Disparities in HIV/AIDS Progression among Children
A Case of Uganda

Ssebiryo Francis Exavious
S1986236
f.ssebiryo.student@rug.nl

Master Thesis,
Master of Science in Population Studies

Supervisor: Dr. Eva Kibele

Population Research Centre,
University of Groningen

August 2011
Groningen, the Netherlands.

Abstract

Background: Uganda has an outstanding account of HIV/AIDS in the sub Saharan region and on global scope. The chronic nature of HIV/AIDS requires many resources in its management, yet knowledge on the rate of HIV infection transition from one stage to another is scanty. *Relevance*: This study sheds light on the estimates of HIV infection progression and its co-factors among children to inform policy intervention into universal and equitable access to ART. *Theory*: The study adopts the lifecourse theoretical perspective to appraise the chronological effect of demographic and socioeconomic factors on the lifecourse of HIV-AIDS. *Methods*: A 136 months retrospective follow-up of 59 children aged 0-15; Kaplan Meier and Cox proportional hazard model were methods of analysis. *Results*: Children contributed 5,108 person months on HIV infection lifecourse of which 55% is lived with asymptomatic stage. The duration of exposure to HIV infection contributed in each stage decreases with progressive amplification in the infection. There is increasingly short expectation of life and great probability of HIV infection progression once a child progresses from asymptomatic stage. Age at initiation of treatment, caregivers, father's survival and religious affiliation causes disparities in HIV infection progression. HIV infection progression was independent of sex of a child, birth-weight and mother's survival.
Conclusion: To optimize survival time on HIV infection lifecourse, HIV/AIDS care and treatment should strive to maintain HIV infection within asymptomatic levels yet initiating treatment on the earliest time possible. Adequate management and monitoring of the infection should prioritize early diagnosis through PMTCT and routine medical reviews.

Keywords: *HIV/AIDS, HIV-infection-progression, HIV-infection stages, Children, Survival-time, HIV/AIDS-lifecourse, ART, Disparities, Co-factors*

Acknowledgement

My word of thanks goes to Eric Bleumink Fund and to the entire Ubbo Emmius Fonds, University of Groningen for its establishment and generosity made it possible to accomplish my Master Studies. I echo the same note of gratitude my supervisor Eva Kibele (PhD) for her encouragement, guidance and suggestions that shaped my conscience to the completion of this research project. I am also very grateful to the entire staff at Population Research Centre (PRC), Faculty of Spatial Sciences, for the many encounters we have shared knowledge; I have scooped the lion's share.

To my coordinator at Mildmay Uganda, Esther Kawuma, you did a great job, thanks a lot for the cordial time. To all my colleagues in the Programme MSc. Population Studies and all at the Faculty, you were a wonderful people who made the study environment jovial.

Lastly, I applaud my Family for your benevolent support, colleagues and friends for your support bestowed to me. I remain greatly indebted to you all.

Reflection

Bazibumbira kwa'tika - ne'ziramira mukyo'kero.

Lit: Moulded to succumb, yet survive through the kiln.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ABC	:	Abstinence, Being faithful and Condom use
AHRQ	:	Agency for Healthcare Research and Quality
AIDS	:	Acquired Immunodeficiency Syndrome
ART	:	Antiretroviral Therapy
ARV	:	Antiretroviral
CD4	:	Cluster of Differentiation 4
CLWH	:	Children Living with HIV/AIDS
HIV	:	Human Immunodeficiency virus
Mug	:	Mildmay Uganda
MDG	:	Millennium Development Goals
MoH	:	Ministry of Health (Uganda)
MSLT	:	Multi State Life Table
MTCT	:	Mother to Child Transmission
MUREC	:	Mildmay Uganda research and Ethics Committee
NIH	:	National Institute of Health
NSP	:	National Strategic Plan
PTINO	:	Patience Identification Number
PLWH	:	People Living with HIV/AIDS
PMTCT	:	Prevention of Mother to Child transmission
STI/D	:	Sexually Transmitted Infections/ Diseases
UN	:	United Nations
UNAIDS	:	Joint United Nations Programme on HIV/AIDS
UNCST	:	Uganda National council for Science and Technology
USAID	:	United States Agency for International Development
VCT	:	Counselling and Testing
WHO	:	World Health Organization

Chapter One: Background to the Study

1.1 Introduction

Uganda has seen improved access to Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) care and treatment in the recent past especially through a corroborative effort between the central government and civil society organizations, though there are still constraints to universal access (61%) in the society (MoH, 2009). In the same way, more efforts goes to improving population health indicators as regards the UN millennium commitments such as, delivering an effective HIV prevention, treatment, care and support needed to curb the global HIV/AIDS epidemic by 2015. Indeed, the number of adolescents who acquired HIV infection through perinatal transmission is now increasing (NIH, 2010), indicating a delayed HIV progression, that is the transition from HIV infection to AIDS or WHO stage IV (WHO, 2007a) due to the improvement in HIV care and treatment.

However, HIV/AIDS continue to grapple Sub-Saharan Africa in general and Uganda in particular, with an estimated 22.5 million adult and children living with HIV/AIDS (CLWH) in 2009, and 1.3 million adult and children having died of AIDS-related causes in Sub-Saharan Africa (AVERT, 2011). In Uganda, 1.2 million people (150,000 children <15) were seropositive and 64,000 persons died of HIV/AIDS and related causes in 2009 yet access to ART is limited to 39% of those in need (UNAIDS, 2010).

