Including all CD4 cut off variables in some cases introduced collinearity leading to the choice to use them one at a time. The analysis revealed that Baseline CD4 cut off at 200, 350, 500 and the 3 group CD4 variables when individually included in a multivariate

survival model along with gender, enrolment age rural/urban residence and old/new regimen classification were all significantly associated with the survival of patients enrolled on ART in Zambia. The four different models in the table had very similar Log Likelihood values indicating that the models were all good and fit the data.

Table 5.3: Hazard ratios from the PH model for the Zambia ART data (multivariate analysis)

Grouping	Covariates	Hazard Ratio	p-value	95% Conf. Interval
CD4 cut off at 200 with other covariates	CD4 < 200	0.998	0.699	(0.990 – 1.006)
	Female	0.857	0.000	(0.849 – 0.864)
	Enrolment Age	0.994	0.000	(0.993 – 0.994)
	Rural	1.027	0.000	(1.013 – 1.041)
	New ART regimen	1.389	0.000	(1.378 – 1.401)
Log Likelihood = -3,022,253		Log Rank χ - square = 7,717 (p<0.000)		
CD4 cut off at 350 with other covariates	CD4 < 350	0.970	0.000	(0.959 – 0.983)
	Female	0.857	0.000	(0.849 – 0.863)
	Enrolment Age	0.994	0.000	(0.993 – 0.994)
	Rural	1.027	0.000	(1.013 – 1.040)
	New ART regimen	1.392	0.000	(1.379 – 1.404)
Log Likelihood = -3,022,243		Log Rank χ - square = 7,739 (p<0.000)		
CD4 cut off at 500 with other covariates	CD4 < 500	0.994	0.490	(0.957 – 1.011)
	Female	0.857	0.000	(0.849 – 0.864)
	Enrolment Age	0.993	0.000	(0.993 – 0.994)
	Rural	1.027	0.000	(1.013 – 1.04)
	New ART regimen	1.390	0.000	(1.378 – 1.402)
Log Likelihood = -3,022,253		Log Rank χ - square = 7,718 (p<0.000)		
CD4 cut off 200 to 349 with other covariates	CD4 200 – 349	0.988	0.006	(0.979 – 0.996)
	Female	0.857	0.000	(0.850 – 0.864)
	Enrolment Age	0.994	0.000	(0.993 – 0.994)
	Rural	1.027	0.000	(1.014 – 1.041)
	New ART regimen	1.391	0.000	(1.379 – 1.403)
Log Likelihood = -3,022,249		Log Rank χ - square = 7,725 (p<0.000)		

The corresponding Log Rank χ^2 values with p-values represent the model goodness of fit criteria which shows that all the models are beneficial in explaining the variation of the observed survival times (exit times) using the indicated time-independent variables. On the other hand, the p-values in the fourth column of Table 5.3 indicate by how much the hazard ratios for each variable differ from 1. In all the models, most of the p-values are such that p < 0.05 which indicates that at the 5% significance level, the differences of hazard ratios from 1 are statistically significant thereby providing a benefit in the model.

Further assessment of overall model fit was conducted by using Cox-Snell (D. R. Cox et al., 1968) residuals. If a Cox regression model fits the data well, then a plot of the estimate of the Nelson-Aalen cumulative hazard function against the Cox-Snell residuals yields a straight line. Formally, for a Cox model of the form (5.21) to hold, the estimate of the survival times given by $\hat{S}(t)$ must be very similar to the survival times from the true$S(t)$. As long as this holds true, then the true cumulative hazard function conditional on the covariate vector has an exponential distribution with hazard rate equal to 1. It follows that the Cox-Snell residual for the j^{th} observation is given by

$$rCS_j = \widehat{\Lambda_0}(t_j)\exp(\boldsymbol{x}_j\widehat{\beta_x}) \tag{5.23}$$

with both $\widehat{\Lambda_0}(t_j)$ and $\widehat{\beta_x}$ are obtained from the fit Cox model (Cleves, Gutierrez, Gould, & Marchenko, 2010).

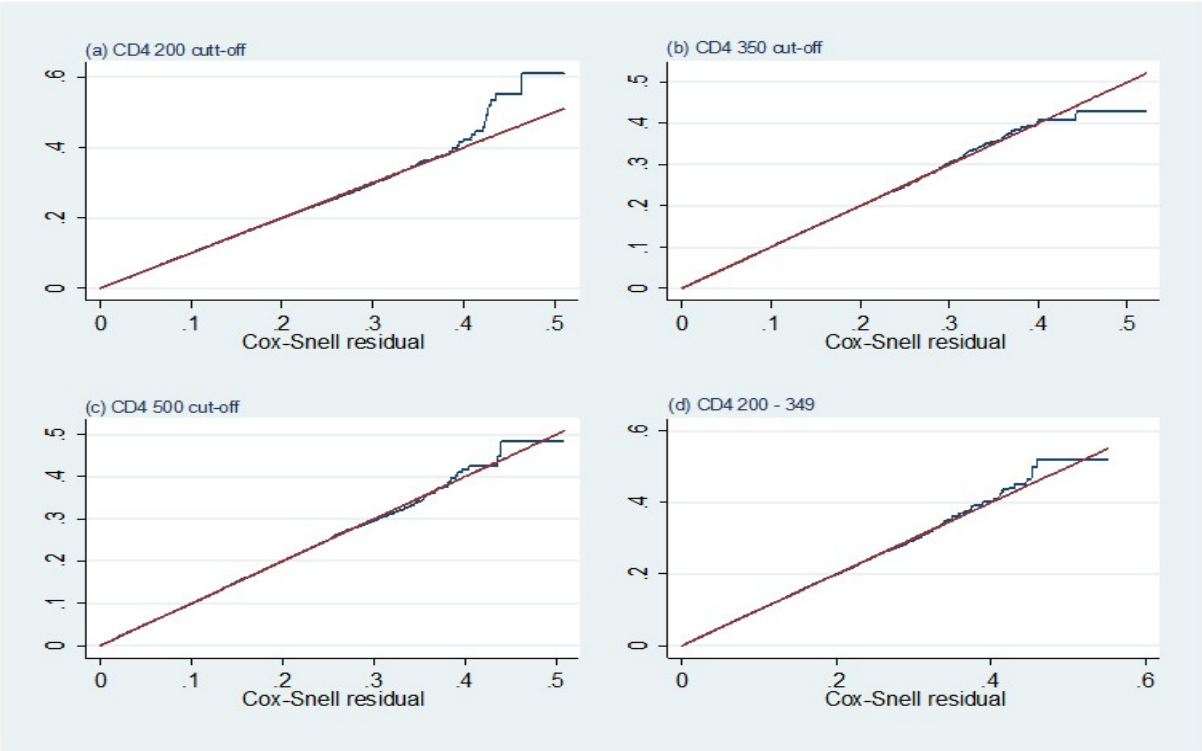


Figure 5.7: Cumulative hazard plots of Cox-Snell residuals for various CD4 cut-offs

The empirical Nelson Aalen cumulative hazard function was derived when the Cox-Snell Residuals were taken to be the survival times with the same censoring variable used in the Cox regression.

Figure 5.7 shows the results of these plots for each of the combinations of models developed above. Clearly all the models fitted represent good fits to the data. The deviations at the ends of the graphs are expected because of the diminishing sample sizes towards the end of the observation period. Other criteria such as Akaike's Information Criteria, AIC (Akaike, 1974) or the Bayes Information criterion, BIC proposed by Schwarz (1978) were not used here. For purposes of this study, ensuring that a model is a good fit without comparison with other model suffices because the interest of this research work is to study the results of the different what-if scenarios in the simulation model that we develop.

5.11.1 Proportionality of hazards in the Zambia ART data

In order to correctly use and interpret the fitted Cox PH model, its coefficients and implications, the proportional hazards assumption needs to be validated. Testing the

proportional hazards assumption is the model specification test equivalent for other regression models. For this research, it was achieved by performing one of a number of model specification tests to verify the adequacy of the choice of the $\beta_i x_i$ terms chosen. For this purpose, the choice of the test to use was a graphical method which plots the estimates of $\ln\left[-\ln\{\widehat{S(t)}\}\right]$ versus $\ln(t)$for each covariate and implemented in Stata. If the hazards are proportional, then the above plot, called the log-cumulative hazard plot is roughly parallel (Collett, 1994). This observation is based on equation (6.21), re-written as

$$h(t) = \lambda_0(t)\exp(\boldsymbol{\beta}'\boldsymbol{x_j}) \tag{5.24}$$

Integrating both sides yields

$$\int_o^t h_j(u)du = \exp(\boldsymbol{\beta}'\boldsymbol{x_j}) \int_0^t h_0(u)du \tag{5.25}$$

and applying equation (5.3) to equation (5.24)

$$H_j(t) = \exp(\boldsymbol{\beta}'\boldsymbol{x_j})H_0(t) \tag{5.26}$$

Taking logs on both sides of the equation gives rise to the expression of interest, which is the subject of the plot

$$\ln H_j(t) = \boldsymbol{\beta}'\boldsymbol{x_j} + \ln H_0(t) \tag{5.27}$$

Equivalently, upon utilization of the relationship between the cumulative hazard and the survival function $\mathrm{S(t)} = \exp\{-\mathrm{H(T)}\}$,

$$-\ln[-\ln S_j(t)] = -\boldsymbol{\beta}'\boldsymbol{x_j} - \ln[-\ln S_0(t)] \tag{5.28}$$

Figure 5.8 shows the results of the plots. The plots shows that both the CD4 cut-off at 200 and the location of the patients' ART clinic predicted proportional hazards of death for the Zambia data because the plots are roughly parallel. There are expected violations of this in the right-

hand tails of the plots because of reduced effective sample sizes as a result of prior failures and censoring. Similar graphs were plotted for each of the other covariates and it was found that all were parallel except CD4 cut-off at 500 and the enrolment age dichotomised into paediatrics and adults and where there were minor deviations in the right hand tails. These deviations in the tail end of the plot were expected to cause possible data unreliability as described above which rendered the deviations inconclusive. For purposes of simulation however, these were not considered serious deviations to warrant completely dropping those covariates from estimating survival of people on ART in Zambia.

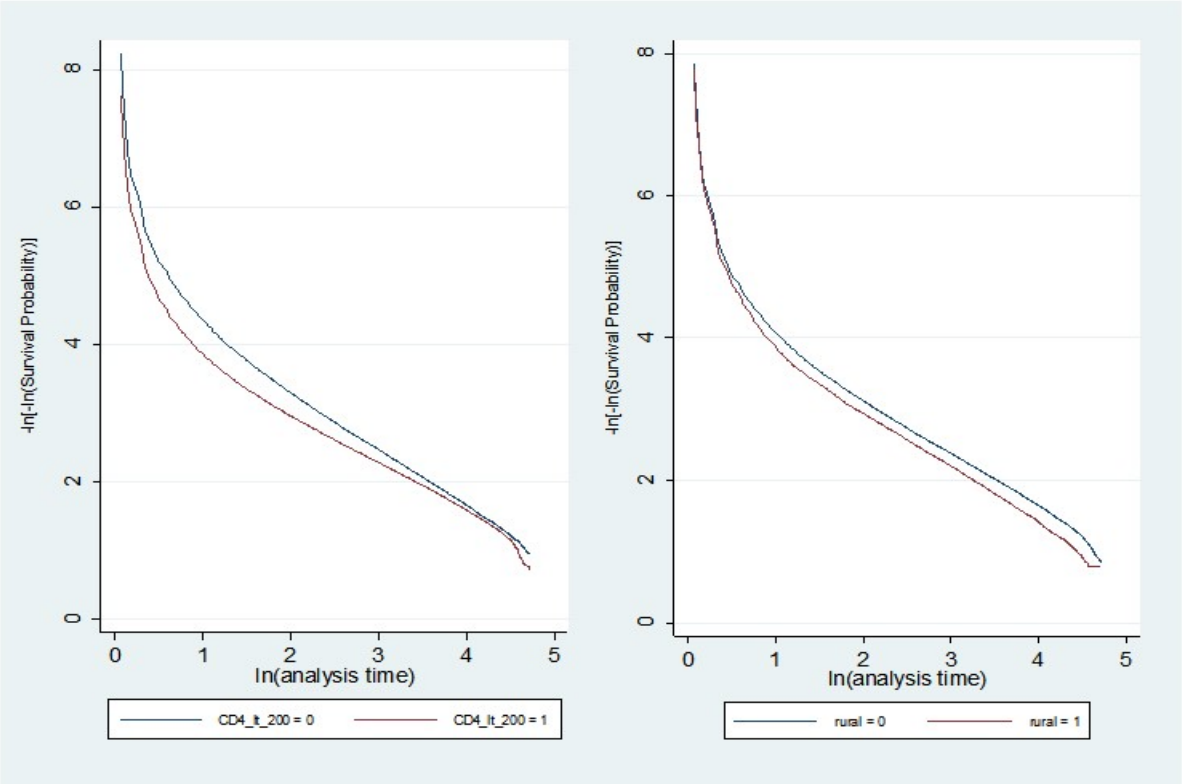


Figure 5.8: Proportional hazards test for covariates in the model

5.12 Final covariates retained for simulation modelling

In view of the forgoing analysis, some covariates were not retained for inclusion in the simulation model in the next chapter for various reasons. The remaining variables were viewed to be sufficient to model the Zambia ART program accurately without much loss of accuracy. The final list of variables to be considered in the simulation is presented in Table 5.4.

Table 5.4: Covariates retained for simulation modelling

Covariate	Status	Reason
CD4 < 200	Excluded	Difference not statistically significant (p = 0.075)
CD4 < 350	Included	p = 0.003
CD4 < 500	Excluded	Difference not statistically significant (p = 0.369)
Female	Included	P < 0.000
Age group	Included	P < 0.000
Residence (rural/urban)	Excluded	Inconsistent definitions (see section 5.8.6)
New ART Regimen	Excluded	Unclear regimens distinction (see section 5.8.6)

The definition of rural and urban in Zambian medical statistics is not standardized to the statistical definition used by the country's Central Statistical Office (CSO). While CSO is the national and official bearer of statistics on behalf of the Government of the Republic of Zambia (GRZ), the Ministry of Health (MOH) has adopted an unclear and undocumented criteria of allocating the rural or urban classification to its health facilities. This discrepancy has created a difficulty in comparing statistics from the country's health institutions with any metrics or statistics compiled by the CSO such as results of the demographic and health surveys (DHS) or census of population and housing. For this reason, the simulations were not performed using this variable. Furthermore, the distribution of patients at rural and urban facilities as classified by the MOH in the dataset is far from comparable with the prevalence or residence of HIV positive persons in the general population.

The baseline regimen each patient was given on enrolment onto ART on the other hand was left out of the simulation modelling because the backbone of what was the second line ART (Tenofovir and Emtricitabine, also known as TDF and FTC) up to 2007 was to be the first line ART regimen going forward. As a result of this, there were patients who were on a combination of drugs that was not possible to tell whether it was first line or second line particularly because during the transition period (of over 12 months), physicians prescribed either according to the new guidelines or the old guidelines depending on stocks of the older drugs which they had been instructed to deplete before fully prescribing on the newer protocols.

5.13 Extraction of survival time distributions for the Zambia ART data

Using the combinations of covariates given in Table 5.4, we estimate the survival distributions for use in the simulation model, using Royston-Parmar (RP) distributions to extrapolate beyond the end of the survey period (Royston & Lambert, 2011).

RP distributions are a set of standard parametric models which have been generalized to include more flexibility with regard to the shapes of the survival distributions they can model. In this regard, the Weibull, loglogistic and lognormal models are extended to become proportional hazards (PH), proportional odds (PO) and probit-scaled RP models respectively (Royston & Lambert, 2011). The baseline distribution is modelled as a restricted cubic spline function of the log of time thereby allowing to follow its shape more accurately.

Royston and Lambert argue that since the RP models are on the log cumulative hazard scale, then using (6.6) and (6.8), the proportional hazards model reduces to

$$\ln\left[H\left\{t\middle|x_j\right\}\right] = \ln[H_0(t)] + \boldsymbol{\beta}'\boldsymbol{x_j} \tag{5.29}$$

If a cubic spline function of the log of time, $\ln(t)$ with knots numbering k_0 is written as $s\{\ln(t)\,|\gamma, \mathrm{k}_0\}$, then replacing the baseline log cumulative hazard in (5.29) gives

$$\ln\left[H\left\{t\middle|x_j\right\}\right] = s\{\ln(t)\,|\gamma, \mathrm{k}_0\} + \boldsymbol{\beta}'\boldsymbol{x_j} = \gamma_0 + \gamma_1 z_{1j} + \gamma_2 z_{2j} + \gamma_3 z_{3j} + \boldsymbol{\beta}'\boldsymbol{x_j} \tag{5.30}$$

where the spline function is expressed as

$$s\{\ln(t)\,|\gamma, \mathrm{k}_0\} = \gamma_0 + \gamma_1 z_{1j} + \gamma_2 z_{2j} + \gamma_3 z_{3j}$$

from which the survival and hazard functions can be easily derived,

$$S\left\{t\middle|x_j\right\} = \exp\left\{-\exp(s\{\ln(t)\,|\gamma, \mathrm{k}_0\} + \boldsymbol{\beta}'\boldsymbol{x_j})\right\} \tag{5.31}$$

$$h\{t|x_j\} = \frac{ds\{\ln(t)\,|\gamma, \mathrm{k}_0\}}{dt} \exp\{s\{\ln(t)\,|\gamma, \mathrm{k}_0\} + \boldsymbol{\beta}'\boldsymbol{x_j}\} \tag{5.32}$$

The form of the RP model used in extracting the survival times for the simulation in the Zambia ART data are Proportional Odds (PO) models. These are derived by replacing $H\{t|x_j\} = -lnS(t|x_j)$, derived in (5.6) into (5.29) and expressing it as a general form with the aid of a monotonic increasing function $f_\delta(\cdot)$ such as Aranda-Ordaz's function (Aranda-Ordaz, 1981) which depends on a parameter δ > 0 given by $f_\delta(x) = \ln\{(x^{-\delta} - 1)/\delta\}$. That is

$$\ln[-lnS(t)] = \ln[-lnS_0(t)] + \boldsymbol{\beta}'\boldsymbol{x_j} \tag{5.33}$$

generalizes to

$$f_\delta lnS(t) = f_\delta\{lnS(t)\} + \boldsymbol{\beta}'\boldsymbol{x_j} \tag{5.34}$$

When δ = 1, rewriting the Aranda-Ordaz function as a function of $S(t)$ instead of it being a function of x and utilizing the relationship $F(t) = 1 - S(t)$ between the survival function and the cumulative distribution function, equation (5.34) reduces to the logit of the cumulative distribution function because $f_1 S(t) = \ln\left[\frac{\{1-\mathrm{S(t)}\}}{\mathrm{S(t)}}\right] = \ln\left[\frac{F(t)}{1-\mathrm{F(t)}}\right]$. This can be expressed as a proportional odds (PO) model of the form

$$logit\{1 - S(t)\} = logit\{1 - S(t)\} + \boldsymbol{\beta}'\boldsymbol{x_j} \tag{5.35}$$

Equation 5.35 defines one type of RP models, which is a PO model. Other transformations exist, based on the choice of $f_\delta(.)$ for example as minus the probit of the normal cumulative distribution function$\Phi^{-1}\{1 - S(t)\}$, where $\Phi^{-1}(\cdot)$ is the inverse of the normal distribution gives rise to probit models.

For purposes of the Zambia ART data, the PO model with splines is used to estimate the baseline survival function from which the simulated survival times are drawn. The

implementation of this process is pre-programmed into Stata under the command *stpm2* followed by the *stsurvsim* command.

The survival times are modelled as weeks of survival rather than months of survival to increase accuracy and a histogram of the survival probabilities for the total number of ART patients is given below. Figure 5.9 presents the histograms of survival times extracted from the data for use in the simulation. Similar histograms for the sub-populations in the data are presented in Appendix 1.

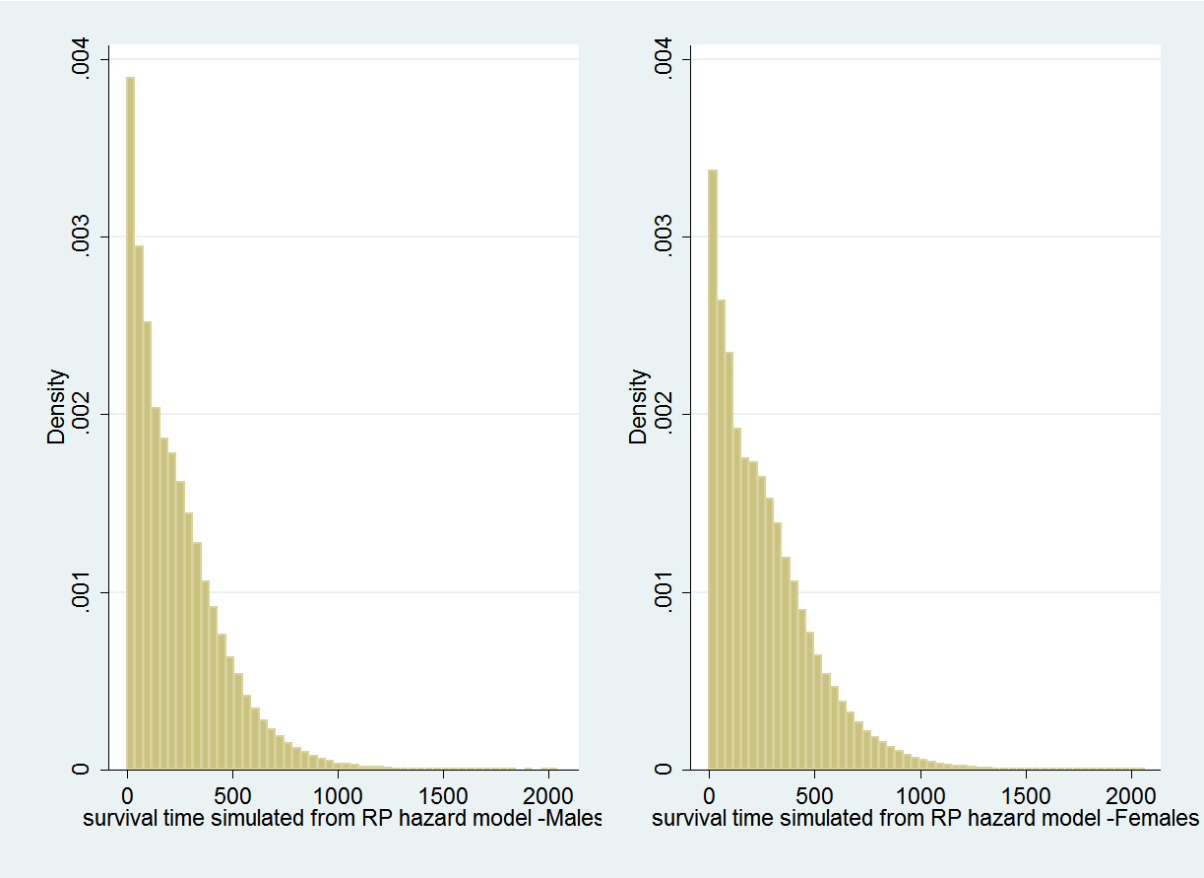


Figure 5.9: Extracted survival times histograms for males and females

5.14 Chapter summary

The initial sections of the chapter have provided:

- A recap of the research questions which correspond to the two main research objectives

- A description of the development of tasks for each research question to enable us answer the research questions
- A justification of the methods chosen to answer the research questions

The analysis in this chapter has shown that:

- The mean survival time (i.e. time to exit the ART program) for patients on ART observed in the Zambia ART data is 48.4 months or 4 years
- The survival times observed for patients whose baseline CD4 counts were less than 350 versus CD4 ≥ 350 were significantly different at the 5 percent level of significance.
- The survival function and survival times of patients were significantly different between males and females (45.8 and 50.0 months respectively)
- Survival functions and survival times for patients attending rural versus urban facilities were different statistically at 48.0 versus 48.5 months respectively
- The type of ART regimens (2007- or 2010-based regimen) given to patients at baseline showed significant differences with the former having a mean survival of 50.6 months and the latter 38.8 months
- The Cox PH model has shown the benefit of using multiple covariates in the same model to estimate exit times for people on ART in Zambia
- Histograms of survival times can be extracted from the data to be used in the simulation model

The findings from the analysis in this chapter provide the basis for the input distributions for the simulation model. Specifically, this chapter provides the evidence that the sub-populations of people on ART in Zambia defined by the different variables above have different survival times before exiting ART.