With HIV/AIDS care and treatment, Antiretroviral Therapy (ART) there is improved survival and health among both children and adults living with HIV/AIDS (NIH, 2010). Thus with advent of ART and HIV/AIDS care and treatment among children and adults, there is advances in improved health living, reduced morbidity. People on ART and HIV/AIDS care and treatment progresses through HIV infection slowly but this differ from individual to individual (Zwahlen & Egger, 2006). Indeed, Blanche et al. (1997) indicates higher mortality among infants living with HIV/AIDS than those aged 1- 6 years of age but the study was limited to paediatric HIV. This makes information on children as a whole and the effect of social economic factors on HIV progression in children scanty. The NIH (2010) indicates that, infants may have faster progression of HIV than do other childhood ages (1-5 years), and have recommended infants to start antiretroviral treatment regardless of their clinical status, CD4 percentage, or viral load.

In addition, only a few studies considered health disparities and socioeconomic characteristic (Hall et al., 2004), but have not paid much attention on disparities in HIV/AIDS progression among population subgroups. Social groups witness different patterns of morbidity and mortality based on socioeconomic status, and access to care. Indeed persons in low social economic status experience poorer health than their counterparts in more advantaged socioeconomic status (AHRQ, 2001).

1.2 Objective and Research Questions

The main objective of this study is to examine the HIV/AIDS progression among children and associated factors following WHO (2007a) immunological staging of established HIV infection (Table 1). In other words, the study set out to describe the HIV/AIDS lifecourse and the factors associated with HIV/AIDS progression among children on HIV/AIDS care and Treatment. Henceforth, the study seeks to answer the following specific research questions:

1. What is the expected duration of stay in each HIV state for children living with HIV/AIDS?
2. What is the proportion of the remaining lifetime that is spent in a given HIV stage for children in Uganda?
3. What are the transition probabilities from a given HIV state to another for children living with HIV/AIDS?
4. What demographic and socioeconomic factors effect differences in HIV/AIDS (event time) progression among children living with HIV/AIDS (CLWH)?

Therefore, this study provides an input in assessing the contribution of HIV/AIDS care and treatment towards improving lives of HIV seropositive persons by estimating survival rates at each stage of HIV progression. That is, the gains of the life-prolonging effect of HIV care and treatment or antiretroviral therapy in improving child health (averting morbidity and mortality). This is a direct contribution to how HIV/AIDS care and treatment programs effort towards attaining the fourth UN millennium development goal (MDG) of reducing under five mortality. Furthermore, results from this study will help to focus treatment guarding against ARV treatment discontinuation. This is essential in maintaining the health benefits of the therapy and in averting viral resistance to drugs and other adverse side effects. In addition, provide information for policy intervention to enhance equity or equal access and health benefit of ART to those who are disadvantaged because of their demographic and socioeconomic traits.

1.3 Rationale

HIV causes chronic infection that requires life-long treatment once one starts the therapy. With HIV/AIDS care and treatment or antiretroviral therapy, HIV-related mortality and morbidity are reduced, and the general quality of life of People Living with HIV/AIDS (PLWH) is improved (USAID, 2010; Schneider et al., 2005). However, how much this differ by individuals' socio-demographic factors along the lifecourse of HIV-AIDS, and the estimates of how many will develop AIDS and when is barely unknown (CDC, 2006).

In addition, while studies have reported on rapid HIV progression without Antiretroviral (ARV) treatment (Abrams et al., 2003), hardly a study has examined this scenario in the face of HIV care or ARV-treatment. Many a times, people of lesser socioeconomic status are highly vulnerable to deaths from certain causes such as malnutrition, yet they are preventable. Indeed, studies in the United States (US) have revealed higher burden of disease in minority population groups (AHRQ, 2001). However, there is dearth of information on how socioeconomic inequalities as factors documented for differences in cause-specific mortality (Bos et al., 2004) may affect HIV/AIDS transition rates among children.

Furthermore, there is considerable evidence of disparities in life expectancy, morbidity, risk factors, and quality of life among segments of the population, defined by, sex, education, income, location, among other aspects (AHRQ, 2001; CDC, 2011). Thus, with incessant HIV/AIDS care and treatment among PLWH, there is need to examine how different, a cohort features along the HIV/AIDS lifecourse. Certainly, we cannot claim overall progress in the fight against HIV/AIDS morbidity if there are certain populations that are disadvantaged

along the course of treatment. While some studies have found rapid HIV virus progression among infants (Newell et al., 2004), there is need to establish the transition rate of these CLWH from one stage of HIV to another. Furthermore, understanding population-health issues require a multidisciplinary approach that examines health determinants, disease and intervention at each stage of health transition, with critical emphasis on morbidity and mortality (Niessen, 2002).

1.4 Structure of Paper

This paper is composed of the Background (chapter one) which introduces and provides a brief description of HIV/AIDS epidemic and strategies of its management in Uganda. The chapter further gives the synopsis of the problem at hand that needs policy intervention, the objectives and research questions of the study.

Chapter two of the paper presents and discusses various theories on HIV/AIDS, its emergency, management on both global and Uganda's scope. The chapter further discusses the different co-factors for HIV infection progression, the theoretical perspective (lifecourse theory) in which the study situates its self. This chapter also presents the conceptual model for HIV infection progression, definition and Operationalization of concepts.