6 The Discrete Event Simulation (DES) Model

6.1 Tasks addressed in this chapter

Task 4: What are the different survival scenarios of ART patients in Zambia based on the different baseline characteristics variables

6.2 Introduction

The main research question in this doctoral work is addressed in this chapter which is concerned with developing a survival profile for people on ART in Zambia. A DES model was developed for this purpose. The model development process is outlined and the various steps taken to achieve this are enumerated. The model description provides an overview of the model and includes a section on model inputs, and conditions. Model performance measurements and outputs are discussed separately to enable the reader understand the important results being generated. The chapter also outlines how different characteristics (or attributes) were assigned to each patient to represent those of real life patients before and as they flow through the system. Finally verification and validation of the model is undertaken.

6.3 Model description

The simulation model to study the different survival scenarios of ART patients in Zambia was developed using the Simul8 software (www.simul8.com). A screenshot of the model is presented in Figure 6.1 showing the various simulation objects and paths followed by patients who enter the system. The model in Figure 6.1 is a simplified version for ease of visualisation while the full model used is identical in terms of the layout of model objects and the underlying logic used to direct the patients through the model but has duplicated workstations processing the patients in $1^{st}/2^{nd}$ Line ART primarily to manage the queues, details which are discussed below.

6.3.1 Input modelling

Patients (entities) enter the system via one entry point which represents all the ART clinics in Zambia. Their arrival times into the model are governed by a Poisson distribution with parameter 0.008369 extracted from the data. This arrival profile is representative of the rate

at which the patients are enrolled onto the ART program at any of the country's public health facilities.

Representative of the real ART program, entities continue to enter the model on a weekly basis ensuring that there are new patients enroling on ART every week while at the same time, some patients exit the system. The Simul8 model (Figure 6.1) is set up to run in time units equal to one week. This implies that the number of ART patients initiated on ART are aggregated to weekly totals and are introduced at once into the system every week instead of every week day. This is a simplification of the model designed to preserve computing resources while maintaining model consistency. The system therefore adjusts its state based on events which occur to patients in multiples of a week instead of daily. The ART clinics in Zambia are only open on weekdays but the model is based on 7-day weeks because the length of time patients spend on ART is based on calendar days. The model output is also provided in number of weeks a patient spends in the system.

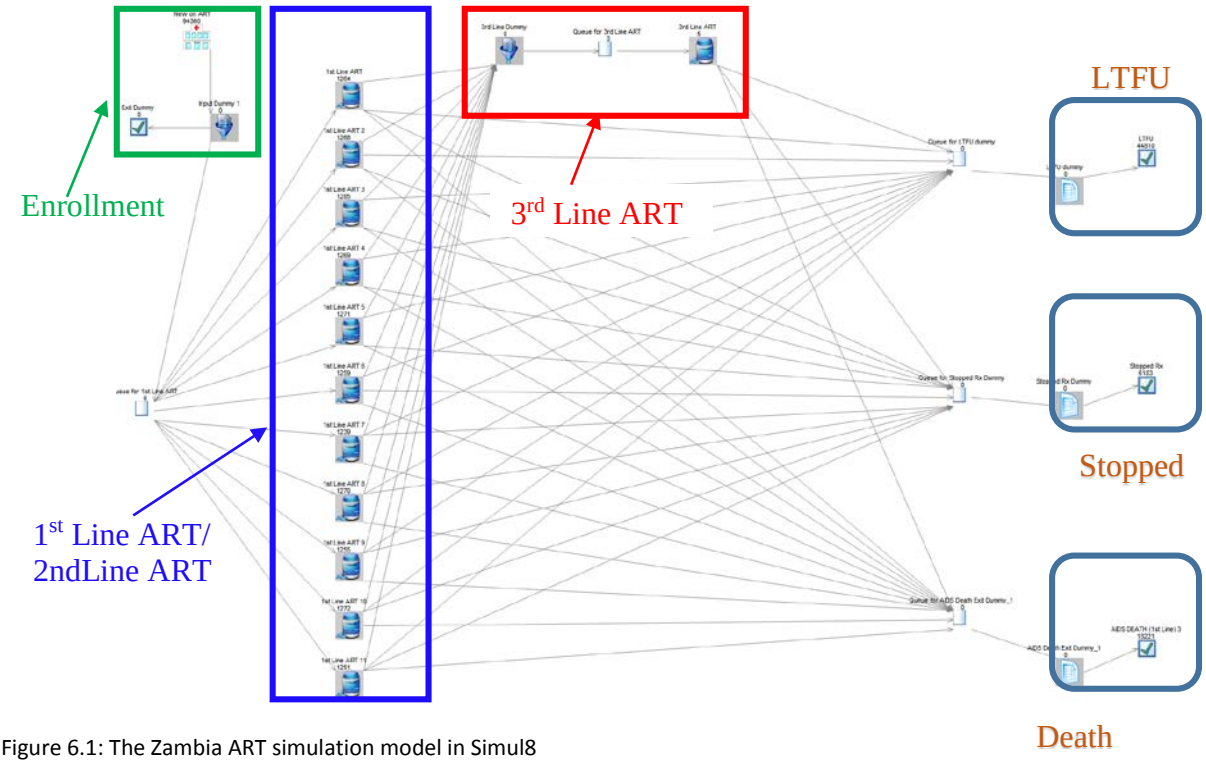


Figure 6.1: The Zambia ART simulation model in Simul8

The amount of time that an entity or patient spends in the system is modelled as a function of the baseline characteristics of the patient at enrolment. For most patients in the program,

attributes such as CD4 count and others are rarely updated after commencement of ART even though some of these may be available for some patients. The majority of patients in the Zambia ART program (> 70%) do not have subsequent CD4 readings after initiation due to the limited (human) resources required to perform these tests. In the model, additional workstations, called 'Dummy' workstations were created to allow for the visual logic code to be written in them in order to collect information on the entities as they travel through the model. In such workstations, entities do not spend any time at all and they transition through to allow the software to record information about their behaviour and which route they have taken.

6.3.2 Transition between ART regimens

On enrolment, patients enter the 1st/2nd Line ART regimen workstation where they accumulate and spend different lengths of time. How long they spend in this regimen is governed by a probability distribution as described in the last sections of the survival analysis chapter and illustrated in Appendix I. The 1st Line and 2nd Line ART regimens have been combined in the model because of the unclear distinction between the regimens over the period from 2003 to 2013. This is because some drug combinations which were classified as 2nd line in the period 2003 – 2007 were used as 1st line regimens in the period after 2007. The two sets of regimen guidelines overlapped for a few years making it difficult to draw a point in time from when the same regimen may be considered first or second line. For example, the ARV drug combination made up of Emtricitabine (FTC) and Tenofovir (TDF) in addition to a third ARV was strictly a second line regimen before 2007 but was adopted as a first line combination based on recommendation of WHO (World Health Organization, 2006). This practice was only fully formalized after the year 2010 meaning that there are patients who could either be on first or second line treatment during that overlap period between 2007 and 2010.

The number of patients in this treatment phase (1st/2nd Line ART and 3rd Line ART) represents the number of patients currently on ART in the country. The patients will stay in this state until they exit the ART program through one of three routes. Of the total number of patients who exit the 1st/2nd Line ART phase of treatment, 0.02% proceed to 3rd Line ART. There is such a small number of patients in this phase of treatment because of the specialized nature of

monitoring required to treat them. Each patient's drug regimen on third line ART is specific to the patient's immunologic profile mapped out by a series of sophisticated and expensive tests and procedures (such as genome sequencing) which can only be performed at the country's highest health institution based in the capital city, Lusaka. Patients are therefore very closely monitored by the country's top specialist HIV clinicians. At censorship point for this research work, there were only 77 patients in Zambia on 3rd Line ART. In a similar way, these patients also follow a distribution which governs how long they remain on this treatment regimen until they also exit the system. For those patients who exit the system, either while in the 1st/2nd Line or 3rd Line of therapy, the details of their exit is discussed below.

6.3.3 Exiting the system (LTFU, Stopped treatment or Died)

When patients have been on treatment in 1st/2nd Line ART for a specified length of time, they exit this phase to various destinations as follows. Of those patients who exit the 1st/2nd Line, 0.02 percent of them proceed to the 3rd line ART, 26% exit the system because they 'Died', 64.98 percent exit as Lost To Follow Up (LTFU) patients while 9 percent have their treatment stopped for various reasons. The primary objective of this research work is to model the duration between entering the ART program and exiting it. These three categories of destinations for the patients namely LTFU, Stopped and Died therefore define patients who have exited the system. In the simulation model, the durations were computed and then analysed for each patient based on information on labels carried by each patient.

Clearly, there are some patients whose time of exit will not have been reached at all times since patients are allowed to enter the simulation model continuously to depict the real life ART program which allows new ART patients to be initiated every week. Those patients who remain on in the system at either 1st/2nd line or 3rd Line ART represent the total number of patients expected to remain on treatment in the country requiring to be provided with care.

6.4 Model logic

As the patients enter the model, different attributes are assigned to them. These include age, residence, gender, CD4 count and so on. Simul8 achieves this by giving each patient a set of labels, where each label is a stamp with such attributes such as 'rural' or 'urban', 'male' or 'female', 'CD4 < 200' or 'CD4 ≥ 200' and so on written on them. The patient carries these

labels throughout the period they are in the system, much as a patient in the real ART program carries with them the same information about their status at baseline or enrolment onto ART. Some of these attributes determine the duration that each patient spends in the system based on the findings in the survival analysis chapter above. Other labels are used to determine which route an entity takes in a model and which exit to follow. Simul8 allows the modeller to use these labels in writing the logic which determines many aspects of the simulation model as required. This is achieved by writing the instruction in Visual Logic which is the programming language embedded in Simul8.

An important label 'stamped' on each entity at entry into the model is the simulation time which represents the time a patient entered the ART program. Different such time labels are stamped onto the patient representing the time a patient enters or exits a workstation such as $1^{st}/2^{nd}$ Line ART or 3^{rd} line ART and so on. The amount of time an entity spends in any object in the model or in the entire model is calculated as the difference between the appropriate time stamps. To compute the time an entity spends in the system, the difference is calculated between the times stamped onto the entity at entry into the model and time stamped onto it at the point of exit from the model. The time stamps are used to compute the average time that each entity spends in each workstation representing an ART regimen and ultimately how much time they spend in the system. These times were compared with the estimated survival times from survival analysis for consistency and as a way of model validation.

Since the model has been set up to run in weeks, the durations computed as described above are reported as weeks. The choice of this time unit was made to accommodate the full observation period of 10 years in a realistic computer simulation time.

6.5 Assumptions and simplifications

According to Robinson (2004), a model that is well simplified preserves the validity and utility obtainable from it thereby maintaining an acceptable level of accuracy and run speed as well as ease of development. Model simplification helps in reducing the complexity of a model yet maintains the essential purpose for which it is developed. In building the model for the Zambia ART program, a number of options and variations of the model were considered. The final model chosen was the least complex but one that maintains all the necessary

components of the process of providing ART to an HIV-infected patient in the context of Zambian public health institutions. A significant simplification of the model was to combine 1st Line and 2nd Line ART into one. This arose out of difficulties with identification of patients who were on either regimen as a result of an overlap between the use of a defining regimen which can be classified as both first line and second line as discussed in the previous sections.

Furthermore, in order for the model to run as efficiently as possible, a number of assumptions have been made. These assumptions are listed below:

1. Patients enter the model as in the real system (aggregated to a weekly sum)
2. The capacity to initiate ART is assumed to be infinite (all PLWHA needing the treatment are put on ART)
3. Death of a patient modelled explicitly as AIDS/non-AIDS combined
4. Patients who stop and re-start ART treatment are considered to be the same as those continuing treatment throughout their life
5. Occurrence of opportunistic infections (OIs) not modelled because of unreliable data
6. Patients exiting the system are considered to be the sum total of those patients who are a) Lost To Follow Up; b) Stopped treatment; and c) Died

6.6 Information variables and outputs

The various processes and activities in the model are tracked, examined and interpreted by studying the information generated by the Simul8 software. This information is written to Microsoft Excel spreadsheets both during model execution and at the end of the run. The data written out to the Excel spreadsheets is possible because of the labels that are assigned to each entity at different stages in the model and at different times as appropriate. These labels help the modeller to record the complexity of the model and provide a means to later assess the performance of the model. The labels carry a wide range of patient attributes which may be categorised as follows: Residence, ID, Routing, Regimen distributions, Entry distributions, Age and Patient conditions.

The labels in the model carry various types of information which identify the patients either throughout the model or while they are at a simulation object as follows: a patient will have been enrolled on ART in a rural or urban health facility; Each patient has a unique ID; a

patient's CD4 count is assigned to them randomly then classified into categorical groupings with cut-offs at 200, 350, 500 and the category between 200 and 350; a patient's WHO stage is in any category from WHO stage I to WHO stage IV depending on clinical presentation at enrolment.

Another set of labels carry information regarding distributions called label based distributions. These labels are used to sample distribution times from pre-determined probability distributions for patients with specific characteristics. The distributions are assigned to each patient and stamped on a label which is interpreted by each simulation object by sampling a duration from an appropriate distribution on entry. This allows the modeller, for example, to ensure that all patients who are male and were enrolled in a rural health facility all experience similar durations in a particular phase such as $1^{st}/2^{nd}$ Line ART which are different from females in the same area. This provides an opportunity to account for the variability of patients in terms of the different durations they take based on their characteristics. This increases model accuracy.

The model also contains routing labels which are used to direct patients to various destinations on exit from a simulation object. These routing labels are assigned to a patient either as they enter the model for the first time or at entry into a simulation object (say $1^{st}/2^{nd}$ Line ART). Once the patient has observed the sampled duration in an object, they are then directed to exit towards a specific object or phase in the model depending on conditions written down in the visual logic. If the patient is exiting the $1^{st}/2^{nd}$ Line ART phase, they may be directed to 3^{rd} Line ART, LTFU, Died or Stopped treatment. Routing is also processed by use of percentage allocations to the appropriate routes in which case Simul8 allows a pre-determined percentage of patients to each exit route as directed.

6.7 Assigning characteristics to the population on ART

In this section, the population of ART patients was reconstructed based on the attributes from the data. The patients were assigned their age, sex and CD4 count following the patterns or distributions observed in the real dataset. This ensures that the patients in the model have attributes matching those of the patients in the ART system in Zambia. As has been stated above, these attributes are very important in the simulation model because they determine

the route and duration each patient spends in the model. The patents were given extra attributes which were not necessarily used for either determining the length of their stay in the model or routing. These attributes were useful for validation purposes and were seen to have possible uses post modelling if the need to analyse the results further arises. The additional variables are the geographical distribution of patients discussed in section 5.8.1 and the residence (rural/urban).

6.7.1 Geographical distribution of ART patients

The distribution of patients in the ART program in Zambia was reproduced from the dataset into the user-defined empirical distribution displayed in Figure 6.2. Using this distribution, Simul8 samples a numerical value from 1 to 9 representing each province according to the probabilities for each province. This value is written to a label carried by each patient. The software assigns an appropriate proportion of patients entering the model to each province such that at any one time, the distribution of patients in the model matches that in the real system being modeled.

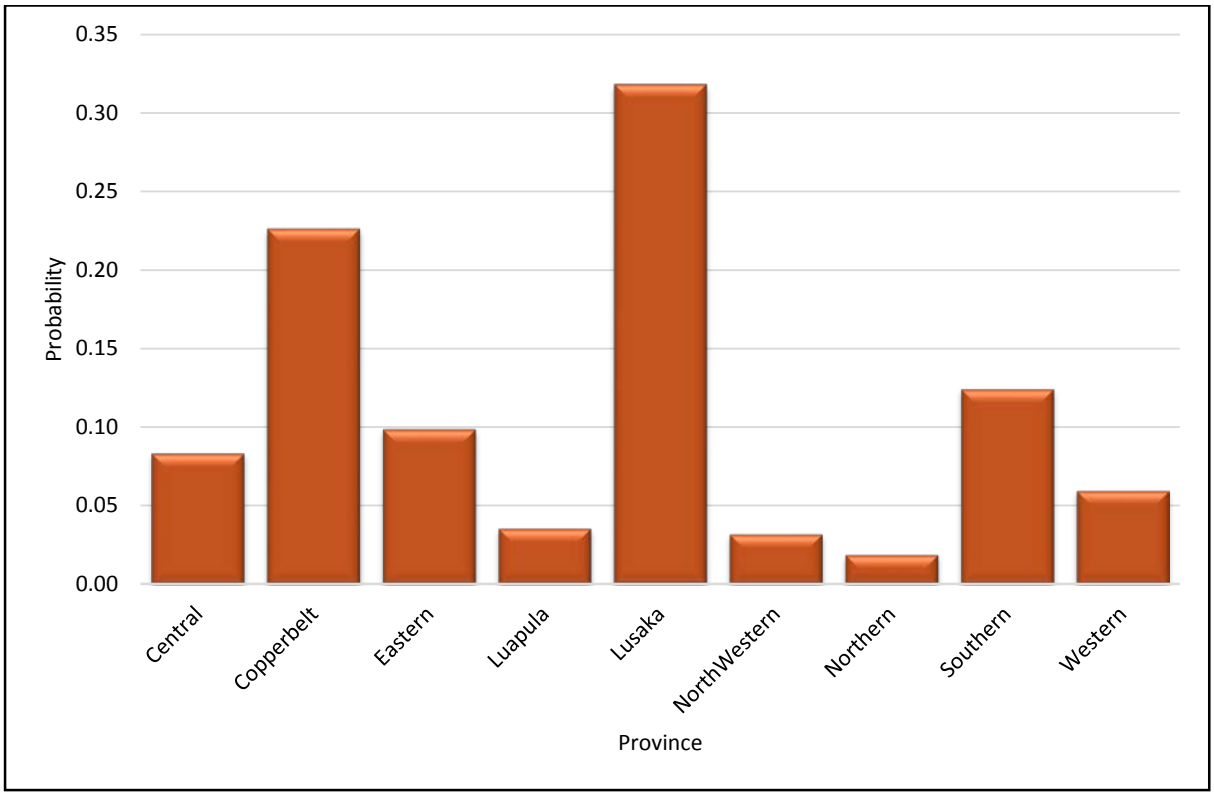


Figure 6.2: Distribution of patients by province

6.7.2 Sex distribution of the patients

In Zambia the national sex ratio is nearly balanced at 49.3 percent males to 50.7 percent female (Central Statistical Office (CSO), 2012a). However, the proportion of females in the ART program is significantly higher than that of men as shown by the probability distribution shown in Figure 6.3.

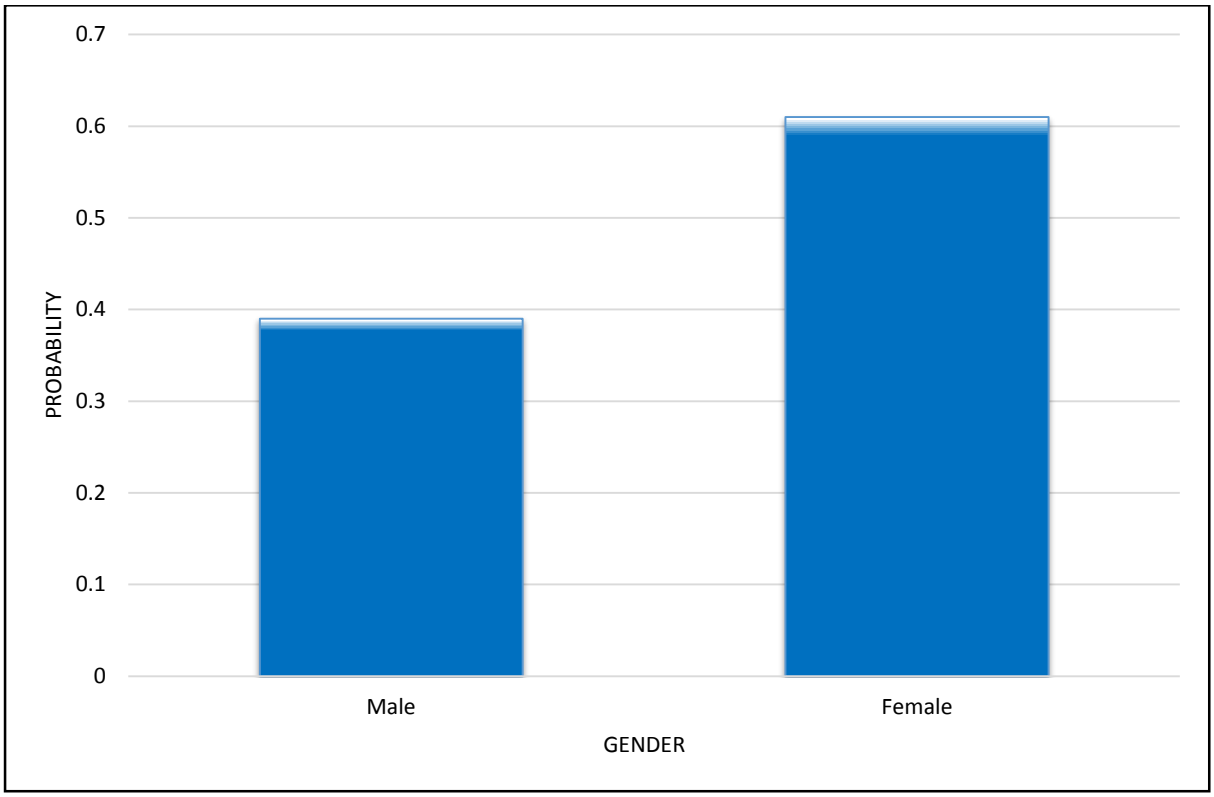


Figure 6.3: Distribution of patients by Gender

The distribution of males and females in the baseline data followed a 39 percent to 61 percent composition. Based on this distribution, the Simul8 software allocates the label “female” to each entity with a probability of 0.61 and the “male” label with a probability of 0.39 as numerical values 1 and 2 respectively. The patients were randomly assigned these labels this way to ensure that the total population of patients in the model represented that in the Zambia ART program.

6.7.3 Distribution of the patients by residence

From the data on persons on ART in the Zambian program, 10 percent of the patients were enrolled onto ART in rural health facilities while the remaining 90 percent were enrolled in urban health facilities. A user defined distribution, known in Simul8 as a label based

distribution samples a value of 1 to represent rural or 2 to represent urban from the probability distribution displayed in Figure 6.4. This number is then written on a label which the patient travels with throughout the model and can be used to influence a number of things that can happen to the patient at any time and at any phase.