Chapter three of the paper presents and discusses the methodology of the study, including the sample design, description of the data sets, and quality of the data, data analysis and ethical considerations.

Chapter four presents the results of the study arranged systematic by study objectives, with a brief description and explanation of the results. Study results are in form of tables and graphs aggregated estimates of factors giving answers to the study questions.

Chapter Five of the paper presents the conclusion and recommendations reflecting on the study objectives and gaps identified in the study. A list of references and appendices appears at the end of the paper.

1.5 Summary of the Chapter

This chapter has given an introduction or the background of the study problem. It starts by describing Uganda's situation of dealing with HIV/AIDS epidemic and highlights the information gap that needs remedy. Specifying the objective and specific research questions, gives the study rationale fresh, which then describes the need and benefit the study, sets out to contribute to the existing body of literature. The chapter lastly presents a snapshot of the organization of the paper.

Chapter Two: Literature Review, Theories and Concepts

2.1 Introduction

This chapter presents literature and theories about HIV virus and infections, the HIV/AIDS epidemic, HIV/AIDS care and treatment. The chapter reviews literature on health determinants as well as biodemographic and socioeconomic cofactors of HIV/AIDS progression. In addition, the chapter describes the lifecourse perspective to conceptualize the HIV/AIDS lifecourse stage-by-stage progression. Then concepts are defined and operationalised, and a conceptual model summarizes the interplay of concepts.

2.2 Human Immunodeficiency Virus (HIV)

In 1959, the first case of HIV infection in a human research detected from a man in Kinshasa, Democratic Republic of the Congo. The term, *Acquired Immunodeficiency Syndrome* (AIDS) came in 1982 to describe the occurrences of opportunistic infections in an infected person. HIV came to limelight when research scientists discovered the virus that causes AIDS in 1983 code named HTLV-III/LAV (human T-cell lymphotropic virus-type III/lymphadenopathy-associated virus) which later changed to HIV (CDC, 2006).

Today, Human Immunodeficiency virus (HIV) virologist knows as a virus of the retrovirus family that causes Acquired Immunodeficiency Syndrome (AIDS), a condition characterized of flail human immune system (CDC, 2006). HIV infection occurs by transfer of body fluids (semen, blood, breast milk etc.) of an HIV-positive person to another, and there are various routes of HIV infection: unsafe sexual intercourse, mother to child transmission (MTCT) being the major route in sub Sahara African (UNAIDS, 2010).

HIV attacks the helper cells (the CD4+ T cells) and other vital cells in the human immune system (CDC, 2006). The impact of HIV is realized by the destruction and reducing the level of CD4+ T cells thereby slumping the immune level of the cells making the body prone to various opportunistic infections (Douek et al., 2009). The persistent progression of HIV virus and rate of destruction of the helper cells give way to the AIDS, a condition of flail immune system. With AIDS condition, a patient is prone to death shortly from any infirmity in absence of care and treatment.

The chronic nature of HIV encompasses four distinct stages from the time of infection to AIDS, these are hierarchical clinical stages that denotes especially the number or the percentage drop in CD4+ lymphocytes per mm3 (WHO, 2007a) coupled with identifiable opportunistic infections. The CD4+ lymphocytes per mm3 drop from the normal value of 1000 to less than 200 CD4+ lymphocytes per mm3 for an AIDS defining condition. There are four distinct states of HIV infection according to clinical and immunological status (CDC, 1994; NIH, 2010; WHO, 2007); asymptomatic/ not significant (N), mild symptomatic (A), moderately symptomatic/ advanced (B), and Severely symptomatic (C), the rate of progression of HIV to AIDS is dependent on individual biological and environmental factors. The advent of HIV/AIDS care and treatment, Anti-Retroviral Therapies (ART) has improved health of PLWH even with AIDS condition (Schneider et al., 2005; UNAIDS, 2010).

2.3 HIV/AIDS Epidemic

2.3.1 Global Epidemic

The world Health Organization declared the HIV infection, a pandemic for its global presence and threat to human life, HIV is responsible for over 25 million death since its discovery in 1981 (UNAIDS, 2006). At the end of the year 2009, 33.5 million globally and 22.5 million people in sub Sahara African were estimated to be living with HIV/AIDS. The global HIV/AIDS prevalence stands at 0.8% and 5% in sub Sahara Africa, 1.8 million adult, and children related deaths globally of which 1.3 millions are in sub Sahara Africa. These rates are decreasing from previous estimates especially among children due increased (30%) access to HIV antiretroviral therapy in the year 2009 as noted by UNAIDS (2010).

It is noted that the rate of new HIV infections has decreased though the number of children living with HIV/AIDS has increased to 2.5 million and the proportion of women to men living with HIV/AIDS has remained higher 52% (UNAIDS, 2010). Sub Sahara Africa shares the greatest pinch of HIV/AIDS with an estimated 5.6 million people living with the epidemic however, the incidence of HIV infection is seen to have declined by 25% in the year 2001-2009 period. In east Africa, the HIV/AIDS prevalence has stagnated between 3% in Rwanda to 6% in Uganda (UNAIDS, 2010).

2.3.2 HIV/AIDS in Uganda

Uganda is one of the countries in sub Sahara Africa that has witnessed the devastating pinch of HIV/AIDS. Research recorded the first case of HIV in Uganda in 1982, diagnosed among fishermen at Kesensero landing site on Lake Victoria (Serwada, et al., 1985). The infection threw the public into agony was locally named 'Slim' due to its devastating opportunistic infection and weight loss to the patients. Due to the dearth of information about the infection among the public, there was unprecedented high HIV prevalence especially in urban areas in early years of the epidemic to the tune of 29% (Serwada, et al., 1985).

However, the political commitment in late 1980s launched the AIDS Control Programme to combat the infection. The main HIV prevention campaign in Uganda has been Abstinence, Being faithfulness to one partner and Condom use (ABC) and Prevention of Mother to Child transmission (PMTCT). The Ugandan Ministry of Health began offering a free PMTCT service in a number of antenatal clinics in 2000, including Counselling and Testing (VCT) to all antenatal mothers and treatment to both mother and child following a positive diagnosis. The committed efforts to curb the epidemic has trimmed its prevalence from its highest in 1986 to 15% in 1991 and to 6.5% since 2001 among adults (UAC, 2007; UNAIDS, 2010).

The epidemic that has no cure, prevention is the best mean to combat the infection (UAC, 2007). However, the availability of now cheap generic drug formulas has intensified HIV/AIDS care and treatment of PLWH (MoH, 2009). ARV distribution programs in Uganda started in 1998 where patients had to pay for the cost of their medication at a subsidized cost (USAID, 2004). With funding from World Bank, Global Fund and PEPFAR, Uganda started offering free ARVs to PLWH, though only 24% of adults in need of ART have had access (WHO, 2007b). Current estimates from UNAIDS (2010) indicate that Uganda has 18% and 43% ARV coverage for children and adult respectively. This is perhaps due to the new ART guidelines, which recommends starting ARVs irrespective of the CD4 counts (WHO, 2008) since adult ARV coverage in 2006 stood over 54% (MoH, 2009). With 1.2 million people living with HIV/AIDS, HIV prevalence in Uganda has stabilized at 6.5% (MoH, 2009; UNAIDS, 2010) and given that the biggest percentage of ART program is donor funded, the

new WHO (2008) ART guideline faces significant challenges of sustainability if funding is compromised. This will potentially jeopardize accessibility to HIV/AIDS high-quality care and support services.

2.4 Antiretroviral Therapy (ART)

Antiretroviral or ARVs therapy is the main HIV/AIDS treatment; it is not a cure, but a safety net against alignments among PLWH for many years. ARV therapy prevents clinical complications of HIV and prolongs survival of patients (NIH, 2010; MoH, 2009). The treatment consists of a combination of drugs taken daily for a person's lifetime. When drugs are taken as prescribed, the ARV regimens stops any weakening of the immune system and allows it to recover from any damage that HIV might have caused already.

The antiretroviral drugs categories are of five major drug classes. Firstly, *Reverse Transcriptase (RT) Inhibitors* interfere with the critical step during the HIV life cycle known as reverse transcription. During this step, the HIV enzyme RT converts HIV RNA to HIV DNA. The most common drug combination given to those beginning treatment (first line) consists of two-nucleoside reverse transcriptase inhibitors (NRTIs) combined with either a non-nucleoside reverse transcriptase inhibitors (NNRTI) or a "boosted" protease inhibitor. Ritonavir (in small doses) is the most common booster prescription; it enhances the effects of other protease inhibitors for small dose administrations. These first line regimens are common in resource limited countries for they have a low pill burden and of low cost making them affordable (MoH, 2009).
Secondly, *Protease Inhibitors* interfere with the protease enzyme that HIV uses to produce infectious viral particles. *Fusion/Entry Inhibitors*: interfere with the virus' ability to fuse with the cellular membrane, thereby blocking entry into the host cell. Thirdly, *Integrase Inhibitors* block *integrase*, the enzyme HIV uses to integrate genetic material of the virus into its target host cell. Fourthly, *Multidrug Combination Products* combine drugs from more than one class into a single product to combat virus strains from becoming resistant to specific antiretroviral drugs (NIH, 2010). This is normally a second line therapy introduced after HIV has become resistant to the first line combination, or if side effects are particularly bad. Second line therapy or Highly Active Anti-Retroviral Treatment (HAART) ideally includes a minimum of three new drugs, with at least one from a new class, in order to increase treatment success.

Initiation to ART is dependent on a number of factors the availability and price of drugs, the number of pills, and the side effects of the drugs. In Uganda, the Ministry of Health (2009) recommends starting ART only in those patients who are symptomatic and/or have evidence of significant immune system damage. ARVs adherence is vital to successful benefit of treatment; non-adherence can lead to the development of drug resistance and increase likelihood of virologic failure (NIH, 2010).

2.5 Factors Associated with Health

Health of an individual is dependent on many factors including socioeconomic and physical environment, and a person's own characteristics and behaviours. Indeed, income, education physical environment and social support, access to health services, gender and genetic makeup of a person are potent determinants of one's health status. Educational attainment is a vital resource in accumulating knowledge and skills in the lifecourse, positive attitude to health behaviours (Caldwell, 1993). In addition, it has a direct relationship with improved livelihood, access to better quality food and housing and health-care services (CDC, 2011).