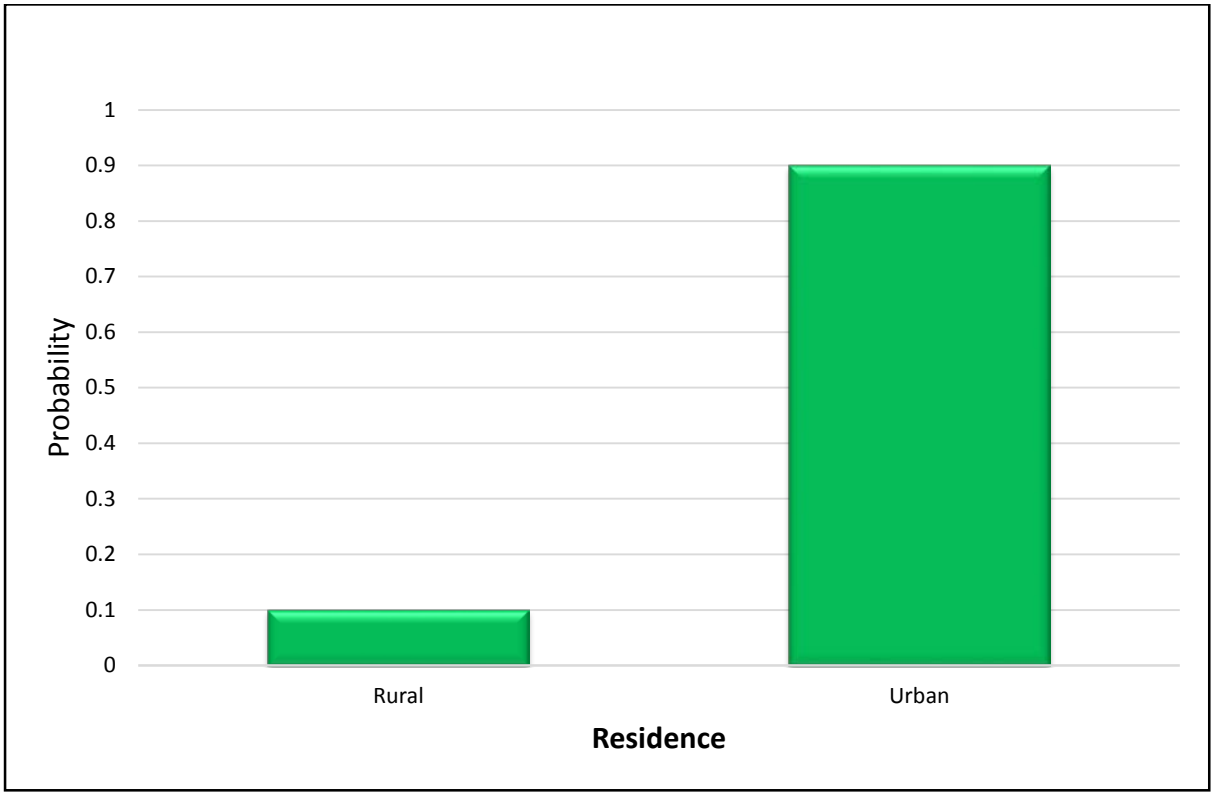


Figure 6.4: Distribution of ART patients by Residence

The residence label is one of the labels which were assigned to each patient as they entered the model.

6.7.4 CD4 count distribution of the patients

The CD4 count is assigned to each patient using a Gamma distribution (1.5488, 135.29). Figure 6.5 shows the fitted distribution and how well it fitted the baseline data. The blue bars represent the baseline data from the database while the thick red line is the fitted Gamma distribution. The Gamma distribution was the better fit among others because it had the smallest Akaike Information Criteria, AIC (Akaike, 1974) value compared to other distributions. The AIC value for the fitted Gamma distribution was 6.111×10^6 compared with Weibull (6.113×10^6), Lognormal (6.118×10^6) and Inverse Gaussian (6.119×10^6) with other distributions showing increasingly larger values of the criteria. As shown in the same figure,

its mean, median and standard deviations were also numerically closest to those of the population in the data base making it a good candidate.

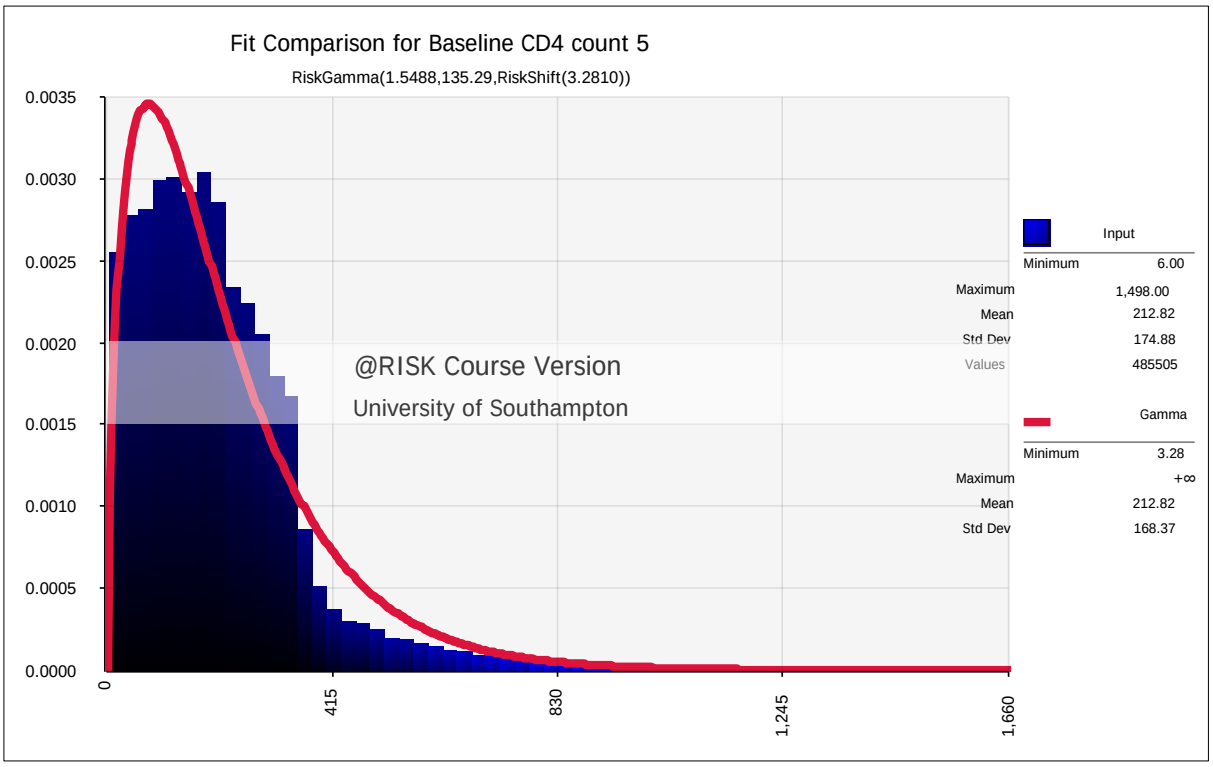


Figure 6.5: The Gamma distribution fitted to the CD4 count baseline data

The CD4 count was generated as a continuous variable and each patient was therefore assigned an individual value following the Gamma distribution. Immediately after that, the variable was dichotomised with a cut-off at 350 thereby creating the categories CD4 < 350 and CD4 ≥ 350 which were directly used in the model.

6.7.5 Age group distribution of the patients

The age of the patients in the model was sampled from the probability distribution in Figure 6.6. The distribution in the figure was obtained from the base population and will ensure that the structure of the age groups remains the same during the simulation thereby providing the possibility to make comparisons with the real life program. Each patient was assigned a sampled age group as a numerical value from 1 to 9 which was, like all other labels, used to develop the logic governing movement and timing of the patient. The categories of the age groups make it possible to combine them, into additional configurations for purposes of comparison with other publication such as national censuses, WHO reports, Demographic and Health Surveys (DHS), Sexual Behaviour Surveys (SBS), etc. For example, the DHS publishes

results based on 5-year age groups from 15 to 49 years for females and 15 to 59 years for men representing the sexually active population. In the simulation model, the patients are

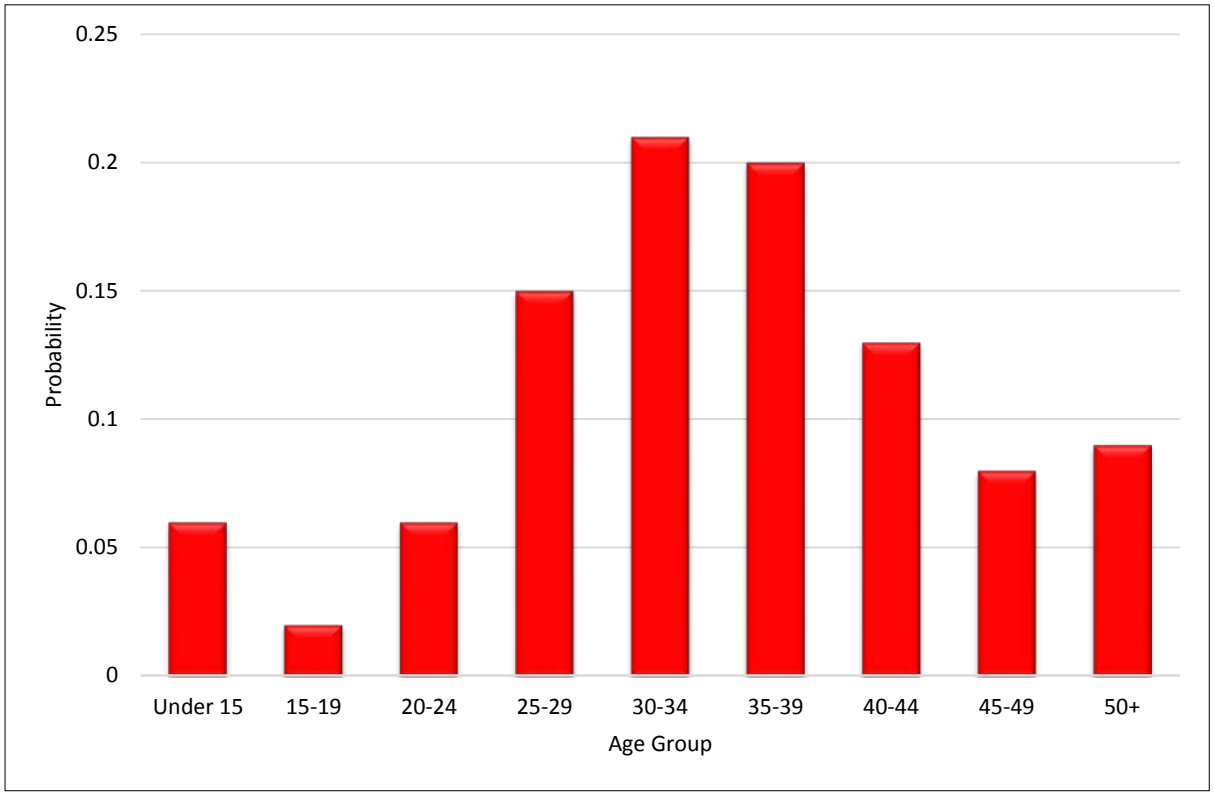


Figure 6.6: Age group distribution of ART patients in Zambia

programmed to follow label based distributions which determine the length of time they spend in the 1st /2nd Line ART phase and/or 3rd Line ART based on whether they belong to the under 15 age group or the 15+ years group. The resulting output will still have the label with the original 9-category age groups assigned as above in addition to the 2-category age groups for further analysis if required.

6.7.6 Baseline WHO stage

The stage at which the HIV infection in each patient has reached is measured by WHO staging as described in chapter 5. The patients in the model are assigned a WHO stage as they enter the simulation based on the probability distribution in Figure 6.7. This information, like all other attributes of each individual is written in a label which the patient carries as they move from phase to phase. Since the WHO stage is only assigned once at start of ART, the value of the stage for each patient remains the same for the duration of the move through the model.

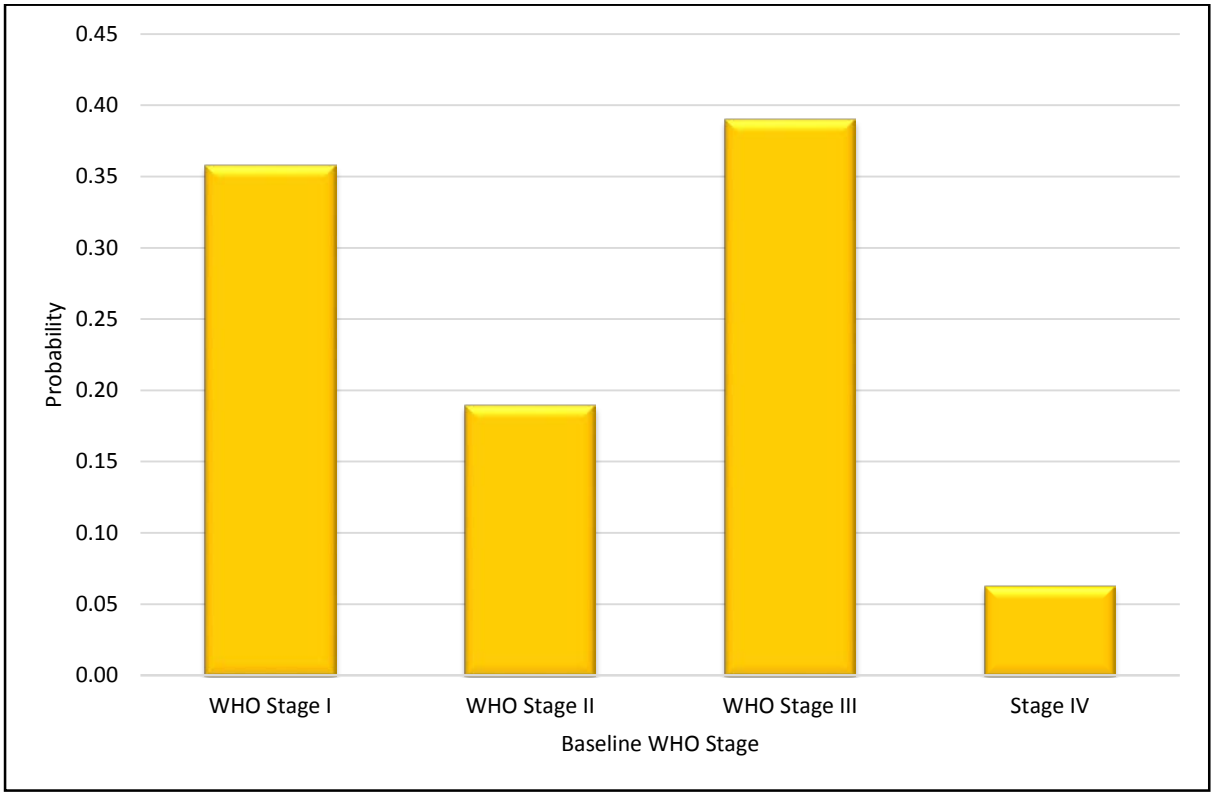


Figure 6.7: Probability distribution of baseline WHO stage

6.8 Risk groups and assigned distributions

The eight risk groups identified for use in the model are shown in the Table 6.1 below. The number of patients in each risk group is also shown with the distributions assigned to the particular risk group. The densities of the distributions are shown in Appendix I

Table 6.1: Risk groups and distributions assigned to patients in the model

Risk group			Assigned distribution*	Number of patients
Gender	Age group	CD4 category		
Male	Paediatrics	CD4<350	Distribution 01	8,530
Male	Paediatrics	CD4 350+	Distribution 02	5,567
Male	Adult	CD4<350	Distribution 03	160,485
Male	Adult	CD4 350+	Distribution 04	16,960
Female	Paediatrics	CD4<350	Distribution 05	8,764
Female	Paediatrics	CD4 350+	Distribution 06	5,777
Female	Adult	CD4<350	Distribution 07	247,320
Female	Adult	CD4 350+	Distribution 08	34,069

*See Appendix I for a listing of the distributions

The number of patients in each risk group is further shown in the pie chart below (Figure 6.8) to make the proportion of patients in each group clearer. The largest risk groups are for adults with CD4 count less than 350 cell/µL of blood.

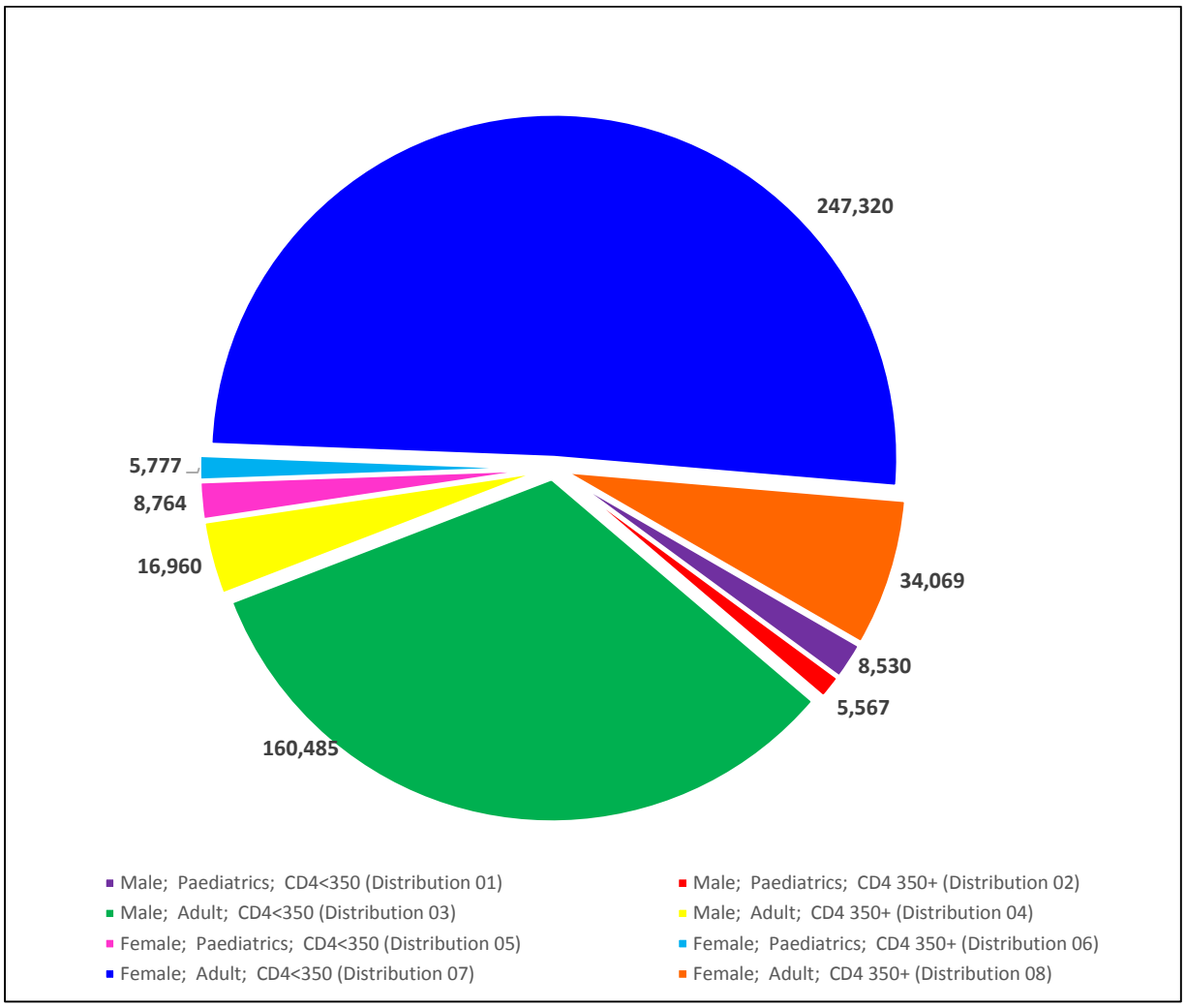


Figure 6.8: Distributions assigned and number of patients by risk groups

6.9 Outputs of interest

The time spent on ART before being declared LTFU, Died or Stopped treatment were directly calculated by Simul8 but the average time spent on ART by the group that remained on treatment at the end of the observation period had to be computed manually from output spreadsheets. The manual calculation is because the simulation is designed such that the patients on ART at censorship point remain in the system and do not exit whereas KPIs are calculated based on information Simul8 analyses at the various exit points in the model. The number of patients on ART at the end of the simulation is calculated as the sum of patients in each work center representing the appropriate regimen or activity. The results from the simulation model runs are presented below

6.10 Running the model

6.10.1 Warm-up period, initial conditions, number of runs and run length

In many simulations, it is necessary to decide what the warm-up period for the model should be. The warm-up period is the duration for which a simulation model should be run in order to remove any initial conditions so that the model attains a steady state. The data for the experimentation is collected for the period after the warm up period to ensure that the effect of the initial conditions is eliminated. In the Zambia ART model, there is no need for a warm-up period because the patients being enrolled onto ART do not need to find any environment different from the very first of the patients who were enrolled. This is because the supplies of the drugs, staff and infrastructure remains the same over the duration of the antiretroviral therapy. This means that there are no initial contents which must reach a certain level for the model to run at the required level.

The real system being modelled has run for a period of approximately 10 years and 8 months and the aim of this study is to simulate this real life system and collect results up to this point and further beyond. The run length is proposed to be up to an additional 10 years in order to observe the expected outcome of the ART program. The model is run for a total of 5 runs in order to achieve stable results and to generate 95 % confidence intervals for any statistics of interest. This number of runs was arrived at after running a test on the minimum number of runs required to achieve this. The results of this test are presented in Appendix II.

6.10.2 Scaling down the model

The real-life system being modelled in this study is a very heavily populated one with patients at censorship point approaching half a million. The number of patients enrolled on ART at the various health facilities in Zambia increases with each week day implying that the system keeps growing despite accounting for the number of patients who exit it daily. For practical reasons, it was decided to run a scaled down number of patients in the Simul8 model to represent the real life system as long as the results from the scaled down model could be scaled back to the real-life system.

In order to verify that the model was scalable, the proportions of patients in each category was observed when different numbers of patients were allowed to enter the model. The first scenario was to observe the case where the inter-arrival time was set to the rate in the real system and the model run for the duration of 520 weeks which is the equivalent of running the model for the duration of the observation period for the Zambia ART data. The second scenario was to allow only 10 percent of the patients into the system. The results are shown in Table 6.2.

Table 6.2: Comparisons of different scenarios for number of patients allowed into the model

	Model (100% arrival rate)			Model (10% arrival rate)		
	Low (95% CI)	Average	High (95% CI)	Low (95% CI)	Average	High (95% CI)
On ART	48.94%	49.51%	50.09%	49.09%	49.54%	49.99%
LTFU	32.38%	32.78%	33.18%	32.49%	32.80%	33.11%
Died	12.95%	13.12%	13.29%	13.02%	13.13%	13.23%
Stopped	4.51%	4.59%	4.67%	4.49%	4.53%	4.57%

The percentages of patients in each category is comparable between the 100 percent and the 10 percent scenarios with very minor discrepancies. The 95 percent confidence intervals for all the proportions are also similar indicating that the precision of the estimates is not affected by scaling down the model.

This is an important result for the model because it provides a basis to run a lighter and therefore faster model representing only 10 percent of the Zambia ART population with results which are comparable. The results are the same for indicators such as the average time each of the patients spend in the system and others.

6.10.3 Number of duplicated workstations

The simulation model under study in this thesis is resource intensive in terms of computing needs. The model is run on a weekly basis in Simul8 and more than 940 patients are enrolled on ART during each week. The software is therefore required to create this number of patients and assign all the attributes discussed in the earlier sections to each patient before they begin to move through the model. At each work station or object, appropriate logic has to be applied to determine what happens to the patient or work item. After each simulation run,

the software writes the results of the simulation, also based on the logic built into the model to spreadsheets.