Furthermore, demographic and socioeconomic status are major factors influencing the utilization of a healthcare system, people of low socioeconomic status often have higher mortality rates. There are cultural differences in child healthcare as regards nurturing and feeding practices responsible for wide child survival differentials. Religion is another factor that influences child survival, religion is responsible for different attitudes families adopt towards care and values of children. Religious affiliation enhances psychological health and instils a sense of higher life satisfaction. Yet, other religious beliefs extend fatalistic attitudes and beliefs to children (Asser & Swan, 1998) affect utilization of health services such as immunization (Antai, 2009). In the same way, distance to health services is an important factor in access to health care with numerous studies describing an inverse relationship between distance and utilization across many diseases (Hall et al., 2004).

Many a times, people with lower socioeconomic status suffer higher mortality, also from preventable causes. Socioeconomic inequalities are responsible for differences in cause-specific mortality between population groups. Often, excess mortality from infectious diseases is among low status population groups especially in young ages and older ages (AHRQ, 2001).

Furthermore, conditions during the early years of life are also contributor of vulnerability to certain diseases due to inherent latency of childhood infections or disease exposure (Lintje et al., 2007). Early childhood nutrition, immunization and the actual environment where a child grows up can have a profound health effect later in life (WHO, 2009). Health differences are common between urban and rural areas, even when demographic and socioeconomic differences between populations are controlled. Affluent communities often have better means to promote hygienic and are better able to take advantage of improvements in medical care (Omran, 1998).

It is also often common that men and women have different vulnerability to disease, this is true given the different gender role men and women assume in the society. Society or culture accord different roles and position to men and women, this exposes the two to different health risks in life. While men may be culprit of occupational health risk women are often victim of reproductive health risks. This gender inequality heightens women's exposure and vulnerability to health risks, limited access to healthcare and information (WHO, 2009).There various gender discriminations based on nutrition (food taboos), status, that put them at a greater health risk than their male counterparts. Caldwell (1993) gives a good example of this gendered discrimination families accorded to their children in regards to healthcare and treatment. This gendered discrimination emanates from the values culture inculcates to men and women in the society.

2.6 Cofactors of HIV/AIDS Progression

Various biodemographic and socioeconomic factors influence (facilitating or impinging conditions) the rate of HIV infection or disease progression. These biodemographic and socioeconomic factors indentified include among others genetic factors, age, co-infections, sex, drug use, smoking and nutrition.

Specific genetic make-ups of a person are a crucial determining factor in the progression of HIV/AIDS. People living with HIV co-receptor molecule (CCR5) gene-1 mutation copy have a lower progression rate than those with two normal copies of CCR5 gene (NIH, 2010). These receptors influence the intensity of infections and consequently the rate of HIV disease progression by destabilizing normal cell activities (Michael et al., 1997).

Viral load is another crucial factor found to influence the rate of HIV infection progression.

Viral load refers to the amount of HIV in a person's blood. The amount of viral load is very influential to HIV infection progression at the time of viral set point. That is, persons with higher viral load have a higher risk of HIV progression (NIH, 2010; Klimas et al., 2008). Moreover, the percentage and absolute count of CD4+ lymphocytes, and the amount of viral load at time of first diagnosis are significant predictors of HIV infection progression (Rodriguez et al., 2010).

Furthermore, the HIV-1 virus subtype is another factor documented to influence the rate of HIV infection progression to WHO stage IV. This means that there are differences in severity of HIV strains. Thus, strong and weak HIV strains are associated with fast and slow HIV infection progression respectively. Persons living with HIV subtype C, D and G are 8 times at risk of progression to AIDS stage than their counterparts infected with subtype-A (Dyer et al., 1999; Kaleebu et al., 2002).

Age is another biological and social aspect, which is crucial in determining health of an individual. For example, infants or children and old people are associated with frail health status. In case of disease progression and particularly HIV infection, age is central in determining the survival and transition rate to AIDS stage. HIV progression is faster among infants and children under five years (Blanche et al., 1997). In addition, there is heightened HIV progression rate at age 40 years and over. Advanced ages (40+) are associated with progressive decline in manufacturing of CD4 cells (Klimas et al., 2008; Morgan et al., 1997).

Furthermore, there is evidence of a gendered effect on HIV infection progression. Females have an elevated risk to HIV infection progression than men (Rodriguez et al., 2010). However, there is still luck of a consensus on the effect of gender on HIV infection progression. A number of studies indicate absence of sex differences in HIV progression and attribute any difference to a lower viral set point among women than males (Dennis, 1998; Liu et al., 2004). At a low viral set point, HIV replication slows and white blood cells replaces it, which is independent of HIV infection progression (Liu et al., 2004).

Likewise, the true racial effect on HIV infection progression is unclear. Studies have found differing effect of HIV infection among white and black people (Page et al., 2009). However, these differences are usually due to differences in access and utilization of healthcare between the two groups. For example, the tendency for African-Americans to access ART at advanced stages is one factor behind racial differences in HIV progression (Page et al., 2009; Mockus, 2007). Thus, limited access to ART and treatment of opportunistic infections due to socioeconomic inequality may be behind these racial differences (Page et al., 2009).

Co-infection with other sexually transmitted diseases (STI/D) and hepatitis B and C virus increases the rate of HIV infection progression (Klimas et al., 2008). These infections facilitate easier and faster damage of cells by the HIV virus and subsequent weakening of the immune system. Continuous damage of the T- helper cell (CD4+) weaken the immune system and give way for other opportunistic infections (Dennis, 1998). Indeed, unsafe sexual practices, a potential route for STI/D co-infection are significantly associated with increased HIV infection progression (Rodriguez et al., 2010). In addition, the presentation of infections such as oral candidiasis or Kaposi's sarcoma in earlier stages of HIV infection is associated with faster progression. This is due to increased impaired immunologic function of the body (Little et al., 2007; Dennis, 1998).