In order to speed up the experimentation, each work station, representing the 1st /2nd Line regimens has been duplicated into 20 stations, each of which is replicated 10,000 times. This implies that the model has a total of 200,000 workstations processing patients at the 1st/2nd Line ART phase. The number of workstations providing the same service at 3rd line is much less because there is a significantly smaller number of patients who make progress to 3rd Line ART (0.02% of the total patients on ART). The replication of work stations ensures that there are enough workstations to process the logic and other tasks in the simulation without causing queues in the system which do not exist in the real life ART program.

6.11 Model verification and validation

Every simulation model should undergo verification and validation during and after construction in order to determine how well the simulation represents the system being modelled. Specifically, model verification is concerned with providing an assurance of how accurately the conceptualised model has been coded into a computer model while model validation is the more detailed and involved process by which the modeller ensures that the model is sufficiently accurate in predicting aspects of the real system (Robinson, 2004). Furthermore, Robinson (1997) suggests that validation of a model should be done at different stages of model building and that there are a number of forms of validation: conceptual model validation, data validation, white-box validation and black-box validation.

6.11.1 Model verification

The Zambia ART simulation model was verified over a long period of time to gain full insight into the various stages and aspects of antiretroviral therapy in Zambia. Consultations were held with different categories of clinicians providing ART in Zambian health facilities. These included medical doctors, nurses, clinical officers (mid-level practitioners of medicine), pharmacists and others. Patient pathways from enrolment on ART to exit were mapped and verified based on clinical practice at public health facilities in the country. Clinical program managers at the country's Ministry of Health were also engaged to verify the model

specifications because they are responsible for critical aspects of the ART program such as the development and distribution of ART guidelines in the country including training of the clinicians who see the patients on a day-to-day basis. The eligibility criteria explained in Chapter 6 which was used to initiate ART during different periods (before and after 2007) was discussed as part of model verification to ensure that the system created in Simul8 is the correct model conceptualised for the purpose at hand.

6.11.2 Model validation

Part of the model validation process is to confirm that both the scope and level of detail in the model is suitable for the purpose at hand. The process to decide the level of detail of the simulation model is described in section 5.2 with the eventual decision explained in the summary of chapter 5. In sections 6.2 and 6.4, the scope and detail of the model in this research project is described. In terms of data validation, this is addressed in Chapter 5 where the different variables used as covariates in the survival analysis which in turn provide the simulation input were checked for accuracy for model construction. Chapter 5 also confirms and concludes with confirmation of the accuracy of the data for the purpose of simulation.

In terms of white-box validation, each simulation object shown in the separate sections of Figure 6.2 replicates an integral process from the real system. In the 1st /2nd Line ART section, the model accomplishes the tasks accomplished by the team of clinicians on the day a patient is enrolled on ART in either 1st line ART or 2nd line ART. In the real system, patients spend either a few weeks of several years receiving antiretroviral therapy depending of their combination of characteristics. This is reproduced in the model so that the total number of weeks each patient spends in this section of the model is represented by a probability distribution specific to the characteristics assigned to them on entry into the model. An example of the distributions from the real system (input) and the output from the model are shown in Figure 6. 9 for comparison. These distributions represent the number of weeks spent in 1st /2nd Line ART by patients who were female, 15 years and over with CD4 count greater than 350.

The Kolmogorov-Smirnov test showed that the input and output distributions were drawn from the same distribution (p = 0.54). This result indicates that the survival times of the entities entering the model (distribution from the real system) and the survival times of the output (output distribution) are statistically the same. The specific distributions followed by different patients are explained in section 6.10 and Appendix I. During this phase, patients experience different events which are modelled as different pathways according to observed distributions and proportions from the real system. This is repeated in the 3rd Line ART section of the model. The patients exit the system, as either LTFU, Stopped or Died in the same way they exit the real system, or remain on ART.

To conduct black-box validation, a comparison of the simulation model and the real system was made, as recommended by Robinson (2004). If the ART system is viewed at the macro level, patients flow into the real system as they are initiated onto ART and remain on ART for different durations of time. That process, at model scale is the arrivals of entities into the model where they spend varying lengths of time. The patients in the real system experience different events during the time they are on ART which determine what their status is at the end of the observation period, at censorship point. At this point, the different time durations each patient will have spent on ART in the Zambian program is summarized as a survival profile which can be used to study the patterns of how long people remain in the system. At model level, probability distributions are used to reproduce comparable durations of time spent by patients in the real system and the resulting survival profile generated by the model is studied and compared with that from the real system.

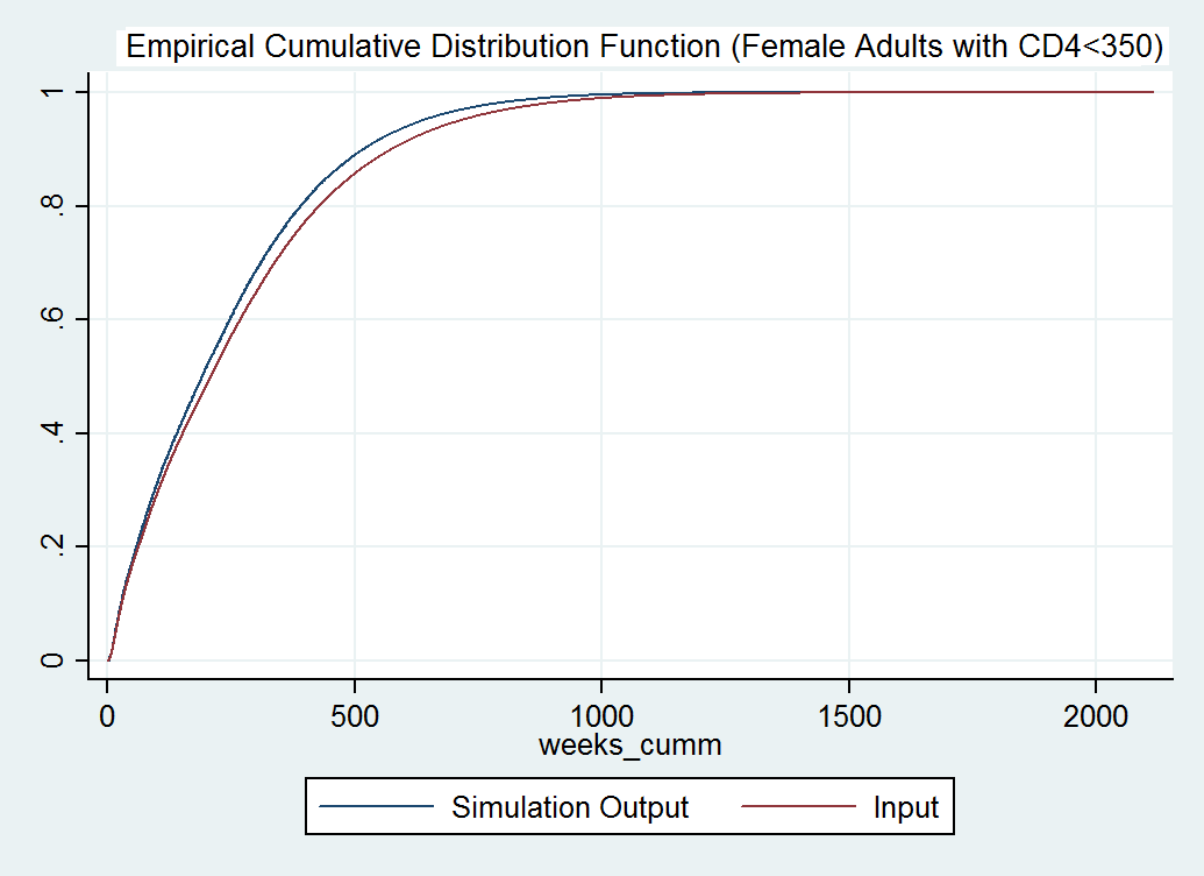


Figure 6.9: Comparison of survival times from the model and the Zambia ART data

In figure 6.9, the survival profile of adult female patients with CD4 < 350 enrolled in ART from the real system is compared with that from the output of the Simul8 model. The EDFs show that the distributions are not very different.

To further validate the overall model, a comparison of the proportions of patients in each of the four categories reported in section 4.8.4 at censorship point was made. The categories studied are: On ART, LTFU, Died and Stopped treatment. The logic and combination of attributes coded into the model to govern how long and which pathway each patient follows in the model may be checked by observing the proportions of patients who end up in each of these categories. The model is thus validated if these proportions are relatively close to the proportions in the real system.

Table 6.3: Comparison of proportions of patients in each category at censorship point

Description	Real System	Simulation model		
	Average	Low (95% CI)	Average	High (95% CI)
Number of patients				
On ART	238,571	226,410	242,610	258,810
LTFU	160,885	158,010	165,020	172,030
Died	64,920	63,540	66,140	68,740
Stopped	23,136	21,950	22,980	24,020
Total patients	487,492	469,900	496,750	523,590
Percentages in each category				
On ART	49%	48.18%	48.84%	49.43%
LTFU	33%	32.63%	33.22%	33.86%
Died	13%	13.13%	13.31%	13.52%
Stopped	5%	4.07%	4.63%	4.99%

The results of the proportions of patients in each category both in the real system and the model are shown in Table 6.3 with appropriate confidence intervals for the model computed from 5 runs. The second and fourth columns in the table show that the model achieved very comparable proportions of patients in each of the four categories with minor, expected differences which will be studied and explained in the results chapter to follow.

This is an indication that in general the Simul8 model is performing tasks comparable to the situation in the real system.

6.12 Chapter summary

This chapter has:

- Provided a description of the simulation model used to represent the Zambia ART program
- Described the model assumptions and considerations made to develop it
- Explained how patient characteristics are assigned to the simulation work items
- How the model is run by explaining the run length, warm-up and initial conditions
- Outlined how the model was verified and validated

7 Results

In the previous chapter, a description of the simulation model for the Zambia ART program was given. Furthermore, the simplifications and assumptions made during model construction were outlined including how the model is run and validated. Different categories of ART patient statuses have been modelled to enable estimation of the percentages of patients who end up in each of these for purposes of determining the associated costs of providing treatment to them. This model will therefore be used to explore the different treatment outcomes and the related economic cost of the provision of ART services in Zambia from a public sector point of view.

The results chapter provides a presentation of the results from the experiments run and how these experiments are transformed into economic costs of ART provision which in turn play the role of input into informing policy in the general HIV epidemic management in Zambia.

7.1 Medium-term projection (5 years)

Treatment outcomes were observed and reported in the tables below after running the model for different periods of time. Projecting the outcome of the ART program in Zambia is an important outcome of this research work and Table 7.1 shows the results of a 5-year projection beyond censorship point. The results from the model run for 5 years after censorship point (referred to hereafter as the medium-term projection) show that an estimated 818, 478 patients (95% CI: 788,260 to 848,690) are expected to have been enrolled onto ART by that date (March 2019). If the conditions in the model are kept as they were in the base model, the overall effect of this on the ART program is projected to be a reduction in the percentage of patients who remain on treatment up to 15 years since commencement of ART based on the total patients who will ever have been enrolled onto the program.

This is not a real reduction because in absolute number terms, the population of persons on ART will have grown to 282,844 (95% CI: 257,554 to 308,135). The sum total of persons LTFU, stopped treatment or died increases cumulatively every month while the number of persons on ART is a current figure as it is the same people continuing from month to month.

Table 7.1: ART treatment outcomes from the model (Medium term projection)

	Simulation model		
	High (95% CI)	**Average**	**Low (95% CI)**
Number of patients			
On ART	257,554	282,844	308,134
LTFU	345,654	348,112	350,570
Died	137,254	139,180	141,106
Stopped	47,802	48,342	48,882
All patients	788,264	818,478	848,692
Percentages in each category			
On ART	32.67%	34.56%	36.31%
LTFU	41.31%	42.53%	43.85%
Died	16.63%	17.00%	17.41%
Stopped	5.76%	5.91%	6.06%
Average time (years) on ART			
On ART	3.57	3.78	3.99
LTFU	2.75	2.80	2.86
Died	2.72	2.78	2.84
Stopped	2.72	2.80	2.88
All patients	2.25	3.04	3.83

This causes the percentage share of persons on ART to appear to be decreasing but the picture is clearer in Figure 7.1 which shows the share of each category of patients at different time points. The model estimates the number of patients who exited the system due to being declared LTFU to be 348,112 (95% CI: 345,656 to 350,570), a larger proportion than that observed at censorship as expected and explained above.

In percentage terms, patients on ART were estimated at 34.56 percent (95% CI: 32.67 to 36.31%) indicating that 65 percent of the patients enrolled continuously on ART would drop out by the end of 15 years. The proportion of patients lost to follow up is projected to increase by 10 percent to 43 percent when compared with the base model (section 6.11) while deaths among the ART patients will account for 17 percent (95% CI: 16.63% to 17.41%) of the patients. The magnitude of the growth in each category can be seen in Figure 8.1 where the LTFU patients were projected to make up the largest proportion of patients at all times during

both the observation and projection periods. This is expected because patients in the real system have a higher chance of being declared LTFU the longer they stay on treatment.

Table 7.1 also displays the average time the patients spent in the system for patients in the medium-term projection. On average, patients were estimated to spend 3.04 years (95% CI: 2.25 to 3.83) on treatment. The patients who remained on treatment at the end of the simulation in the medium-term projection were estimated to spend the longest time in the system compared with patients who exited the treatment program for one reason or another. As seen in the table, patients on ART spent 3.78 years (95% CI: 3.57 to 3.99) compared to patients declared LTFU who spent 2.80 years (95% CI: 2.75 to 2.86), patients who died spent 2.78 (95% CI: 2.72 to 2.84) and patients who stopped treatment spent 2.80 years (95% CI: 2.72 to 2.88).

7.2 Long-term projection (10 years)

The simulation model was run for a longer time horizon of 10 years beyond censorship point in order to observe what the situation would be of providing ART for patients in Zambia. This 10-year horizon meant that the program was run for a total of about 20 years from the beginning of the ART program. As can be seen in Table 7.2, the projected patient load would accumulate to 1,114,122 patients (95% CI: 1,089,024 to 1,139,220). The model estimated that the number of patients on ART at the end of the 10 year projection period was 277,598 (95% CI: 267,713 to 290,483). In terms of treatment outcomes, the largest category was that of patients who enrolled on ART but were declared lost to follow up sometime during the observation period. This category accounted for a total of 543,684 patients (95% CI: 536,391 to 550,977) ever enrolled on ART. In percentage terms, as argued above, nearly half of the patients or 49 percent (95% CI: 48.36 to 49.25) ever enrolled on ART in the program were estimated to exit the treatment program as LTFU patients. Death accounted for 19.53 percent of the all patients ever enrolled into the system (95% CI: 19.48 to 19.59).

The average time patients were on ART was estimated to be 3.57 years (95% CI: 3.49 to 3.64) overall. The table reveals that the length of time spent by all patients who exited the ART treatment program before censorship point was comparable and was approximately 3.3 years with the 95% confidence intervals ranging from 3.27 to 3.42 years. This is in contrast with the

longer average time spent on ART by patients who were still alive and on treatment at the of the 10 year projection. Patients who remained in the system and were on treatment were estimated to spend an average of 4.24 years (95% CI: 4.06 to 4.42) in the system.

Table 7.2: ART treatment outcomes from the model (Long-term projection)

	Simulation model		
	Low (95% CI)	**Average**	**High (95% CI)**
Number of patients			
On ART	264,713	277,598	290,483
LTFU	536,391	543,684	550,977
Died	213,391	217,628	221,865
Stopped	74,529	75,212	75,895
Total patients	1,089,024	1,114,122	1,139,220
Percentages in each category			
On ART	24.31%	24.92%	25.50%
LTFU	48.36%	48.80%	49.25%
Died	19.48%	19.53%	19. 59%
Stopped	6.66%	6.75%	6. 84%
Average time (years) in the system			
On ART	4.06	4.24	4.42
LTFU	3.32	3.34	3.37
Died	3.30	3.33	3.36
Stopped	3.27	3.35	3.42
Total patients	3.49	3.57	3.64

7.3 Comparison of medium-term and long-term projections

The simulation results for the medium-term projection and the long-term projection were compared to make observations in the two cases. One aspect of interest in the comparison was the structure of the patient outcomes for the two cases. Figure 7.1 shows the trend in

patient outcomes for the base model (at x = 0), the medium-term projection (halfway through the x-axis) and the long-term projection (at the maximum point on the x-axis)

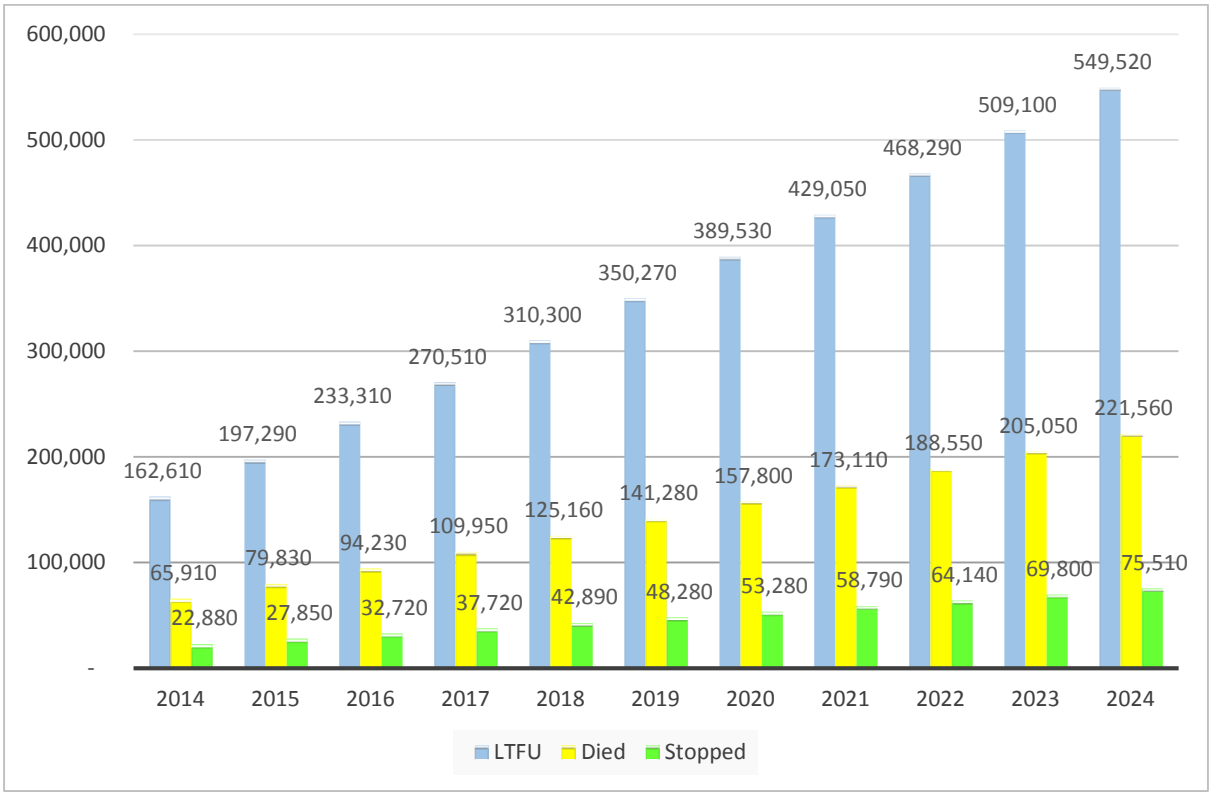


Figure 7.1: Distribution of patient status at Baseline, Mid-term and Long-term end of run

In absolute terms, the number of patients on ART remained at almost the same level for both the medium and long term model runs as shown in Figure 8.1 and in the tables in the previous section. This situation was achieved with a constant arrival time of patients on ART across the 20-year run time. The other category which remained nearly unchanged in terms of the absolute number of patients over time was the category of those patients who stopped treatment at some point during the observation period. Significant growth, however, was recorded for the categories of patients who died during the observation period as well as those declared lost to follow up. Overall, the structure of the composition of the patients is maintained in the two cases under consideration as depicted in Figure 7.2.

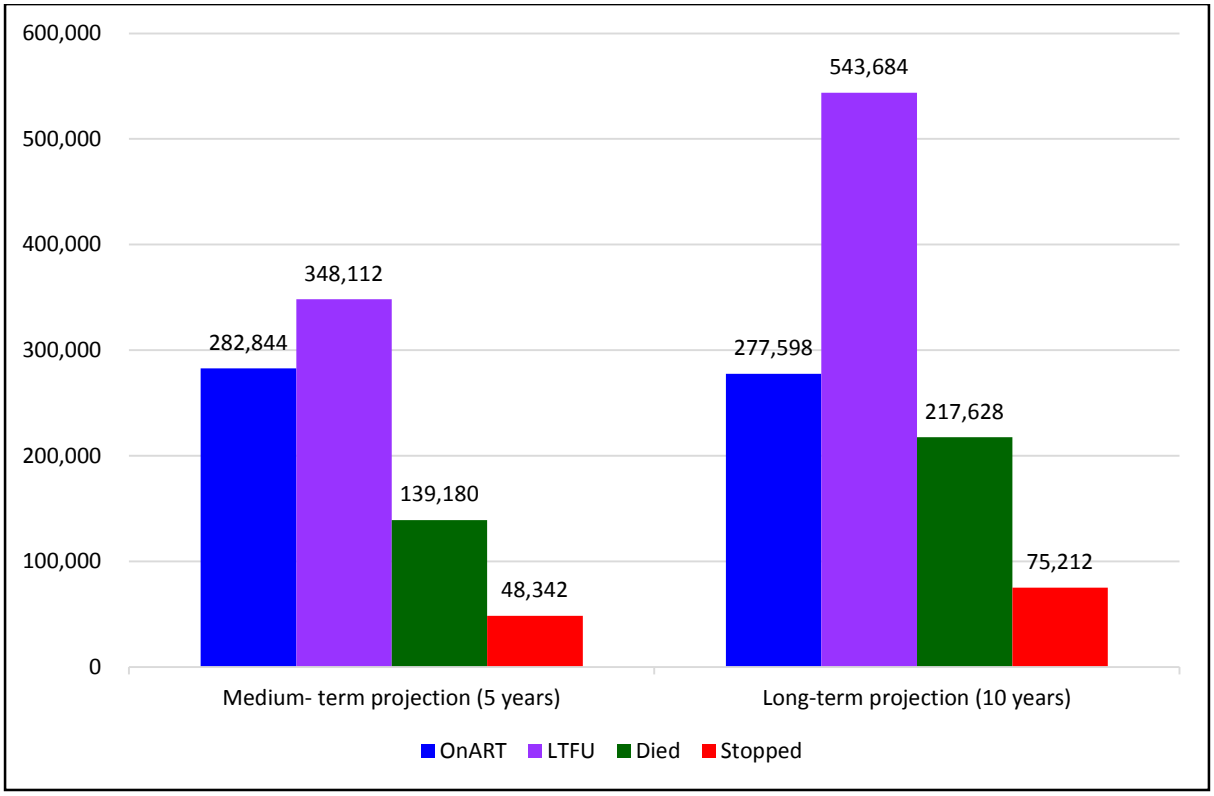


Figure 7.2: Distribution of patient outcome categories by projection window

The figure shows that LTFU is the biggest category and the number of people who die while on treatment is the next biggest group among those who exit the system with the category of patients who stop treatment being the smallest in both medium term and long-term projection windows.