As observed earlier, the rate of HIV infection progress accrues from interplay of both biological and socioeconomic factors. The following paragraphs review the contribution of socioeconomic factors other than biological factors to facilitate or hamper the HIV infection progression rate.

Social behaviours such as alcohol consumption, smoking and drug use are also associated with increased rates of HIV progression. Alcoholism is associated with the development of opportunistic infections such as tuberculosis following impaired immune system. PLWH and with a long history of alcohol consumption, and still consuming alcohol have faster HIV infection rates. In addition, studies have observed a strong relationship between alcoholism, drug abuse and depression, which eventually interrupts the course of HIV/AIDS treatment (Klimas et al., 2008). Drug use may interfere with compliance to treatment and appointment schedule yet adherence to treatment has a significant effect on viral load (Klimas et al., 2008; Ironson et al., 2008).

Furthermore, social support has a profound positive effect in management of chronic illness. Social support boosts psychological wellbeing of a person and instils a sense of belongingness. This makes people feel secure and comforted knowing that there people to turn to for information and guidance. Indeed, marriage couples living with HIV/AIDS show positive results as regards to ART adherence than singles. This is because of social support from a partner (Parruti et al., 2006). Likewise, there a number of psychological factors documented to affect disease progression. This is because psychological status of a PLWH is crucial in dealing with stigma and adherence to ART. Emotional stress or depression has a significant negative effect on CD4 count and viral load (Ironson et al., 2008). Thus, social support might be a profound determining factor of HIV progression to children living with HIV under care of a parent in a risky marital status.

Education is another important social economic factor in effecting attitudes and change against fatalistic tendencies. Education influences people's way of thinking and association to modern and healthier living (Caldwell, 1993). Certainly, research reveals a strong education effect on HIV/AIDS infection progression rate. Low education level among PLWH are associated with higher progression rate to AIDS stage, and death than those with advanced or university level education (del Amo et al., 2002). The argument for this effect is that persons with high education easily adhere to treatment than those with low education attainment. Similarly, the socioeconomic conditions that surround PLWH influence the rate of HIV infection progression. Children infected with HIV who lives in resource limited settings progress faster to AIDS and death than children in affluent socioeconomic conditions (Little et al., 2007).

Furthermore, proper nutrition is a vital aspect that keeps up the body in a healthier form. Proper nutrition boosts growth and a body's immune system, which helps fight any illness. Studies have shown that poor nutrition and absence of other micronutrients among PLWH is a potential predictor of HIV infection progression rate (Deschamps et al., 2000; Dennis, 1998). Malnutrition observed from Vitamin A deficiency is associated with diarrhoea and wasting syndrome in children, which heightens the HIV progression rate (Kennedy et al., 2000). In addition, malnutrition is responsible for dehydration, anaemia and zinc deficiency, the presence of which accelerates HIV infection progression (Deschamps et al., 2000).

The introduction of ART or HAART is to slow down the rate of HIV infection progression to AIDS and death. Antiretroviral therapies alters and slows the rate of HIV viral replication,

this consequently lessens the rate of HIV infection progression. One study has shown that, admission to antiretroviral therapies was responsible for a 66% and 84% reduction in the rate of progression to AIDS and death respectively (del Amo, 2002).

The health provider's experience in giving HIV/AIDS healthcare is an important factor in explaining the HIV infection progression rate. Health providers with good knowledge of HIV/AIDS related illness are able to take appropriate management of the infections and prescribe necessary treatment than those with less experience (Kitahata et al., 2003). Indeed, patients who receive HIV/AIDS care and treatment from experienced health-workers are more likely to survive than patients who received care from the least-experienced doctors (Kitahata et al., 2003).
Furthermore, many a studies have hypothesized the mode of HIV infection to influence the HIV infection progression rate. People infected through blood transfusion and injectable drug use have faster progression than those infected through other modes (Dennis, 1998). In addition, paediatric HIV infection (MTCT) heightens HIV progression to death by the second birth date (Little et al., 2007).

Maternal health and care is a very important determinant of infant and child health. Healthy mothers have higher chances to bare and raise healthy children than mothers in poor health. Mothers who are in poor health are anaemic and are very likely to face pregnancy and labour complications as well to bare underweight babies. Indeed, there is an elevated risk of infant mortality among HIV positive mothers due to ill health or death (Little et al., 2007). In addition, maternal survival is as important as maternal health to the survival of the offspring (Little et al., 2007).

The study notes that, most of the factors cited above come from studies, conducted among adults. Nevertheless, it is important to understand how these factors shape the HIV/AIDS lifecourse among children based on a lifecourse perspective. The lifecourse perspective facilitates examination of the cumulative impact of biodemographic, socioeconomic and environmental factors on health (Hutchison, 2007; Brent, 2004; Amy, 1996). Moreover, biodemographic, socioeconomic and behavioural factors are well known determinants of health (Caldwell, 1993), of which their health effect on the entire lifecourse need to be established (Merete, 2006) especially how they shape the survival of children living with HIV-AIDS. HIV/AIDS infection is composed of a hierarchy of transition stages or states and people exhibit different event histories.