7.4 Projected economic costs of ART

Based on the number of patients enrolled and their treatment outcomes at the medium-term and long-term projection points, the economic cost of providing ART in Zambia was estimated. In order to quantify 'economic costs', the cost of provision of ART was considered to include an extensive range of facility level HIV related medical services. The costs of these services are in three broad groups namely capital costs (buildings and other fixed assets), Human resources costs and consumables. In no particular order, some examples of these costs include staff time (both clinical and non-clinical), medical and office supplies, antiretroviral medications (ARVs), opportunistic infection medication (OI), physical infrastructure (clinic rent, cost of water, electricity, sanitation), laboratory costs, nutritional support, equipment, staff training and others. The cost of ART provision in Zambia is inclusive

of non-clinical support staff called Adherence Support Workers (ASWs) (Torpey, Kabaso, Mutale, Kamanga, & Mwango, 2008) whose role in the ART clinic is to provide adherence counselling to patients on ART. This cadre of staff plays an important role in the provision of ART services because adherence to treatment has been proved to be a very important factor in retention on ART (Koole et al., 2014).

Taking into consideration the above factors and other related inputs, Tager et. al. (2014) reported that the average annual cost of ART across Malawi, Rwanda, Ethiopia and Zambia was $208 per patient year (ppy) in 2010 – 2011. This multi-country costing of ART services is one of the most comprehensive and up to date work available at present and compares well with other, earlier research (Bratt et al., 2011). The specific annual cost ppy for Zambia calculated by Tager and his team of researchers was $278. This value was reported as based on nominal costs in 2010 – 2011.

For purposes of the current research, this dollar value is taken to be 2010 US dollars. The estimated cost of ART service delivery was converted to 2014 US dollars to determine the cost of providing the service during that year which was the censorship point of the data used to run the simulations. The conversion was achieved by first converting the cost of the services to the local currency, the Kwacha. This is because goods and services in the provision of ART services in the county are borne in this currency. This was followed by applying the annual inflation as computed using the Consumer Price index (CPI) obtained from the country's Central Statistical Office (CSO) which is the only institution mandated by the Government of The Republic of Zambia to compile the CPI. The Zambian Kwacha (ZMW) value in 2014 was later converted back to US dollars at the average exchange rate between the two currencies for that year. At the end of 2014, the cost of providing ART services in Zambia was thus estimated to be US$284 ppy. This is the unit cost that was applied to the total person years at censorship point to compute the cost of ART service provision in Zambia during 2014.

The second part of determining unit costs of ART service provision was to project the value of the cost of the service into the future. To do this, an average projected inflation rate was computed from the CPI and applied year-on-year to get an estimated CPI for the years through to 2024. This CPI was then applied to the cost of ART service provision, in Kwacha

beginning with 2014 and then each year until 2024. The US dollar value of ART service provision in the years on interest namely 2019 and 2024 were obtained by converting the projected ZMW value to UD dollars using the official Zambian Ministry of Finance's projected annual exchange rates. The computed values of service provision are $304 in 2019 and $322 in 2024. Since the cost of the ART service is in the future, it is often desirable to estimate it in present value (in this case 2014 US dollars). To do this, the future value of service provision is multiplied by a discounting factor which effectively expresses the future value in terms of the present value according to the following expression:

$$\$\mathrm{P} = \$\mathrm{F}(1+i)^{-n} \qquad (7.1)$$

where $P is the present value, $F is the future value, i is the discounting rate and n is the year in the future in which $F is to be estimated. The discounting factor used to compute the present value of the cost of ART in the future is 3.5 percent as recommended by the National Institute for Health and Care Excellence (2013). These calculations are shown in Appendix III.

Some of the most important simulation model outputs after each run were the number of years each patient has been on ART before they experienced any event such as LTFU, death or stop treatment. Some patients entered the model and did not experience any of the events above but stayed on ART at censorship point and were thus classified as patients 'On ART' but even for such patients, the model was able to compute the number of years they spent in the model. A sum of all these durations in each category constituted the patient years spent on ART in that category. The total person years on ART for all patients in the model is a total of all their person years on ART. These person years are displayed alongside costs for the base model, the medium-term projection and the long-term projection.

The results are presented in two ways for ease of comparison. Table 7.3 shows the cost of ART service provision in Zambia in 2014 US dollars while Table 7.4 shows the same costs in discounted US dollars thereby giving a present value of the nominal cost of ART service provision in the future.

7.4.1 Economic costs of ART provision at current (2014) prices

The person years for each of the three cases considered are indicated in Table 7.3 which reveals that the long-term projection consists of higher numbers of person years experienced by the patients in the baseline case. The table further shows the estimated cost of ART service provision up to the censorship point and what it is estimated to have cost the Zambian government on an annual basis in 2014 US dollars. On average in 2014, it cost $44.5 million (95% CI: $42.9m to $46.2m) per year to treat all the patients on ART during that year.

Table 7.3: Economic costs of ART provision in Zambia, in 2014 US Dollars

	Simulation model		
	Low (95% CI)	**Average**	**High (95% CI)**
Person years			
Baseline	1,229,490	1,229,490	1,229,490
Medium (5-year) projection	1,281,952	1,334,896	1,387,839
Long-term (2019 - 2024) projection	1,353,878	1,404,591	1,455,305
Cost of treatment ($'000)			
Baseline			
2014 US$ cost per person per year	n/a	$284	n/a
All patients per year in 2014	$42,859	$44,504	$46,148
January 2003 to March 2014	$33,675	$349,175	$362,076
Medium (5-year) projection			
2019 US$ cost per person per year	$281	$304	$305
All patients per year in 2019	$72,020	$81,162	$84,547
April 2015 to March 2019	$360,100	$405,808	$422,736
Long-term (10 year) projection			
2024 US$ cost per person per year	$310	$322	$323
All patients per year in 2024	$83,859	$90,456	$93,925
April 2019 to March 2024	$419,296	$452,278	$469,627
April 2015 to March 2024	$779,396	$858,087	$892,363

This average annual cost of ART service provision was calculated as the average of the annualised product of the total number of person years and the cost of providing the service to patients. Appropriate confidence intervals of the average cost were calculated and are

presented with the result in the table. For the same baseline case, the cost of providing ART treatment to patients in the country from 2003 to 2014 was calculated to be approximately $349,175 million (95% CI: $336.3m to $362.1m).

Similar estimates were produced for the cost of service provision for the case where the ART program was run till 2019 representing 5 years of projections. At the censorship point ending 2019, the model estimates that the ART system would have provided services equivalent to an additional 1,334,896 person years (95% CI: 1,281,952 to 1,387,839). In dollars terms, the cost of the service was estimated to be about $81.2 million (95% CI: $72.0m to $84.6m) per year. This estimate takes into consideration the patient load at the projected time period and uses the estimated person years during the period.

For the long-term projection window, the table provides three cost estimates, namely, the annual cost of ART in the last year (2024), the cost of ART for the 5 years from the previous estimate (i.e. from 2019 to 2024) and the cost of ART service provision from 2014 to 2024 (i.e. over a 10 year time window from the censorship point of the baseline data. The additional person years added to the system between 2019 and 2024 were estimated to be about 1.40 million (95% CI: 1.35m to 1.46m). This number represents the number of additional person years which needed to be provided ART by the program during the 5 year period. An annual average cost of $90.5 million (95% CI: $83.9m to $93.9m) was projected to be required to pay for ART services for these additional life years. The cost of running the ART program for the full 5-year period (at 2024 US dollars) was estimated at $452.3 million (95% CI: $419.3m to $469.6m). The corresponding costs of running the ART program for the 10 years from 2014 to 2024 were estimated to be approximately $858.1 million (95% CI: $779.4m to $892.4m) in 2014 US dollars.

7.4.2 Economic costs of ART provision (discounted 2014 US dollars)

The cost of providing ART services to the Zambian public in need of treatment in the future is presented in Table 7.5 at discounted 2014 dollars, representing the 2014 value of the currency. The displayed US dollar amount under the section ‘Future unit cost’ is how much the $284 (estimated in 2014) will be worth at each future date. At the applicable discount rate discussed above, if measured in the year 2014, $239 in 2019 is worth the same as $284 in 2014.

The table reveals that the future cost of providing ART in Zambia (in 2019) on an annual basis to the entire population of patients needing treatment will be approximately $68.3 million (95 CI: $60.6m to $71.2m).

Table 7.4: Economic costs of ART provision in Zambia, at discounted 2014 US Dollars

	Simulation model		
	Low (95% CI)	**Average**	**High (95% CI)**
Person years			
Baseline	1,229,490	1,229,490	1,229,490
Medium (5-year) projection	1,281,952	1,334,896	1,387,839
Long-term (2019 - 2024) projection	1,353,878	1,404,591	1,455,305
Cost of treatment ($'000)			
Baseline			
2014 US$ cost per person per year	n/a	$284	n/a
All patients per year in 2014	$42,859	$44,504	$46,148
January 2003 to March 2014	$33,675	$349,175	$362,076
Medium (5-year) projection			
2019 US$ cost per person per year	$237	$256	$256
All patients per year in 2019	$60,639	$68,336	$71,186
April 2015 to March 2019	$303,195	$341,680	$355,932
Long-term (10 year) projection			
2024 US$ cost per person per year	$220	$228	$229
All patients per year in 2024	$59,449	$64,126	$66,585
April 2019 to March 2024	$297,247	$320,629	$332,927
April 2015 to March 2024	$600,442	$662,308	$688,860

The corresponding cost of providing ART to the entire population enrolled for the period from 2014 to 2019 was estimated at $341.7 million (95% CI: $303.2m to $355.9m). This cost was based on a constant enrolment rate of 1,194 new ART patients per week during the entire period resulting in more than 2.5 million person years on treatment as discussed in the previous section. For the long-term projection, the simulation model estimates that in 2024, the annual cost of ART service provision in 2014 US dollars will be $64.1 million (95% CI:

$59.9m to $66.6m). The corresponding cost of treating all patients in the program up to that year was estimated to be approximately $662.3 million (95% CI: $600.4m to $688.9m).

7.5 Chapter summary

This chapter has:

- Presented simulation results for medium-term projections of ART service provision
- Presented simulation results for long-term projection of ART service provision
- Made comparisons between medium-term and long term simulation projections
- Shown economic cost of ART service provision for medium and long-term projections
- Compared current and discounted costs of ART service provision

8 Conclusions, Limitations and Future Work

The aim of this thesis is to develop a planning tool and reference guide for health intervention planners and financiers on the long-term outcomes and economic costs of ART in Zambia. Section 8.1 summarizes the key findings and provides conclusions based on those findings while section 8.2 is a discussion of future work based on the results of this research project.

8.1 Research summary

A simulation model was developed with the purpose of observing the survival patterns of people enrolled on ART in Zambia. Specifically, the survival patterns of patients disaggregated by treatment outcomes were modelled. This made it possible to make inferences on the long-term retention patterns of the patients. In order for this simulation model to be constructed, statistical analyses were performed on the data to determine the overall survival profile and to obtain parameters required during model construction.

In order to provide a complete overview of the Zambian ART program, initially the country's demographic profile was described. Based on this demographic picture of the country, the HIV/AIDS epidemic was put into context. This provided a description of the spread of the epidemic across different age groups and geographic regions in the country. An account of the national response to HIV/AIDS was given pointing out the initial response leading to the setting up of a national body tasked with the responsibility to coordinate the various efforts aimed at combating the pandemic. The national response to the epidemic is aligned to a set of national and international development agendas such as The Revised Sixth National Development Plan (RSNDP) 2014 – 2016, the Millennium Development Goals, United Nations General Assembly Special Session (UNGASS), Political Declaration of HIV and AIDS Targets and SADC HIV and AIDS Strategic Framework 2010 – 2015.

A review of the literature focused on operational research methods applied to HIV-related studies was conducted. Various HIV-related issues have been investigated using OR methods including HIV transmission, outcomes of different treatment strategies and HIV transmission from concentrated populations (MSM, IDU and CSW) to heterosexual populations. Others

include the effect of ART on viral loads, determining which prognostic factors have an impact on HIV evolution etcetera. A variety of approaches have been employed in estimating the survival of HIV-infected people. This research work fills in the knowledge gap of estimating survival of people on ART with the events of interest to include death, LTFU and stopped treatment. This essentially defines retention on treatment.

To achieve this goal, data from the Zambia ART program was statistically analysed with the use of survival analysis techniques to establish the survival pattern of the people on ART based on the definition above. Furthermore, scientific arguments were made on the heterogeneity of the data in terms of the survival of different risk groups in the population. Based on these different classifications of risk groups, survival distributions were fitted for each statistically different risk group. The distributions acted as part of the input into the simulation model developed in Simul8 to represent the real life system of persons receiving ART. Additional input parameters for the simulation model were determined directly from the data to form the base model.

In order to generate required results, the model was run for two separate time-windows: a medium-term projection time window equivalent to 5 years from the endpoint of the base model; and a long-term projection time window equivalent to 10 years from the same point. Results of the created patient profile in both the medium-term and long-term projections have been presented and described in the previous chapter. Furthermore, the economic costs of the provision of ART to these patients has been computed based on the number of patients in the model. The costs have been presented as both current 2014 costs and discounted costs at the applicable future dates.

8.2 Conclusions

The aim and objectives of this PhD research were stated in the first chapter of the thesis. For each research objective, a research question was asked and in order to answer the research question, specific tasks were set out as a step-by-step guide. The conclusions and

recommendations related to each of these research questions are discussed in relation to the tasks drawn out to address them.

8.2.1 Task 1 – What are the main covariates which have an effect on survival of ART patients in Zambia?

To address this task, a decision was taken to first run the survival analysis on the data with death only as the event of interest (section 5.8) followed by a more extensive analysis with the events of interest listed as 'exited ART' which is defined as the combination of death, stopped treatment and lost to follow up (LTFU) in section 5.9 and beyond. Results from the analysis of death only as the event of interest showed that a person on ART in Zambia had a 70 percent chance of surviving beyond 7 years 10 months of treatment. When the survival pattern is viewed from the gender perspective, female patients were estimated to survive this long with a higher chance than the men (71 percent versus 68 percent). Similar analyses were performed on the same data with survival redefined 'exited ART' (event = died, stopped or LTFU) and the results showed that the chance of an ART patient remaining on ART after 7 years 10 months of treatment was only 16 percent for both sexes and 18 and 14 percent for females and males respectively. These percentages in effect indicate the retention levels on treatment. Survival was from this point onwards only discussed in the context of the event of interest being 'exited ART' as defined above.

Using univariate Cox proportional hazards techniques in survival analysis, the set of covariates which have significant effects on survival in Zambia were identified. The covariates or variables were tested one at a time to check whether they predicted survival well or not. This was achieved by performing Cox regression in which the output was survival and the covariate or predictor was any one of the variables of interest (as a dichotomised variable). Section 6.8 lists the covariates which were determined to have an effect ($p < 0.05$) on survival (as univariate predictors) to be CD4 count cut off at 200 and 350 cells µl of blood, gender, age at enrollment, residence and ART regimen (New or old regimen in the treatment program).

8.2.2 Task 2 – What measure of effect do the covariates have on survival of ART patients?

In order to enumerate the effect of the various covariates on survival, Cox regression was again utilised. The effect of each covariate on survival is measured as a hazard ratio. A hazard

ratio close to 1 means that the variable does not have much effect on survival. The results in this research indicate that CD4 cut off at 500 and the three category CD4 count did not have a significant effect on survival as univariates. From the results it can be seen that the risk of dropping out of the treatment program by female is 86 percent that of a male patient. This is the case only when gender is the only predictor of survival in the model. The variable with the biggest effect on survival is the ART regimen (i.e. new or old) where the hazard ratio of the new to the old regimens was estimated at 1.365 which means that a patient on an old regimen was 36 percent more likely to drop out of the treatment program than a patient on the new ART regimens. Similarly, CD4 at 200 has a hazard ratio of 0.989, CD4 cut off at 350 has a hazard ratio of 0.979, age at enrollment (HR = 0.996) Rural/Urban (HR = 1.027).

8.2.3 Task 3 – What is the best combination of covariates predicting survival for patients on ART in Zambia?

The question in this task was answered in section 6.8 in the multivariate analysis output. Whereas Tasks 1 and 2 were answered with performing Cox regression with one covariate at a time, to determine the combination of covariates which predicted survival the best, all the covariates were used in the model in a number of combinations and the best was selected from these. The choice of the combinations of variables was based on the realization that the three CD4 cut off variables at 200, 350 and 500 if included in the same model would introduce obvious collinearity. As a result they were separated to be in models each along with the other variables with the exception of the Rural/Urban and Old/New ART regimen variables for reasons given in Chapter 4.

Based on the Log Likelihood and Log Rank Chi-square values (Table 6.3), the results indicate that all the 4 models show that it was beneficial to model survival using the different combinations of variables. However, the individual covariates' p-value for inclusion in each model falls short of desirable levels of significance for the model containing CD4 count cut off at 200 (p = 0.699) and for CD4 cut off at 500 (p = 0.490). For similar reasons, the inclusion of the CD4 count interval 200 – 349 was dropped (p = 0.758 and HR = 0.993 to 1.010), based on the univariate analysis even though it was showing statistical significance in the multivariate analysis. This means the selected combination of covariates to estimate survival were CD4 cut off at 350, gender and enrollment age

8.2.4 Task 4 – What is the survival profile of patients on ART in Zambia?

One of the main achievements of chapter 6 was to assign probability distributions to each group of patients from which to sample their length of stay in the system. These distributions were labelled 01 to 08 with a distribution assigned to one of the 8 different risk groups to which each patient belongs. The risk groups were constructed based on gender, age group and CD4 category based on the 350 cut off (as per conclusion in Task 3). These results are in tabular form in section 6.8. The number of runs required to achieve stable results was determined in this chapter. It was determined that 5 runs would be sufficient.

The results of the DES model are presented in chapter 8. The simulation model results indicate that 5 years after the censorship point or end of the real system data, there were 35 percent of the patients who enrolled on ART still alive and on treatment, essentially the retention rate. This means the simulation was run from April 2014 March 2019. The ART system had enrolled a cumulative total of about 818,478 patients at this point of whom 330,986 were enrolled in the period after the censorship point of the observational data. The largest number of patients at this point had been declared LTFU (42 percent) which is expected in long-term treatment programs and has been reported in a number of studies (Koole et al., 2014). Further, 17 percent of the patients were estimated to have died during the observation period and 6 percent stopped treatment. The overall drop out from the program at the end of 5 years post censorship was therefore calculated to be 65 percent of all patients who had ever enrolled onto the ART program.

The same results were generated for the long-term projection window case where the model was run for 10 years beyond the censorship point in order to observe what the system would look like based on the conditions at censorship point. This represents the years from April 2014 to March 2024. This also means that the total model running time reached 20 years from the beginning. At this point, approximately 1.1 million patients were enrolled onto ART by the system and of these, the number on ART at that date was nearly 278,000 patients. In percentage terms, the number of patients retained on treatment was estimated to be about 24 percent of the cumulative new patients. This percentage may look smaller than the case at the 5 year projection endpoint but as explained in the previous chapter, the current

number on ART is a current result which is carried on from each previous period while the other categories (LTFU, died and stopped treatment) have completely new patients added to their final total with the passing of each time period. Whereas the retention on ART was estimated to be about 35 percent in the 5 year time window, the model estimates it as a lower value of 25 percent for the 10 year projection horizon.

The length of time the patients spend on ART is directly related to the cost of providing the service. Owing to the large numbers of patients who exit the system, the estimated average length of time the patients spend on ART is very short. The estimated average length of stay on the program for the medium case was 3.04 years and 3.57 years for the long-term horizon. The longer the model runs, the more new ART patients enter the model and as seen in all the distributions in Appendix I, the highest probabilities are for dropping out of the treatment program in the earliest years. For the medium-term projection window, the minimum time spent in the model was 1 week and the maximum was 14 years and 8 months while that for the long-term projection window ranged from a week to 19 years and 3 months.

8.2.5 Task 5 – What are the long-term economic cost estimates of ART provision in Zambia?

The response to Task 5 constitutes the answer to the second question aimed at providing an economic perspective to ART service provision in Zambia. The economic costs of providing ART in Zambia were computed based on published unit costs of providing ART to a single person per year (Tagar et al., 2014). The definition of economic costs of provision of ART adopted in this research were therefore based on assumptions made in the quoted unit costs and included all health facility costs associated with the provision of ART services to persons in a public health facility in Zambia. The costs were a sum of clinical and non-clinical staff time, capital costs (rent of buildings and fixed assets) and clinical and non-clinical consumables as long as they were expended on ART service provision (both HIV and non HIV drugs, other clinical consumables.

Estimates from the model indicated that the annual cost of providing ART to patients in 2014 stood at approximately US$44.5m at current prices. This estimate was based on the 2010 US$278 unit cost reported by Tager et al (Tagar et al., 2014) which adjusted for inflation was

worth approximately $284 in 2014. When the model was run for 5 years in the medium-term time window, the cost of service provision increased to $81.2m per annum in 2019. At program level, it was estimated that it would cost about $405.8m to provide ART to all patients during that period. For the 10 year time window, the model estimated that the annual cost of providing ART services in the country would be in the region of $90.5m at the projected unit cost of $322 per person per year. This cost level would translate to $452.3 to provide ART in the 5 years from 2019 to 2024 or as much as $858.1m for the service covering the 10 years from 2014 to 2024.

8.3 Limitations and Future Work

The main limitation of this study is its inability to project much further into the future. This is a consequence of survival analysis because the behaviour of the survival functions after the censorship point is not very easy to predict for long time periods. From a clinical perspective, the shorter time window limits the clinicians' understanding of the long-term treatment outcomes of the patients. The inability to project treatment outcomes over a longer time window also has the effect of making it difficult to project the costs of ART service provision for longer periods of time into the future.

The second limitation is that the model could not be built to predict the differences in survival for patients who were started on the new ART regimens versus the old regimens. This would help the clinicians with decision making with regard to treatment outcomes based on the comparisons. On the economic front, since the costs of the newer regimens are higher than the old regimens, a simulation of these would have provided health planners with a clearer picture of these costs in the long term depending on the simulated outcomes.

Future work in estimating survival or retention of patients on ART in Zambia would supplement this work by attempting to use more accurate data on a sample basis which could be used as long as it were scalable. May it be noted however, that a full database such as used in this research is preferable if it can provide higher accuracy and completeness than before. Use of data from only those ART sites where the databases are always up to date and where sufficient follow up of LTFU patients is consistently done would provide additional benefits to

the current model where the LTFU seems over represented. That LTFU is being over represented is postulated to be a direct consequence of the ART roll out model adopted by the country. ART was first offered in larger provincial and district hospitals for some years until the number of patients enrolled at these central health facilities became unmanageable. A roll out to primary health facilities in the localities where patients resided was embarked on and at present, ART is offered very close to the family in Zambia. When this roll out process commenced and ART was available at clinics close to their homes, thousands of patients simply enrolled as 'new' patients at these facilities and subsequently became declared 'LTFU' at the original sites.

More work on estimating what proportion of the LTFU in Zambia are truly dead will help with more accurate survival estimates for the classical case (i.e. event = death only). Such a study would also likely reveal that some supposedly LTFU patients have enrolled in ART at different facilities. This could be done by targeting health facilities with well-developed community follow up systems to help with patient tracing. A full study on the LTFU to determine what really happens to them when they drop out of care would really help answer a lot of questions in many ART related studies and lay a solid foundation on which future research could stand.

Reference List

Aalen, O. O., Farewell, V. T., De Angelis, D., Day, N. E., & Gill, O. N. (1997). A Markov model for HIV disease progression including the effect of HIV diagnosis and treatment: application to AIDS prediction in England and Wales. *Statistics in Medicine*, *16*(19), 2191–210. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9330428

Abdollah, F., Sun, M., Schmitges, J., Thuret, R., Bianchi, M., Shariat, S. F., … Karakiewicz, P. I. (2012). Survival benefit of radical prostatectomy in patients with localized prostate cancer: estimations of the number needed to treat according to tumor and patient characteristics. *The Journal of Urology*, *188*(1), 73–83. doi:10.1016/j.juro.2012.03.005

Abu-Raddad, L. J., Magaret, A. S., Celum, C., Wald, A., Longini, I. M., Self, S. G., & Corey, L. (2008). Genital Herpes Has Played a More Important Role than Any Other Sexually Transmitted Infection in Driving HIV Prevalence in Africa. *PLoS ONE*, *3*(5), 15. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2377333&tool=pmcentrez&rendertype=abstract

Adams, A. L., Barth-Jones, D. C., Chick, S. E., & Koopman, J. S. (1998). Simulations to Evaluate HIV Vaccine Trial Designs. *Sumulation*, *71*(4), 228–241.

Akaike, H. (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control*, *19*(6). doi:10.1109/TAC.1974.1100705

Aktas, E., Ulengin, F., & Onselsahin, S. (2007). A decision support system to improve the efficiency of resource allocation in healthcare management. *SocioEconomic Planning Sciences*, *41*(2), 130–146. doi:10.1016/j.seps.2005.10.008

Aledort, J. E., Ronald, A., Le Blancq, S. M., Ridzon, R., Landay, A., Rafael, M. E., … Wilfert, C. (2006). Reducing the burden of HIV/AIDS in infants: the contribution of improved diagnostics. *Nature*, *444 Suppl* , 19–28. doi:10.1038/nature05443

Allison, P. D. (2010). *Survival Analysis Using SAS: A Practical Guide*. *Survival* (Vol. 1). SAS Publishing. Retrieved from http://www.amazon.com/Survival-Analysis-Using-SAS-Practical/dp/155544279X

American Cancer Society. (2012). *HIV Infection , AIDS , and Cancer*.

Amundsen, E. J., Aalen, O. O., Stigum, H., Eskild, A., Smith, E., Arneborn, M., … Magnus, P. (2000). Back-calculation based on HIV and AIDS registers in Denmark, Norway and Sweden 1977-95 among homosexual men: estimation of absolute rates, incidence rates and prevalence of HIV. *Journal of Epidemiology and Biostatistics*, *5*(4), 233–243. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-0034571954&partnerID=40&md5=dc2774d889da715f05d3fa86001c67db

Anderson, R. M., May, R. M., Boily, M. C., Garnett, G. P., & Rowley, J. T. (1991). The spread of HIV-1 in Africa: sexual contact patterns and the predicted demographic impact of AIDS. *Nature*, *352*(6336), 581–589. Retrieved from http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=1865922

Anderson, R. M., May, R. M., & McLean, A. R. (1988). Possible demographic consequences of AIDS in developing countries. *Nature*, *332*(6161), 228–234. Retrieved from http://www.nature.com/nature/journal/v332/n6161/abs/332228a0.html

Anderson, R., Medley, G., May, R., & Johnson, A. (1986). A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *IMA Journal Of Mathematics Applied In Medicine And Biology*, *3*(4), 229–263. Retrieved from http://discovery.ucl.ac.uk/86807/

Andresen, M. a, & Boyd, N. (2010). A cost-benefit and cost-effectiveness analysis of Vancouver's supervised injection facility. *The International Journal of Drug Policy*, *21*, 70–6. doi:10.1016/j.drugpo.2009.03.004

Andridge, R. R., & Little, R. J. A. (2010). A review of hot deck imputation for survey non-response. *International Statistical Review*.

Antiretroviral Therapy Cohort Collaboration. (2008). Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*, *372*(9635), 293–9. doi:10.1016/S0140-6736(08)61113-7

Aranda-Ordaz, F. J. (1981). On two families of transformations to additivity for binary response data. *Biometrika*, *68*(2), 357–363.

Atun, R. A., Lebcir, R. M., McKee, M., Habicht, J., & Coker, R. J. (2007). Impact of joined-up HIV harm reduction and multidrug resistant tuberculosis control programmes in Estonia: System dynamics simulation model. *Health Policy*, *81*(2-3), 207–217. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16854499

Bagni, R., Berchi, R., & Cariello, P. (2002). A comparison of simulation models applied to epidemics. *Journal of Artificial Societies and Social Simulation*, *5*(3), 1–23. Retrieved from http://jasss.soc.surrey.ac.uk/5/3/5.html

Bagshaw, S. M., Laupland, K. B., Doig, C. J., Mortis, G., Fick, G. H., Mucenski, M., … Rosenal, T. (2005). Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Critical Care*, *9*(6), R700–R709. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16280066

Bärnighausen, T., Salomon, J. A., & Sangrujee, N. (2012). HIV Treatment as Prevention: Issues in Economic Evaluation. *PLoS Medicine*, *9*(7), e1001263. doi:10.1371/journal.pmed.1001263

Barton, P., Bryan, S., & Robinson, S. (2004). Modelling in the economic evaluation of health care: selecting the appropriate approach. *Journal of Health Services Research Policy*, *9*(2), 110–118. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15099459

Baveewo, S., Ssali, F., Karamagi, C., Kalyango, J. N., Hahn, J. A., Ekoru, K., … Katabira, E. (2011). Validation of World Health Organisation HIV/AIDS clinical staging in predicting initiation of antiretroviral therapy and clinical predictors of low CD4 cell count in Uganda. *PLoS ONE*, *6*(5).

Bewick, V., Cheek, L., & Ball, J. (2004). Statistics review 12: Survival analysis. *Critical Care*, *8*(5), 389–394. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15469602

Beyrer, C., Baral, S. D., van Griensven, F., Goodreau, S. M., Chariyalertsak, S., Wirtz, A. L., & Brookmeyer, R. (2012). Global epidemiology of HIV infection in men who have sex with men. *Lancet*, *380*(9839), 367–377. doi:10.1016/S0140-6736(12)60821-6

Binquet, C., Le Teuff, G., Abrahamovicz, M., Mahboubi, A., Yazdanpanah, Y., Rey, D., … Piroth, L. (2009). Markov modelling of HIV infection evolution in the HAART era. *Epidemiology and Infection*, *137*(9), 1272–1282. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19134234

Bogard, E., & Kuntz, K. M. (2002). The impact of a partially effective HIV vaccine on a population of intravenous drug users in Bangkok, Thailand: a dynamic model. *Journal of Acquired Immune Deficiency Syndromes*, *29*(2), 132–141. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11832681

Bongaarts, J. (1989). A model of the spread of HIV infection and the demographic impact of AIDS. *Statistics in Medicine*, *8*(1), 103–120. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2919241

Bongaarts, J., Pelletier, F., & Gerland, P. (2009). *POVERTY , GENDER , AND YOUTH: Global Trends in AIDS Mortality* (No. 16). Washington, DC. Retrieved from http://www.popcouncil.org/pdfs/wp/pgy/016.pdf

Bradburn, M. J., Clark, T. G., Love, S. B., & Altman, D. G. (2003). Survival Analysis Part II : Multivariate data analysis – an introduction to concepts and methods. *British Journal of Cancer*, 431–436. doi:10.1038/sj.bjc.6601119

Brailsford, S. (2005). Overcoming the barriers to implementation of operations research simulation models in healthcare. *Clinical and Investigative Medicine Medecine Clinique et Experimentale*, *28*(6), 312–315. Retrieved from http://eprints.soton.ac.uk/37344/

Branas, C. C., MacKenzie, E. J., & ReVelle, C. S. (2000). A trauma resource allocation model for ambulances and hospitals. *Health Services Research*, *35*(2), 489–507. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1089130&tool=pmcentrez&rendertype=abstract

Brandeau, M. L., Owens, D. K., Sox, C. H., & Wachter, R. M. (1993). Screening Women of Childbearing Age for Human Immunodeficiency Virus: A Model-Based Policy Analysis. *Management Science*, *39*(1), 72–92. doi:10.1287/mnsc.39.1.72

Brandeau, M. L., Sainfort, F., & Pierskalla, W. P. (2004). *OPERATIONS RESEARCH AND HEALTH CARE - A Handbook of Methods and Applications*.

Bratt, J. H., Torpey, K., Kabaso, M. E., & Gondwe, Y. (2011). Costs of HIV／AIDS outpatient services delivered through Zambian public health facilities. *Tropical Medicine and International Health*, *16*(1), 110–118. doi:10.1111/j.1365-3156.2010.02640.x

Brennan, A., Chick, S. E., & Davies, R. (2006). A taxonomy of model structures for economic evaluation of health technologies. *Health Economics*, *15*, 1295–1310. doi:10.1002/hec

Caro, J. J. (2005). Pharmacoeconomic analyses using discrete event simulation. *PharmacoEconomics*, *23*(4), 323–332. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15853433

Carter, R. J., Dugan, K., El-Sadr, W. M., Myer, L., Otieno, J., Pungpapong, N., … Abrams, E. J. (2010). CD4+ cell count testing more effective than HIV disease clinical staging in identifying pregnant and postpartum women eligible for antiretroviral therapy in resource-limited settings. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *55*(3), 404–410.

Censor, Y. (2003). Mathematical Optimization For The Inverse Problem Of Intensity-Modulated Radiation Therapy. *Intensity Modulated Radiation Therapy The State of The Art American Association of Physicists in Medicine Medical Physics Monograph*, (29), 25–49. Retrieved from http://imrt1.persiangig.com/Articles/Optimizing/Math

Centers for Disease Control and Prevention. (1981). Pneumocystis Pneumonia - Los Angeles. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm

Centers for Disease Control and Prevention. (1992). *1993 Revised Classification System for HIV Infection and Expanded Case Definitions for AIDS among Adolescents and Adults. MMWR. 1992;41(RR-17)*. Retrieved from www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

Central Statistical Office (CSO). (2012a). *ZAMBIA 2010 CENSUS OF POPULATION AND HOUSING - NATIONAL ANALYTICAL REPORT*.

Central Statistical Office (CSO). (2012b). *Zambia 2010 Census of Population and Housing, Population Summary Report*.

Central Statistical Office (CSO), & Ministry of Health Zambia (MOH). (2003). *Demographic and Health Survey 2001 - 2002*.

Central Statistical Office (CSO), & Ministry of Health Zambia (MOH). (2009). *Demographic and Health Survey 2007*.

Central Statistical Office (CSO), Ministry of Health Zambia (MOH), National HIV/AIDS/STI/TB Council National HIV, & MEASURE Evaluation. (2010). *Zambia Sexual Behaviour Survey*.

Chen, X., Fan, Y., Pouzo, D., & Ying, Z. (2010). Estimation and model selection of semiparametric multivariate survival functions under general censorship. *Journal of Econometrics*, *157*(1), 129–142. doi:10.1016/j.jeconom.2009.10.021

Chevalier, M. J., Smith, D. J., & Dean, D. W. (2012). The reliability of structural systems operating at high temperature: Replacing engineering judgement with operational experience. *International Journal of Pressure Vessels and Piping*, *98*, 65–75. doi:10.1016/j.ijpvp.2012.07.004

Chi, B. H., Yiannoutsos, C. T., Westfall, A. O., Newman, J. E., Zhou, J., Cesar, C., … Thiebaut, R. (2011). Universal definition of loss to follow-up in HIV treatment programs: A statistical analysis of 111 facilities in Africa, Asia, and Latin America. *PLoS Medicine*, *8*(10). doi:10.1371/journal.pmed.1001111

Clark, H. W., & Corbett, J. M. (1993). Needle exchange programs and social policy. *Journal Of Mental Health Administration*, *20*(1), 66–71.

Cleves, M., Gutierrez, R., Gould, W., & Marchenko, Y. (2010). *An Introduction to Survival Analysis Using Stata* (Third.). College Station, Texas: Stata Press. Retrieved from http://www.stata.com/bookstore/survival-analysis-stata-introduction/

Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., … Fleming, T. R. (2011). Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine*, *365*(6), 493–505. doi:10.1056/NEJMoa1105243

Collett, D. (1994). *Modelling survival data in medical research*. (C. Chatfield, M. Tanner, & J. Zidek, Eds.)*Texts in statistical science* (Vol. 46). Chapman & Hall. doi:10.1198/tech.2004.s817

Cook, J., Dasbach, E., Coplan, P., Markson, L., Yin, D., Meibohm, A., … Mellors, J. (2004). Modeling the long-term outcomes and costs of HIV antiretroviral therapy using HIV RNA levels: application to a clinical trial. *AIDS Research and Human Retroviruses*, *15*(6), 499–508. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10221527

Cox, D. R. (1972). Regression Models and Life-Tables. *Journal of the Royal Statistical Society*, *34*(2), 187–220.

Cox, D. R., Snell, E. J., Journal, S., Statistical, R., Series, S., & Cox, B. D. R. (1968). A General Definition of Residuals. *Journal of the Royal Statistical Society. Series B (Methodological)*, *30*(2), 248–275. Retrieved from http://www.jstor.org/stable/2984505\nhttp://www.jstor.org/stable/pdfplus/2984505.pdf?acceptTC=true

Creese, A., Floyd, K., Alban, A., & Guinness, L. (2002). Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. *Lancet*, *359*(9318), 1635–43. doi:10.1016/S0140-6736(02)08595-1

Cruz, A. G., Walter, E. H. M., Cadena, R. S., Faria, J. a. F., Bolini, H. M. a., Pinheiro, H. P., & Sant'Ana, A. S. (2010). Survival analysis methodology to predict the shelf-life of probiotic flavored yogurt. *Food Research International*, *43*(5), 1444–1448. doi:10.1016/j.foodres.2010.04.028

Dangerfield, B. C., Fang, Y., & Roberts, C. a. (2001). Model-based scenarios for the epidemiology of HIV/AIDS: The consequences of highly active antiretroviral therapy. *System Dynamics Review*, *17*(2), 119–150. doi:10.1002/sdr.211

Dasbach, E. J., Elbasha, E. H., & Insinga, R. P. (2006). Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiologic Reviews*, *28*(22), 88–100. doi:10.1093/epirev/mxj006

Davies, H. T. O., & Davies, R. (1995). Simulating health systems: modelling problems and software solutions. *European Journal of Operational Research*, *87*(1), 35–44. doi:10.1016/0377-2217(94)00148-6

Dixon, S. (2002). The impact of HIV and AIDS on Africa's economic development. *Bmj*, *324*(7331), 232–234. doi:10.1136/bmj.324.7331.232

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B. J., & Stoddart, G. L. (2005). *Methods for the Economic Evaluation of Health Care Programs* (Third Edit.). Oxford University Press.

Egger, M., May, M., Chêne, G., Phillips, A. N., Ledergerber, B., Dabis, F., … Sterne, J. a C. (2002). Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*, *360*(9327), 119–29. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12126821

Engels, J. (2003). Imputation of missing longitudinal data: a comparison of methods. *Journal of Clinical Epidemiology*, *56*(10), 968–976. doi:10.1016/S0895-4356(03)00170-7

European Centre for Disease Prevention and Control. (2011). *Annual Epidemiological Report 2011. Reporting on 2009 surveillance data and 2010 epidemic intelligence data.*

Finch, H. (2008). Estimation of item response theory parameters in the presence of missing data. *Journal of Educational Measurement*, *45*(3), 225–245.

Flagle, C. D. (2002). Some Origins of Operations Research in the Health Services. *Operations Research*, *50*(1), 52–60. doi:10.1287/opre.50.1.52.17805

Fletcher, D., Lebreton, J.-D., Marescot, L., Schaub, M., Gimenez, O., Dawson, S., & Slooten, E. (2012). Bias in estimation of adult survival and asymptotic population growth rate caused by undetected capture heterogeneity. *Methods in Ecology and Evolution*, *3*(1), 206–216. doi:10.1111/j.2041-210X.2011.00137.x

Forrester, J. W. (1968). Industrial Dynamics - After the First Decade. *Management Science*, *14*(7), 398–415.

Fox, M. P., & Rosen, S. (2010). Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: Systematic review. *Tropical Medicine and International Health*, *15*(june), 1–15. doi:10.1111/j.1365-3156.2010.02508.x

FPA. (2008). *HIV, Looking after your sexual health*.

Freedberg, K. A., Losina, E., Weinstein, M. C., Paltiel, A. D., Cohen, C. J., Seage, G. R., … Goldie, S. J. (2001). The cost effectiveness of combination antiretroviral therapy for HIV disease. *The New England Journal of Medicine*, *344*(11), 824–831. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11248160

French, K., Riley, S., & Garnett, G. (2006). Simulations of the HIV epidemic in sub-Saharan Africa: sexual transmission versus transmission through unsafe medical injections. *Sexually Transmitted Diseases*, *33*(3), 127–134. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16508523

Fusaro, R. E., Jewell, N. P., Hauck, W. W., Heilbron, D. C., Kalbfleisch, J. ., Neuhaus, J. ., & Ashby, M. . (1989). An Annotated Bibliography of Quantitative Methodology Relating to the AIDS Epidemic. *Statistical Science*, *4*(3), 264–281.

Fylkesnes, K., Ndhlovu, Z., Kasumba, K., Mubanga Musonda, R., & Sichone, M. (1998). Studying dynamics of the HIV epidemic: population-based data compared with sentinel surveillance in Zambia. *AIDS*, *12*(10), 1227–1234. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9677172

Garnett, G. P. (2002). An introduction to mathematical models in sexually transmitted disease epidemiology. *Sexually Transmitted Infections*, *78*(1), 7–12. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1763694&tool=pmcentrez&rendertype=abstract

Garnett, G. P., & Anderson, R. M. (1993). Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. *Philosophical Transactions of the Royal Society of London - Series B: Biological Sciences*, *342*(1300), 137–159. Retrieved from

http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=7904355

Geng, E. H., Nash, D., Kambugu, A., Zhang, Y., Braitstein, P., Christopoulos, K. A., … Martin, J. N. (2011). Retention in care among HIV-infected patients in resource-limited settings: Emerging insights and new directions. *Current HIV/AIDS Reports*, *7*(4), 234–244. doi:10.1007/s11904-010-0061-5.Retention

Getz, W. M., Lloyd-Smith, J. O., Cross, P. C., Bar-David, S., Johnson, P. L., Porco, T. C., & Sanchez, M. S. (2005). Modeling the Invasion and Spread of Contagious Diseases in Heterogeneous Populations. In *Disease Evolution: Models, Concepts, And Data Analyses (DIMACS Series in Discrete Mathematics and Theoretical Computer Science)* (pp. 1–32).

Ghate, M., Deshpande, S., Tripathy, S., Nene, M., Gedam, P., Godbole, S., … Mehendale, S. (2009). Incidence of common opportunistic infections in HIV-infected individuals in Pune, India: analysis by stages of immunosuppression represented by CD4 counts. *International Journal of Infectious Diseases IJID Official Publication of the International Society for Infectious Diseases*, *13*(1), e1–e8. Retrieved from http://dx.doi.org/10.1016/j.ijid.2008.03.029

Golestanian, E., Liou, J.-I., & Smith, M. A. (2009). Long-term survival in older critically ill patients with acute ischemic stroke. *Critical Care Medicine*, *37*(12), 3107–3113. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2783898&tool=pmcentrez&rendertype=abstract

Gona, P., Van Dyke, R. B., Williams, P. L., Dankner, W. M., Chernoff, M. C., Nachman, S. A., & Seage, G. R. (2006). Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *Jama The Journal Of The American Medical Association*, *296*(3), 292–300. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16849662

Graham, J. W. (2009). Missing data analysis: making it work in the real world. *Annual Review of Psychology*, *60*, 549–76. doi:10.1146/annurev.psych.58.110405.085530

Granich, R., Kahn, J. G., Bennett, R., Holmes, C. B., Garg, N., Serenata, C., … Williams, B. G. (2012). Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011-2050. *PloS One*, *7*(2), e30216. doi:10.1371/journal.pone.0030216

Granich, R. M., Gilks, C. F., Dye, C., De Cock, K. M., & Williams, B. G. (2009). Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lance*, *373*(9657), 48–57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19038438

Graw, F., Leitner, T., & Ribeiro, R. M. (2012). Agent-based and phylogenetic analyses reveal how HIV-1 moves between risk groups: Injecting drug users sustain the heterosexual epidemic in Latvia. *Epidemics*, *4*(2), 104–16. doi:10.1016/j.epidem.2012.04.002

Grover, G., & Shakeri, N. (2007). Nonparametric estimation of survival function of HIV+ patients with doubly censored data. *The Journal of Communicable Diseases*, *39*(1), 7–12.

Guihenneuc-Jouyaux, C., Richardson, S., & Longini, I. M. (2000). Modeling markers of disease progression by a hidden Markov process: application to characterizing CD4 cell decline. *Biometrics*, *56*(3), 733–741. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10985209

Gunal, M., & Pidd, M. (2009). Discrete Event Simulation for Performance Modelling in Healthcare: A Review of the Literature. *Management Science*, *4*(1), 1–22. Retrieved from http://eprints.lancs.ac.uk/27923/

Hallett, T. B., Gregson, S., Dube, S., & Garnett, G. P. (2008). The impact of monitoring HIV patients prior to treatment in resource-poor settings: insights from mathematical modelling. *PLoS Medicine*, *5*(3), e53. doi:10.1371/journal.pmed.0050053

Harris, J. E. (1990). Improved short-term survival of AIDS patients initially diagnosed with Pneumocystis carinii pneumonia, 1984 through 1987. *JAMA*, *263*(3), 397–401. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=2294306&site=ehost-live

Hartl, W. H., Wolf, H., Schneider, C. P., Küchenhoff, H., & Jauch, K.-W. (2007). Acute and long-term survival in chronically critically ill surgical patients: a retrospective observational study. *Critical Care*, *11*(3), R55. Retrieved from http://ccforum.com/content/pdf/cc5915.pdf

Heidenberger, K., & Flessa, S. (1993). A SYSTEM DYNAMICS MODEL FOR AIDS POLICY SUPPORT IN TANZANIA. *European Journal Of Operational Research*, *70*(2), 167–176. doi:10.1016/0377-2217(93)90036-M

Hellinger, F. J. (1993). The lifetime cost of treating a person with HIV. *JAMA : The Journal of the American Medical AssociationThe Journal Of The American Medical Association*, *270*(4), 474–478.

Henriques, J., Pujades-Rodriguez, M., McGuire, M., Szumilin, E., Iwaz, J., Etard, J.-F., & Ecochard, R. (2012). Comparison of methods to correct survival estimates and survival regression analysis on a large HIV African cohort. *PLoS ONE*, *7*(2), e31706. doi:10.1371/journal.pone.0031706

Ho, K. M., Knuiman, M., Finn, J., & Webb, S. A. (2008). Estimating long-term survival of critically ill patients: the PREDICT model. *PloS One*, *3*(9), e3226. doi:10.1371/journal.pone.0003226

Hogan, D. R. (2005). Cost effectiveness analysis of strategies to combat HIV/AIDS in developing countries. *British Medical Journal*, *331*(7530), 1431–1437. doi:10.1136/bmj.38643.368692.68

Hogg, R. S., Heath, K. V, Yip, B., Craib, K. J., O'Shaughnessy, M. V, Schechter, M. T., & Montaner, J. S. (1998). Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA : The Journal of the American Medical Association*, *279*(6), 450–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9466638

Homer, J. B., & St. Clair, C. L. (1991). A model of HIV Transmission through Needle Sharing, *21*(3), 26–49.

Hosmer, D. W., Lemeshow, S., & May, S. (2007). *Applied Survival Analysis: Regression Modeling of Time to Event Data*. *New York* (Second Edi., Vol. 91). Wiley.