2.7 Theoretical Perspective

This study adopts the Lifecourse Theory, which examines how chronological demographic and socioeconomic factors shape people's lives from birth to death (Hutchison, 2007). This framework is relevant in studying the causal effects of chronic disease and infectious disease (Ben-Shlomo & Kuh, 2002; Hall et al., 2002). The lifecourse theory enables the understanding of individuals by construction of an event history (series of different events and transitions) from birth to death and examines how people transit through different life periods. In addition, the lifecourse perspective reflects how society and social institutions shape the pattern of a person's life (Elder 1985). With lifecourse perspective, the interplay of human lives and historical time provide an understanding of how people in a given cohort feature differently with their life experience (Elder, 1998). There is wealth of evidence that early experiences affect later morbidity and mortality (Halfon et al., 2005) especially with chronic diseases.

Thus, the lifecourse theory examines events that take place in individuals' lives at various stages and specifically look at how historical time and society affects the individual experience constituting both risk and protective factors that affect health in later life (Halfon et al., 2005). Through observing, a cohort of people in a stage like process enables the examination of any event or transitions for each member of the cohort. This is because even within a cohort, there is diversity in lifecourse patterns or trajectories of individuals' (Elder, 1998).

In addition, lifecourse is composed of different life events, which are vital incidents constituting sudden change but of lasting effect; these are transitions of distinct shifts from the original or previous status to a new state. The timing of life transitions has profound effect on subsequent transitions, and this relates to age especially in predicting of time at which a certain life event and transition take place (Elder, 1998).
Furthermore, lifecourse perspective observe health as a function of multiple factors that interplay in a genetic, biological, behavioural and socioeconomic context, health changes as experience changes (Halfon et al., 2005; Merete, 2006), and because each person has a unique lifecourse trajectory, research on irregularities in timing of life events can help in developing plausible interventions (Brent, 2004). The pace or rate of transition and the length of time a person spends in a given state are other aspects of interest in the study of lifecourse.

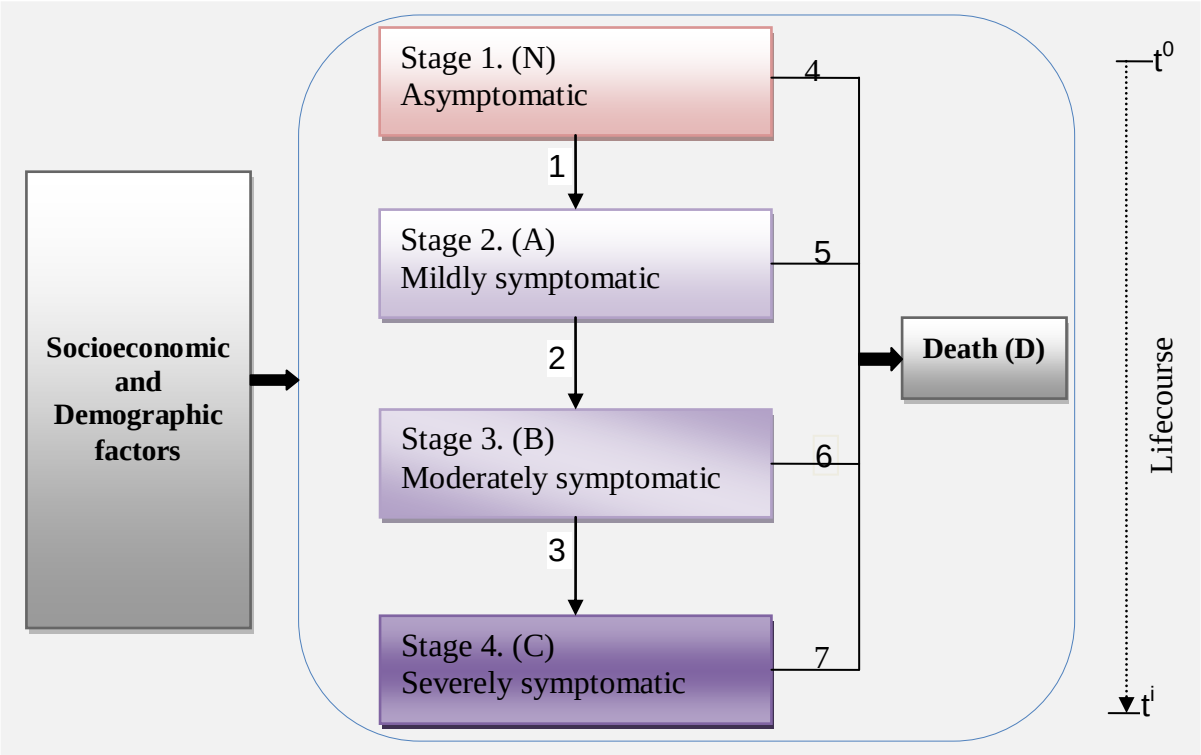
Henceforth, considering the six principles of lifecourse perspectives (Elder, 1994, 1998), we operationalised different factors to examine the HIV/AIDS progression (lifecourse) as follows.
Socio-historical and geographical location- that is human life is understood in a historical context and the places they live in, this is exemplified by the place of residence of the child, and to whom he/she is living with.
Timing of lives- the intrinsic impact of life events that are dependent on time/ age at which they occur in one's life. Here, age of the children is an important biological and social factor that influences vulnerability to disease. Time the basic measure while denoting transitions (Elder, 1998) is synonymous to age; moreover, timing of a transition is a vital input in estimating expectation of life or transition rates.
Linked lives- assume that social and historical influences are expresses through a network of shared relationships. This is associated with factors that relate to parental survival, counselling, religion, and these represent interactions of shared relationships (Elder, 1998) as they affect self-esteem and wellbeing.
Human agency in making choices- this relate to lifecourse as determined by individual's choices and constraints in life and social circumstances. This study does not discuss this principle due to data constraint making it implausible to identify makers of decision-making and choices.
Diversity in life course trajectories- assumes that differences in life course transitions are due to differences in background traits; social economic status, religion, gender, sex, among others. These factors influence disparities in HIV/AIDS progression in the cohort (Blanche et al., 1997; Klimas et al., 2008; Morgan et al., 1997).
Impact of the past to the future- describes the impact prior experiences in life transition have on subsequent transitions and events, indeed factors such as mode and time of infection, start of treatment, caretakers in early years of life, among others, in this perspective may influence HIV infection progression. These themes will provide a basis of selecting input to the conceptual model and describing covariates during the analysis.