Ioannidis, J., & Wilkinson, D. (2003). HIV: prevention of opportunistic infections. *Clinical Evidence*, *2006*(10), 834–853. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16135281

Jackson, C. H., Sharples, L. D., & Thompson, S. G. (2010). Survival Models in Health Economic Evaluations: Balancing Fit and Parsimony to Improve Prediction. *The International Journal of Biostatistics*, *6*(1). doi:10.2202/1557-4679.1269

Jackson, C. H., Sharples, L. D., Thompson, S. G., Duffy, S. W., & Couto, E. (2003). Multistate Markov models for disease progression with classification error. *Journal of the Royal Statistical Society Series D The Statistician*, *52*(2), 193–209. doi:10.1111/1467-9884.00351

Jacquez, J. A. (1972). *Compartmental Analysis in Biology and Medicine*. *Elseiver Amsterdam*. (2nd Edition), The University of Michigan Press, Ann Arbor. Retrieved from http://books.google.com/books?id=Uc1qAAAAMAAJ&pgis=1

Jebakumar, S. P., Woolley, P. D., & Curless, E. (1993). Lifetime cost of treating a person with HIV infection. *International Journal of STD AIDS*, *6*(6), 444–446. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8845405

Jevtovic, D., Salemovic, D., Ranina, J., Dulovic, O., Ilic, D., & Brmboliic, B. (2010). The prognosis of highly active antiretroviral therapy (HAART) treated HIV infected patients in Serbia, related to the time of treatment initiation. *Journal of Clinical Virology*, *47*, 131–135.

Johansson, K. A., Robberstad, B., & Norheim, O. F. (2010). Further benefits by early start of HIV treatment in low income countries: Survival estimates of early versus deferred antiretroviral therapy. *Aids Research And Therapy*, *7*(1), 3. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2836271&tool=pmcentrez&rendertype=abstract

Johnson, L. F., Mossong, J., Dorrington, R. E., Schomaker, M., Hoffmann, C. J., Keiser, O., … Boulle, A. (2013). Life expectancies of South African adults starting antiretroviral

treatment: collaborative analysis of cohort studies. *PLoS Medicine*, *10*(4), e1001418. doi:10.1371/journal.pmed.1001418

Judson, F. N. (1990). Partner notification for HIV control. *Hospital Practice (Office Ed)*, *25*(12), 63–70, 73. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11651235

Kadengye, D. T., Cools, W., Ceulemans, E., & Van den Noortgate, W. (2012). Simple imputation methods versus direct likelihood analysis for missing item scores in multilevel educational data. *Behavior Research Methods*. doi:10.3758/s13428-011-0157-x

Kagaayi, J., Makumbi, F., Nakigozi, G., Wawer, M. J., Gray, R. H., Serwadda, D., & Reynolds, S. J. (2007). WHO HIV clinical staging or CD4 cell counts for antiretroviral therapy eligibility assessment? An evaluation in rural Rakai district, Uganda. *AIDS (London, England)*, *21*(9), 1208–1210.

Kaminski, D., & Geisler, C. (2012). Survival analysis of faculty retention in science and engineering by gender. *Science*, *335*(6070), 864–6. doi:10.1126/science.1214844

Kanekar, A. (2010). Markers predicting progression of human immunodeficiency virus-related disease. *Clinical Microbiology Reviews*, *2*(2), 55–61.

Kaplan, E. ., & Meier, P. (1958). Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*, *53*(282), 457–481.

Katsaliaki, K., & Mustafee, N. (2010). Applications of simulation within the healthcare context. *Journal of the Operational Research Society*, *62*(8), 1431–1451. doi:10.1057/jors.2010.20

Keiser, P., Nassar, N., Kvanli, M. B., Turner, D., Smith, J. W., & Skiest, D. (2001). Long-term impact of highly active antiretroviral therapy on HIV-related health care costs. *Journal of Acquired Immune Deficiency Syndromes*, *27*(1), 14–19. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11404515

Kilmarx, P. H. (2009). Global epidemiology of HIV. *Current Opinion in HIV and AIDS*, *4*(4), 240–246. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19532059

King, J. T., Justice, A. C., Roberts, M. S., Chang, C.-C. H., & Fusco, J. S. (2003). Long-Term HivAids Survival Estimation in the Highly Active Antiretroviral Therapy Era. *Medical Decision Making*, *23*(1), 9–20. doi:10.1177/0272989X02239652

Kleinbaum, D. G., & Klein, M. (2005). *Survival Analysis: A Self-Learning Text*. (M. Gail, K. Krickeberg, J. Samet, A. Tsiatis, & W. Wong, Eds.)*Statistics for Biology and Health*. Springer. doi:10.1007/0-387-29150-4

Koch, O., & Weigl, H. (2003). Modeling ambulance service of the Austrian Red Cross. *Proceedings of the 2003 Winter Simulation Conference 2003*. Ieee. doi:10.1109/WSC.2003.1261622

Koole, O., Tsui, S., Wabwire-mangen, F., Kwesigabo, G., Menten, J., & Mulenga, M. (2014). Retention and risk factors for attrition among adults in antiretroviral treatment programmes in Tanzania , Uganda, *19*(12), 1397–1410. doi:10.1111/tmi.12386

Kresel, J. J., Hutchings, H. C., MacKay, D. N., Weinstein, M. C., Read, J. L., Taylor-Halvorsen, K., & Ashley, H. (1987). Application of decision analysis to drug selection for formulary addition. *Hospital Formulary*, *22*(7), 658–663, 673, 676.

Kuhn, L., Thomas, P. A., Singh, T., & Tsai, W. Y. (1998). Long-term survival of children with human immunodeficiency virus infection in New York City: estimates from population-based surveillance data. *American Journal of Epidemiology*, *147*(9), 846–854. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9583715

La Croix, S. J., & Russo, G. (1996). A cost-benefit analysis of voluntary routine HIV-antibody testing for hospital patients. *Social Science & Medicine*, *42*(9), 1259–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8733196

Lasry, A., Zaric, G. S., & Carter, M. W. (2007). Multi-level resource allocation for HIV prevention: A model for developing countries. *European Journal Of Operational Research*, *180*(2), 786–799. doi:10.1016/j.ejor.2006.02.043

Lebcir, R. M., Atun, R. A., & Coker, R. J. (2010). System Dynamic simulation of treatment policies to address colliding epidemics of tuberculosis , drug resistant tuberculosis and injecting drug users driven HIV in Russia. *Journal of the Operational Research Society*, *61*(8), 1238–1248. doi:10.1057/jors.2009.90

Lee, E. T., & Go, O. T. (1997). Survival Analysis in Public Health Research. *Annual Review of Public Health*, *18*, 105–34.

Lemp, G. F., Payne, S. F., Neal, D., Temelso, T., & Rutherford, G. W. (1990). Survival trends for patients with AIDS. *JAMA : The Journal of the American Medical Association*, *263*(3), 402–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2294307

Libertino, L. M., Osornio, M. M. L., & Hough, G. (2011). Number of consumers necessary for survival analysis estimations based on each consumer evaluating a single sample. *Food Quality and Preference*, *22*(1), 24–30. doi:10.1016/j.foodqual.2010.06.006

Lieb, S., White, S., Grigg, B. L., Thompson, D. R., Liberti, T. M., & Fallon, S. J. (2010). Estimated HIV incidence, prevalence, and mortality rates among racial/ethnic populations of men who have sex with men, Florida. *Journal of Acquired Immune Deficiency Syndromes*, *54*(4), 398–405. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20182358

Lohse, N., Eg Hansen, A.-B., Pedersen, G., Kronborg, G., Gerstoft, J., Sørensen, H., … Obel, N. (2007). Annals of Internal Medicine Article Survival of Persons with and without HIV Infection in Denmark ,. *Annals of Internal Medicine*, *146*, 87–95.

Long, Z.-J., Lee, S.-K., & Kim, J.-Y. (2010). Estimation of survival probability for a ship in beam seas using the safe basin. *Ocean Engineering*, *37*(4), 418–424. doi:10.1016/j.oceaneng.2009.11.003

Lopez, O. (2012). A generalization of the Kaplan–Meier estimator for analyzing bivariate mortality under right-censoring and left-truncation with applications in model-checking for survival copula models. *Insurance: Mathematics and Economics*, *51*(3), 505–516. doi:10.1016/j.insmatheco.2012.07.009

Machin, D., Cheung, Y. B., & Parmar, M. K. (2006). *Survival Analysis. A Practical Approach*. John Wiley and Sons, Ltd.

Maclean, C. C., & Stringer, J. S. A. (2005). Potential cost-effectiveness of maternal and infant antiretroviral interventions to prevent mother-to-child transmission during breast-feeding. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *38*(5), 570–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15793368

Malunguza, N., Mushayabasa, S., Chiyaka, C., & Mukandavire, Z. (2010). Modelling the effects of condom use and antiretroviral therapy in controlling HIV/AIDS among heterosexuals, homosexuals and bisexuals. *Computational and Mathematical Methods in Medicine*, *11*(3), 201–222. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20721763

Marasca, G., & McEvoy, M. (1986). Length of survival of patients with acquired immune deficiency syndrome in the United Kingdom. *British Medical Journal (Clinical Research Ed.)*, *292*(6537), 1727–9. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1340646&tool=pmcentrez&rendertype=abstract

Mathieu, E., Loup, P., Dellamonica, P., & Daures, J. P. (2005). Markov modelling of immunological and virological states in HIV-1 infected patients. *Biometrical Journal Biometrische Zeitschrift*, *47*(6), 834–846. Retrieved from http://doi.wiley.com/10.1002/bimj.200410164

May, M., Sterne, J. a C., Sabin, C., Costagliola, D., Justice, A. C., Thiébaut, R., … Egger, M. (2007). Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS (London, England)*, *21*(9), 1185–97. doi:10.1097/QAD.0b013e328133f285

McGarvey, R., Linnane, A. J., Feenstra, J. E., Punt, A. E., & Matthews, J. M. (2010). Integrating recapture-conditioned movement estimation into spatial stock assessment: A South Australian lobster fishery application. *Fisheries Research*, *105*(2), 80–90. doi:10.1016/j.fishres.2010.03.006

Mellor, G. R., Currie, C. S. M., & Corbett, E. L. (2011). Incorporating household structure into a discrete event simulation model of tuberculosis and HIV. *ACM Transactions On Modeling And Computer Simulation*, *21*(4), 1–17. Retrieved from http://eprints.soton.ac.uk/156177/

Meyer-Rath, G., & Over, M. (2012). HIV Treatment as Prevention: Modelling the Cost of Antiretroviral Treatment—State of the Art and Future Directions. *PLoS Medicine*, *9*(7), e1001247. doi:10.1371/journal.pmed.1001247

Mills, E. J., Bakanda, C., Birungi, J., Chan, K., Ford, N., Cooper, C. L., … Hogg, R. S. (2011). Life Expectancy of Persons Receiving Combination Antiretroviral Therapy in Low-Income Countries : A Cohort Analysis From Uganda. *Annals of Internal Medicine*.

Ministry of Health Zambia (MOH). (2007). *Zambia Antenatal Clinic Sentinel Surveillance Report 1994 - 2006*.

Ministry of Health Zambia (MOH). (2010). Zambia Adult And Adolescent Antiretroviral Therapy Protocols 2010.

Ministry of Health Zambia (MOH), & National HIV/AIDS/STI/TB Council Zambia. (2009). *ZAMBIA: HIV Prevention Response and Modes of Transmission Analysis*.

Ministry of Health Zambia (MOH), & National HIV/AIDS/STI/TB Council Zambia. (2012). *ZAMBIA COUNTRY REPORT: Monitoring the Declaration of Commitment on HIV and AIDS and the Universal Access*.

Mishra, S., Fisman, D. N., & Boily, M.-C. (2011). The ABC of terms used in mathematical models of infectious diseases. *Journal of Epidemiology & Community Health*, *65*(1), 87–94. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20966445

Nagelkerke, N. J., Moses, S., De Vlas, S. J., & Bailey, R. C. (2007). Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa. *BMC Infectious Diseases*, *7*(1), 16. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1832203&tool=pmcentrez&rendertype=abstract

Nakagawa, F., Lodwick, R., Smith, C., Smith, R., Cambiano, V., Lundgren, J., … Phillips, A. (2011). Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS*, *26*(September 2011), 1–9. Retrieved from http://discovery.ucl.ac.uk/1331854/

National HIV/AIDS/STI/TB Council Zambia. (2010). *National AIDS Strategic Framework 2011 - 2015*. *Framework*. Retrieved from http://www.nac.org.zm/index.php/publications/policy-and-planning/doc_download/140-n

National HIV/AIDS/STI/TB Council Zambia. (2015). *National HIV/AIDS Strategic Framework*.

National Institute for Health and Care Excellence. (2013). *Guide to the methods of technology appraisal 2013*. National Institute for Health and Care Excellence (NICE). Retrieved from http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf

Ndeffo Mbah, M. L., Kjetland, E. F., Atkins, K. E., Poolman, E. M., Orenstein, E. W., Meyers, L. A., … Galvani, A. P. (2013). Cost-effectiveness of a community-based intervention for reducing the transmission of Schistosoma haematobium and HIV in Africa. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(19), 7952–7. doi:10.1073/pnas.1221396110

Niu, S., Zhang, X., Zhao, C., & Niu, Y. (2012). Variations in energy consumption and survival status between rural and urban households: A case study of the Western Loess Plateau, China. *Energy Policy*, *49*, 515–527. doi:10.1016/j.enpol.2012.06.046

Noelle, G., Jaskulla, E., & Sawicki, P. T. (2006). Aspects of economic evaluation in health care. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*, *49*(1), 28–33. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-33644899436&partnerID=40&md5=9fb720651dfc80b56d9a45373d4f2031

Nyabadza, F., & Mukandavire, Z. (2011). Modelling HIV/AIDS in the presence of an HIV testing and screening campaign. *Journal of Theoretical Biology*, *280*(1), 167–179. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21536051

Odafe, S., Idoko, O., Badru, T., Aiyenigba, B., Suzuki, C., Khamofu, H., … Chabikuli, O. N. (2012). Patients' demographic and clinical characteristics and level of care associated with lost to follow-up and mortality in adult patients on first-line ART in Nigerian hospitals. *Journal of the International AIDS Society*, *15*(2).

Okasha, N. M., Frangopol, D. M., & Orcesi, A. D. (2012). Automated finite element updating using strain data for the lifetime reliability assessment of bridges. *Reliability Engineering & System Safety*, *99*, 139–150. doi:10.1016/j.ress.2011.11.007

Olafsson, A., Jeraj, R., & Wright, S. J. (2005). Optimization of intensity-modulated radiation therapy with biological objectives. *Physics in Medicine and Biology*, *50*(22), 5357–79. doi:10.1088/0031-9155/50/22/010

Palombi, L., Bernava, G. M., Nucita, A., Giglio, P., Liotta, G., Nielsen-Saines, K., … Marazzi, M. C. (2012). Predicting trends in HIV-1 sexual transmission in sub-Saharan Africa through the Drug Resource Enhancement Against AIDS and Malnutrition model: antiretrovirals for 5 reduction of population infectivity, incidence and prevalence at the district level. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *55*(2), 268–75. doi:10.1093/cid/cis380

Palombi, L., Marazzi, M. C., Guidotti, G., Germano, P., Buonomo, E., Scarcella, P., … De Luca, A. (2009). Incidence and predictors of death, retention, and switch to second-line regimens in antiretroviral- treated patients in sub-Saharan African Sites with

comprehensive monitoring availability. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *48*(1), 115–122.

Patten, S. B. (2007). An animated depiction of major depression epidemiology. *BMC Psychiatry*, *7*, 23. doi:10.1186/1471-244X-7-23

Peffer, D., Osman, N. B., & Vaz, P. (2002). Cost–benefit analysis of a PMTCT program in Mozambique. *Evaluation and Program Planning*, *25*(4), 433–445. doi:10.1016/S0149-7189(02)00054-X

Perelson, A. S. (2002). Modelling viral and immune system dynamics. *Nature Reviews Immunology*, *2*(1), 28–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11905835

Phillips, A. N., Pillay, D., Miners, A. H., Bennett, D. E., Gilks, C. F., & Lundgren, J. D. (2008). Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: a computer simulation model. *Lancet*, *371*(9622), 1443–51. doi:10.1016/S0140-6736(08)60624-8

Pierskalla, W. P., & Brailer, D. J. (1994). Applications of Operational Research in Health Care Delivery. Handbooks in OR & MS.

Pinkerton, S. D., Bogart, L. M., Howerton, D., Snyder, S., Becker, K., & Asch, S. M. (2010). Cost of rapid HIV testing at 45 U.S. hospitals. *AIDS Patient Care and STDs*, *24*(7), 409–413. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2933554&tool=pmcentrez&rendertype=abstract

Piroth, L., Fournel, I., Mahy, S., Yazdanpanah, Y., Rey, D., Rabaud, C., … Binquet, C. (2005). A decision tree to help determine the best timing and antiretroviral strategy in HIV-infected patients. *Epidemiology and Infection*, *20*(1), 23–25. doi:10.1017/S0950268810002980

Porco, T. C., Small, P. M., & Blower, S. M. (2001). Amplification dynamics: predicting the effect of HIV on tuberculosis outbreaks. *Journal of Acquired Immune Deficiency Syndromes 1999*, *28*(5), 437–444. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11744831

Raimundo, S. M., Engel, A. B., Yang, H. M., & Bassanezi, R. C. (2003). An Approach to Estimating the Transmission Coefficients for AIDS and for Tuberculosis Using Mathematical Models. *Systems Analysis Modelling Simulation*, *43*(4), 423–442. doi:10.1080/02329290290027175

Rais, A., & Viana, A. (2011). Operations Research in Healthcare: a survey. *International Transactions in Operational Research*, *18*(1), 1–31. doi:10.1111/j.1475-3995.2010.00767.x

Rauner, M. S., Brailsford, S. C., & Flessa, S. (2004). Use of discrete-event simulation to evaluate strategies for the prevention of mother-to-child transmission of HIV in developing countries. *Journal of the Operational Research Society*, *56*(2), 222–233. doi:10.1057/palgrave.jors.2601884

Resch, S., Lee, M., Kombe, G., Sinyinza, E., Wong, W., & Wehbe, S. (2008). *Sustainability Analysis of HIV/AIDS Services in Zambia*.

Richardson, L., & Grund, T. (2012). Modeling the impact of supra-structural network nodes: The case of anonymous syringe sharing and HIV among people who inject drugs. *Social Science Research*, *41*(3), 624–636. doi:10.1016/j.ssresearch.2011.12.004

Robberstad, B., & Evjen-Olsen, B. (2010). Preventing mother to child transmission of HIV with highly active antiretroviral treatment in Tanzania--a prospective cost-effectiveness study. *Journal of Acquired Immune Deficiency Syndromes*, *55*(3), 397–403. doi:10.1097/QAI.0b013e3181eef4d3

Roberts, C., & Dangerfield, B. (1990). Modelling the Epidemiological Consequences of HIV Infection and AIDS : A Contribution from Operational Research. *The Journal of the Opersational Research Society*, *41*(4), 273 – 289.

Robinson, S. (1997). Simulation Maidel Verification And Validation: Increasing The Users' Confidence. *Winter Simulation Conference Proceedings,*.

Robinson, S. (2004). *Simulation : The Practice of Model Development and Use*. John Wiley and Sons, Ltd.

Roeger, L.-I. W., Feng, Z., & Castillo-Chavez, C. (2009). Modeling TB and HIV co-infections. *Mathematical Biosciences and Engineering MBE*, *6*(4), 815–837. doi:10.3934/mbe.2009.6.815

Royston, P., & Lambert, P. C. (2011). *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model* (Vol. 8272). Stata Press. Retrieved from http://www.stata.com/bookstore/flexible-parametric-survival-analysis-stata/

Salomon, J. a, Gakidou, E. E., Murray, C. J. L., & Ebd, E. I. P. G. P. E. (1999). *Methods for Modeling the HIV/AIDS Epidemic in Sub-Saharan Africa*.

Sanne, I. M., Westreich, D., Macphail, A. P., Rubel, D., Majuba, P., & Van Rie, A. (2009). Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study. *Journal of the International AIDS Society*, *12*(1), 38. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2811100&tool=pmcentrez&rendertype=abstract

Satten, G. A., & Longini Ira M, J. (1996). Markov Chains With Measurement Error: Estimating the `True' Course of a Marker of the Progression of Human Immunodeficiency Virus

Disease. *Applied Statistics*, *45*(3), 275–309. Retrieved from http://links.jstor.org/sici?sici=0035-9254(1996)45:3<275:MCWMEE>2.0.CO;2-I

Schackman, B. R., Metsch, L. R., Colfax, G. N., Leff, J. a., Wong, A., Scott, C. a., … Walensky, R. P. (2012). The cost-effectiveness of rapid HIV testing in substance abuse treatment: Results of a randomized trial. *Drug and Alcohol Dependence*. doi:10.1016/j.drugalcdep.2012.08.009

Schwarz, G. (1978). Estimating the Dimension of a Model. *The Annals of Statistics*, *6*(2), 461–464.

Simpson, K. N., Strassburger, A., Jones, W. J., Dietz, B., & Rajagopalan, R. (2009). Comparison of Markov model and discrete-event simulation techniques for HIV. *PharmacoEconomics*, *27*(2), 159–165. doi:10.2165/00019053-200927020-00006

Simul8 Corporation. (2011). *SIMUL8 Corporation, Cochrane House, 29 Cochrane Street, Glasgow G1 1HL, Scotland, United Kingdom*. Retrieved from www.simul8.com

Sloot, P. M. A., Ivanov, S. V, Boukhanovsky, A. V, Van De Vijver, D. A. M. C., & Boucher, C. A. B. (2008). Stochastic simulation of HIV population dynamics through complex network modelling. *International Journal of Computer Mathematics*, *85*(8), 1175–1187. doi:10.1080/00207160701750583

Smith, D. B., & Aaronson, W. (2003). The perils of healthcare workforce forecasting: a case study of the Philadelphia metropolitan area. *Journal of Healthcare Management American College of Healthcare Executives*, *48*(2), 99–110; discussion 110–111.

Smith, H. K., Harper, P. R., Potts, C. N., & Thyle, A. (2009). Planning sustainable community health schemes in rural areas of developing countries. *European Journal Of Operational Research*, *193*(3), 768–777. Retrieved from http://eprints.soton.ac.uk/149835/

Smith, P. C., & van Ackere, A. (2002). A note on the integration of system dynamics and economic models. *Journal of Economic Dynamics and Control*, *26*(1), 1–10. doi:10.1016/S0165-1889(00)00025-7

Stahl, J. E. (2008). Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. *PharmacoEconomics*, *26*(2), 131–148. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18198933

Stover, J. (1999). Influence of Mathematical Modelling of HIV and AIDS on Policies and Programs in the Developing World. *Sexually Transmitted Diseases*, 572 – 578.

Sullivan, P. S., Carballo-Diéguez, A., Coates, T., Goodreau, S. M., McGowan, I., Sanders, E. J., … Sanchez, J. (2012). Successes and challenges of HIV prevention in men who have sex with men. *Lancet*, *380*(9839), 388–99. doi:10.1016/S0140-6736(12)60955-6

Tagar, E., Sundaram, M., Condliffe, K., Over, M., Matatiyo, B., Chimbwandira, F., … Gwinnell, D. (2014). Multi-Country analysis of treatment costs for HIV/AIDS (MATCH): Facility-

Level ART Unit Cost Analysis in Ethiopia, Malawi, Rwanda, South Africa and Zambia. *PLoS ONE*, *In Press*(11). doi:10.1371/journal.pone.0108304

Tang, L., Song, J., Belin, T. R., & Unützer, J. (2005). A comparison of imputation methods in a longitudinal randomized clinical trial. *Statistics in Medicine*, *24*(14), 2111–2128.

Tao, R., & Tam, C.-M. (2012). System reliability optimization model for construction projects via system reliability theory. *Automation in Construction*, *22*, 340–347. doi:10.1016/j.autcon.2011.09.012

Taylor, K., & Lane, D. (1998). Simulation applied to health services: opportunities for applying the system dynamics approach. *Journal of Health Services Research Policy*, *3*(4), 226–232. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=10187203;

Tebas, P., Henry, K., Nease, R., Murphy, R., Phair, J., & Powderly, W. G. (2001). Timing of antiretroviral therapy. Use of Markov modeling and decision analysis to evaluate the long-term implications of therapy. *AIDS (London, England)*, *15*(5), 591–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11316996

Tekwe, C. D., Carroll, R. J., & Dabney, A. R. (2012). Application of Survival Analysis Methodology to the Quantitative Analysis of LC-MS Proteomics Data. *Bioinformatics*, *28*(15), 1998–2003. doi:10.1093/bioinformatics/bts306

Titman, A. C., & Sharples, L. D. (2009). Model diagnostics for multi-state models. *Statistical Methods in Medical Research*, *19*(6), 621–651. Retrieved from http://dx.doi.org/10.1177/0962280209105541

Torpey, K., Kabaso, M. E., Mutale, L. N., Kamanga, M. K., & Mwango, A. J. (2008). Adherence Support Workers : A Way to Address Human Resource Constraints in Antiretroviral Treatment Programs in the Public Health Setting in Zambia. *Public Health*, *3*(5). doi:10.1371/journal.pone.0002204

Torpey, K., Lartey, M., Amenyah, R., Addo, N. A., Obeng-Baah, J., Rahman, Y., … Colebunders, R. (2009). Initiating antiretroviral treatment in a resource-constrained setting: does clinical staging effectively identify patients in need? *International Journal of STD & AIDS*, *20*(6), 395–398.

Trofimov, A., Vrancic, C., Chan, T. C. Y., Sharp, G. C., & Bortfeld, T. (2008). Tumor trailing strategy for intensity-modulated radiation therapy of moving targets. *Medical Physics*, *35*(5), 1718–1733. Retrieved from http://link.aip.org/link/MPHYA6/v35/i5/p1718/s1&Agg=doi

Twisk, J., & De Vente, W. (2002). Attrition in longitudinal studies: How to deal with missing data. *Journal of Clinical Epidemiology*, *55*(4), 329–337.

UNAIDS. (2008). *Fast facts about HIV*.

UNAIDS. (2009). *HIV Prevention fast Facts*.

UNAIDS. (2010). *Global Report: UNAIDS report on the global AIDS epidemic 2010*.

UNAIDS. (2011). *UNAIDS World AIDS Day report - 2011*. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_en.pdf

UNAIDS. (2012). *UNAIDS Report on the global AIDS epidemic - 2012*. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_with_annexes_en.pdf

UNAIDS. (2013). *Global Report: UNAIDS report on the global AIDS epidemic 2013*.

UNAIDS. (2014). *UNAIDS Global Statistics Fact Sheet 2014*. Retrieved from http://www.gwec.net/global-figures/graphs/

Vaughan, T. G., Drummond, P. D., & Drummond, A. J. (2012). Within-host demographic fluctuations and correlations in early retroviral infection. *Journal of Theoretical Biology*, *295*, 86–99. doi:10.1016/j.jtbi.2011.11.016

Vercelli, M., Lillini, R., Capocaccia, R., & Quaglia, A. (2012). Use of SERTS (Socio-Economic, health Resources and Technologic Supplies) models to estimate cancer survival at provincial geographical level. *Cancer Epidemiology*, 1–9. doi:10.1016/j.canep.2012.07.010

Vermeulen, I. B., Bohte, S. M., Elkhuizen, S. G., Lameris, H., Bakker, P. J. M., & La Poutré, H. (2009). Adaptive resource allocation for efficient patient scheduling. *Artificial Intelligence in Medicine*, *46*(1), 67–80. doi:10.1016/j.artmed.2008.07.019

Vieira, I. T., Cheng, R. C. H., Harper, P. R., Senna, V., & De Senna, V. (2010). Small world network models of the dynamics of HIV infection. *Annals of Operations Research*, *178*(1), 173–200. doi:10.1007/s10479-009-0571-y

Walensky, R. P., Paltiel, a D., Losina, E., Mercincavage, L. M., Schackman, B. R., Sax, P. E., … Freedberg, K. A. (2006). The survival benefits of AIDS treatment in the United States. *The Journal of Infectious Diseases*, *194*(1), 11–9. doi:10.1086/505147

Walensky, R. P., Wood, R., Fofana, M. O., Martinson, N. a, Losina, E., April, M. D., … Paltiel, D. A. (2011). The clinical impact and cost-effectiveness of routine, voluntary HIV screening in South Africa. *Journal of Acquired Immune Deficiency Syndromes*, *56*(1), 26–35. doi:10.1097/QAI.0b013e3181fb8f24

Wandel, S., Egger, M., Rangsin, R., Nelson, K. E., Costello, C., Lewden, C., … Zwahlen, M. (2008). Duration from seroconversion to eligibility for antiretroviral therapy and from ART eligibility to death in adult HIV-infected patients from low and middle-income countries: collaborative analysis of prospective studies. *Sexually Transmitted Infections*, *84*(Suppl_1), i31–i36. Retrieved from

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2569418&tool=pmcentrez&rendertype=abstract

Ward, A., Bozkaya, D., Fleischmann, J., Dubois, D., Sabatowski, R., & Caro, J. J. (2007). Modeling the economic and health consequences of managing chronic osteoarthritis pain with opioids in Germany: comparison of extended-release oxycodone and OROS hydromorphone. *Current Medical Research and Opinion*, *23*(10), 2333–45. doi:10.1185/030079907X219643

Welte, R., Van Den Dobbelsteen, G., Bos, J. M., De Melker, H., Van Alphen, L., Spanjaard, L., … Postma, M. J. (2004). Assessing the impact of wastage on pediatric vaccine immunization formulary costs using a vaccine selection algorithm. *Vaccine*, *22*(4), 2307–2315. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15530695

White, L., Smith, H., & Currie, C. (2011). OR in developing countries: A review. *European Journal of Operational Research*, *208*(1), 1–11. doi:10.1016/j.ejor.2010.02.015

WHO UNAIDS UNICEF. (2011). *Global HIV/AIDS Response: Epidemic update and health sector progress towards Universal Access*. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20111130_UA_Report_en.pdf

Williams, J. R., Foss, A. M., Vickerman, P., Watts, C., Ramesh, B. M., Reza-Paul, S., … Boily, M.-C. (2006). What is the achievable effectiveness of the India AIDS Initiative intervention among female sex workers under target coverage? Model projections from southern India. *Sexually Transmitted Infections*, *82*(5), 372–380. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17012512

World Bank. (2011). World Bank Country and Lening Groups. Retrieved from http://data.worldbank.org/about/country-classifications/country-and-lending-groups

World Health Organization. (2004). *Scaling up Antiretroviral Therapy In Resource-Limited Settings: Treatment Guidelines for a Public Health Approach*. Retrieved from http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf

World Health Organization. (2006). *Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach*. Retrieved from http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

World Health Organization. (2010a). *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*.

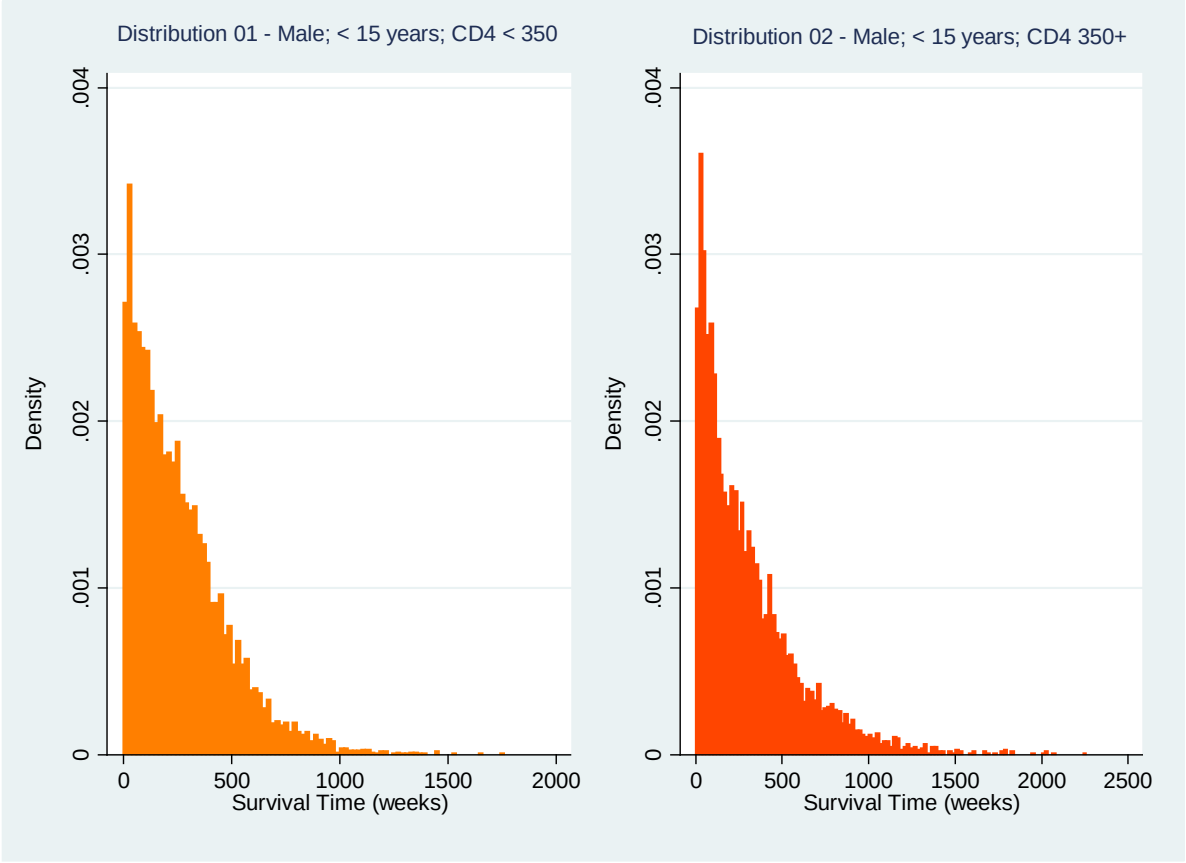
World Health Organization. (2010b). *Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations for a public health approach*. *World Health*.

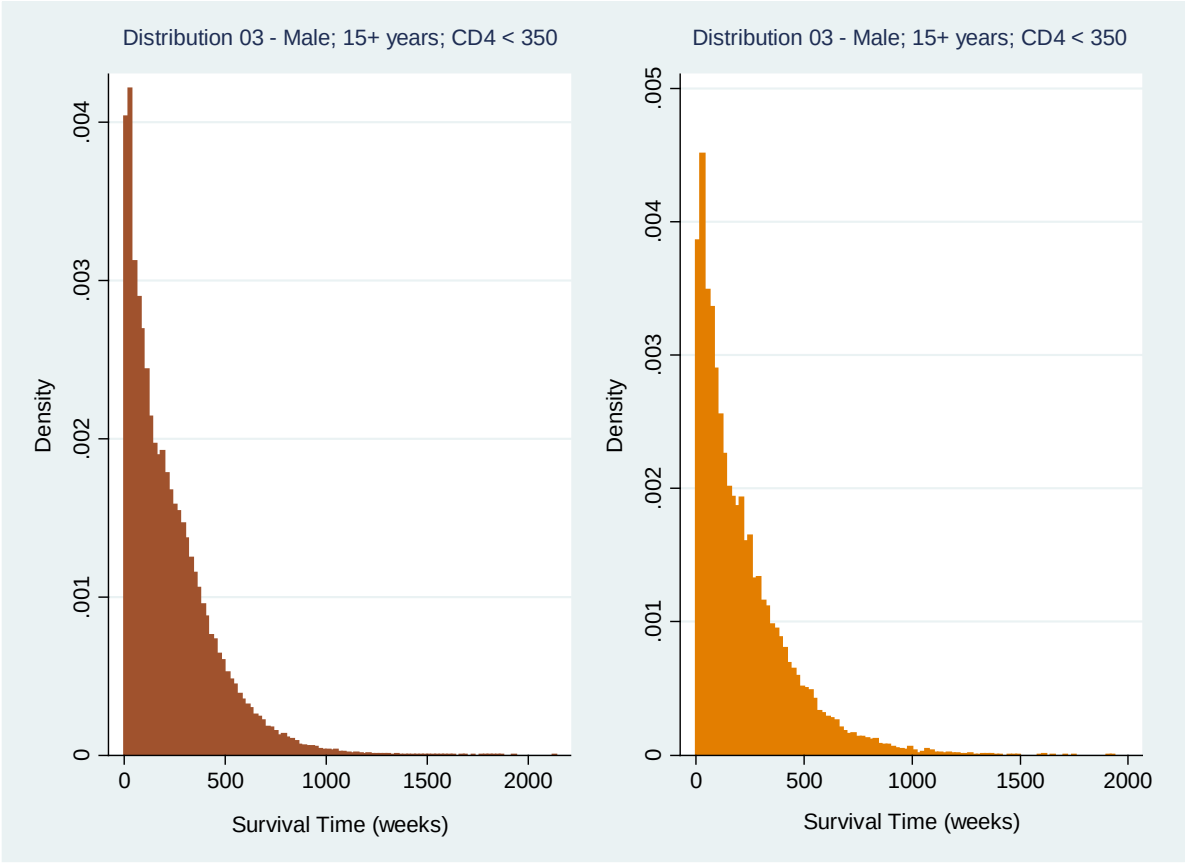
Yazdanpanah, Y., Goldie, S. J., Losina, E., Weinstein, M. C., Lebrun, T., Paltiel, D. A., … Freedberg, K. A. (2002). Lifetime cost of HIV care in France during the era of highly active antiretroviral therapy. *Antiviral Therapy*, *7*(4), 257–66. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12553480

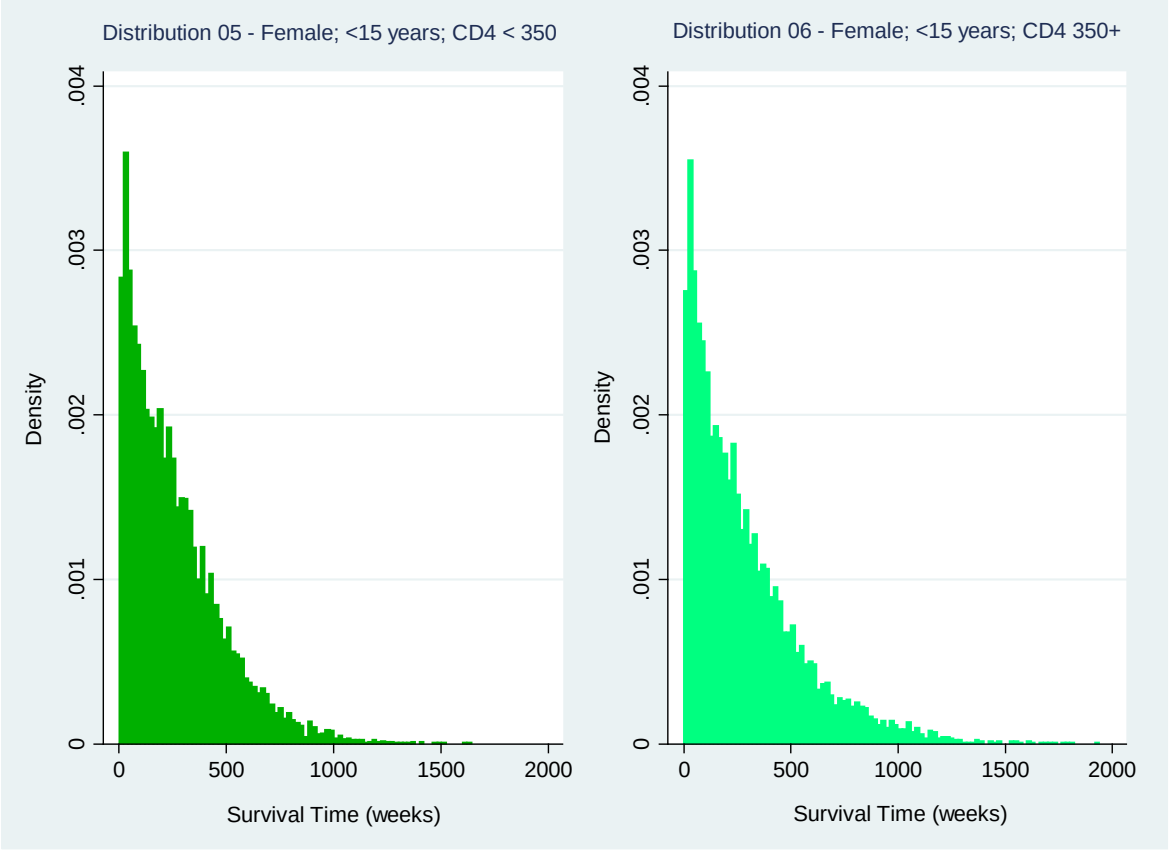
Yiannoutsos, C. T. (2009). Modeling AIDS survival after initiation of antiretroviral treatment by Weibull models with changepoints. *Journal of the International AIDS Society*, *12*(1), 9. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2715375&tool=pmcentrez&rendertype=abstract

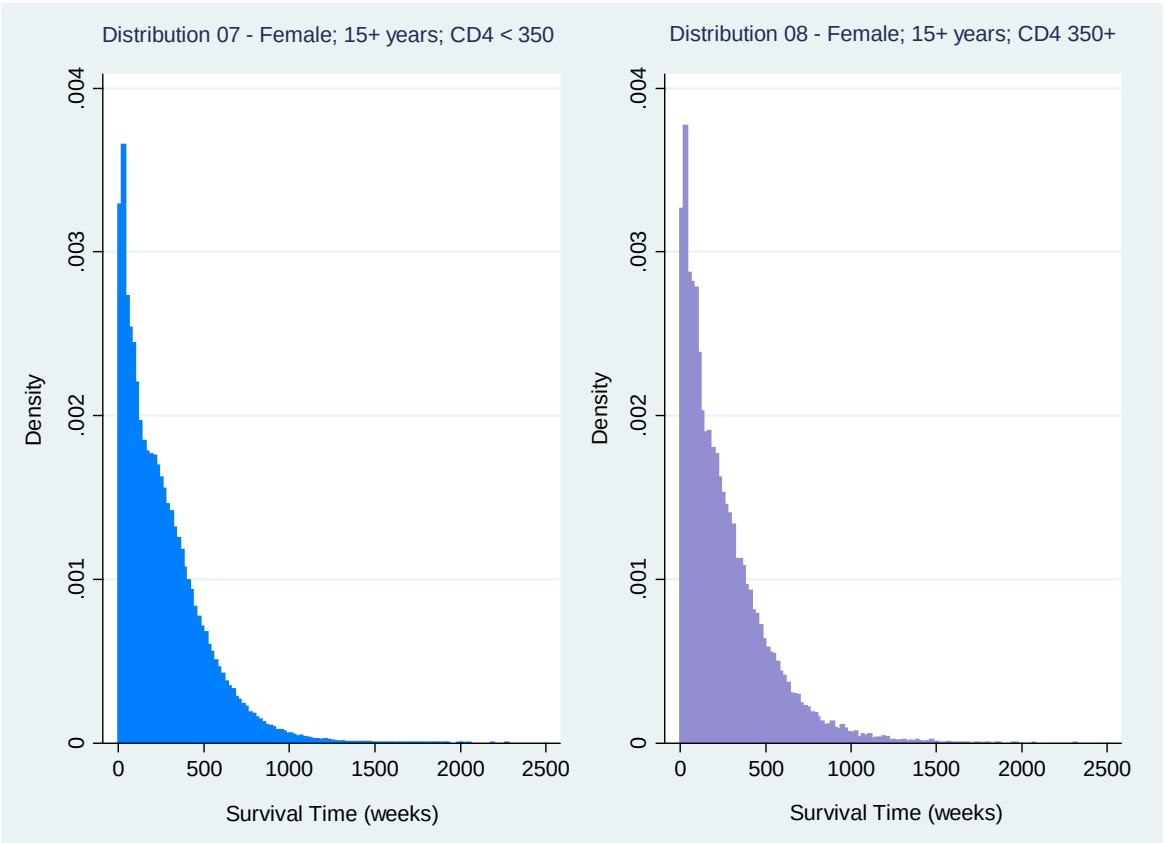
Yuan, Y., & Allen, L. J. S. (2011). Stochastic models for virus and immune system dynamics. *Mathematical Biosciences*, *234*(2), 1–9. doi:10.1016/j.mbs.2011.08.007

APPENDIX I: Distributions

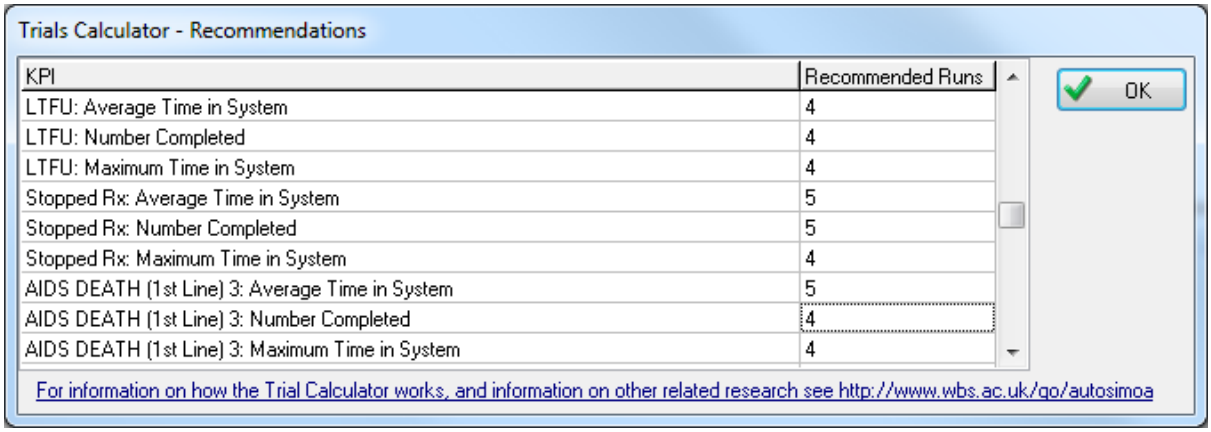





Distribution 05 - Female; <15 years; CD4 < 350
Density
0
.001
.002
.003
.004
0
500
1000
1500
2000
Survival Time (weeks)
Distribution 06 - Female; <15 years; CD4 350+
Density
0
.001
.002
.003
.004
0
500
1000
1500
2000
Survival Time (weeks)


Distribution 07 - Female; 15+ years; CD4 < 350
Density
0
.001
.002
.003
.004
0
500
1000
1500
2000
2500
Survival Time (weeks)
Distribution 08 - Female; 15+ years; CD4 350+
Density
0
.001
.002
.003
.004
0
500
1000
1500
2000
2500
Survival Time (weeks)

APPENDIX II: **Number of runs**



APPENDIX III: **Present value calculations of the cost of ART in the future**

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Dollar amount	$278	$292	$294	$300	$284	$280	$287	$294	$299	$304	$309	$313	$317	$320	$322
Discounted dollar amount										$239					$201
Exchange rate	4.80	4.86	5.15	5.39	6.15	6.59	6.79	6.99	7.20	7.42	7.64	7.87	8.11	8.35	8.60
Consumer Price Index (2010=100)	100.00	106.44	113.44	121.35	130.83	138.54	146.25	153.95	161.66	169.37	177.08	184.79	192.49	200.20	207.91
Kwacha equivalent @ 2010 prices	1,333.60	1,419.43	1,512.77	1,618.33	1,744.77	1,847.56	1,950.35	2,053.14	2,155.94	2,258.73	2,361.52	2,464.31	2,567.10	2,669.89	2,772.68
Discounting factor (3.5%)						0.97	0.93	0.90	0.87	0.84	0.81	0.79	0.76	0.73	0.71