Therefore, while studying differences in HIV/AIDS progression in children, the factors that influence HIV infection progression embeds within the key principles of the lifecourse perspective. In addition, the study models some parental background characteristics such as survival status, education attainment to measure their effect on child survival. Figure 1 summarises this linkage henceforth, factors affect the transition rate from one stage of HIV/AIDS to another. This is concurs with Omran's (1998) observation that health transitions are influenced by demographic and socioeconomic factors.

2.8 Conceptual Model for HIV/AIDS Progression

People living with HIV (PLWH) develop AIDS condition in a gradual process with distinct clinical stages, developing opportunistic infections and eventually die. The model below (Figure 2.1) describes the stages of HIV/AIDS progression among patients and death as a terminal state; the progression from stage to another is dependent on demographic and socioeconomic factors that characterize a patient's lifecourse.

Figure 2.1 Conceptual Model for the Study of HIV/AIDS Progression



1-7 Transition possibilities; Death is the End state (absorbing state). State space: N, A, B & C are transient states and describe HIV progression rate. 4-7- mortality rates from each HIV infection stage.

The four stages of HIV/AIDS lifecourse are immunologically, clinically determined depending on certain health symptoms a PLWH attains (CDC, 1994; NIH, 2010; WHO, 2007a), and Death is the definitive stage. The model thus, indicates that PLWH can stay or progress from the initial stage or state (N) to the next health state (A, B, C) or may die (D).

2.9 Definition and Operationalization of Concepts

From the theoretical model (Figure 2.1.) and literature reviewed above, a number of concepts that have emerged. This subsection puts these concepts into context through operational definitions, as well as specifying the measurements and criteria of measuring the concepts contained in this study.

The HIV infections consists of four distinct stages, which are immunologically and clinically, determined (WHOM, 2007a). These stages are what we refer to as *states*, that is, the state of being HIV/AIDS stage N, A, B, C, or dead at a given age (Figure 2.1. and Table 2.1.). Thus, state here describes a specific attribute of an individual's (Mamun, 2003) being in a given HIV stage of infection. An individual can attain a given HIV infection stage at a time. Attaining another stage involves a *transition*, which is the movement through a set of discrete states in a given time interval (Blossfeld & Rohwer, 2002). Transition only takes place when an individual experiences an event that sparks a change of state. On the other hand, *event* denotes the change of an attribute/state (Mamun, 2003). It is a vital incident or occurrence constituting sudden change that may produce serious and lasting effect (Hutchison, 2007). That is the change from a prior HIV/AIDS state to another or death for the case of this study.

The occurrence of events is time dependent, thus the number of individual who are exposed to an event at the beginning of an interval experience the event at certain intensity. This transition or hazard rate (Blossfeld & Rohwer, 2002) is the probability per time unit that an individual that has survived to the beginning of a given interval fails within the interval. Thus, transition rate denotes the number of failures per time in the interval to the average number of survivors in the interval (StatSoft, Inc., 2011).

The series of HIV infection transition from the first stage (Asymptomatic) to the fourth stage (severely asymptomatic) and or death constitute what is referred to as *HIV/AIDS infection progression*. These stages of HIV infections: asymptomatic, mildly asymptomatic, moderately asymptomatic and severely asymptomatic are Clinical and immunologically determined WHO (2007a), NIH (2010), CDC (1994) as indicated in Table 1.

Table 2.1. WHO Immunological Classification for Established HIV Infection (WHO, 2007a)

	Age Related CD4+ count per mm^3 of blood			
HIV- Associated immunodeficiency	<11 months (%CD4+)	12 -35 months (%CD4+)	36 - 59 months (%CD4+)	>5 years (absolute number or (%CD4+)
1. None/ Not significant	>35	>30	>25	>500
2. Mild	30-35	25-30	20-25	350-499
3. Advanced	25-29	20-24	15-19	200-349
4. Severe	<25	<20	<15	<200 or <15%

Source: World Health Organization (2007a)

Table 2.1 shows the four immunological stages of HIV infection progression, their cut-off points by age of persons. The Immunologic categories based on age-specific CD4+ T-lymphocyte counts and percent of total lymphocytes (CDC, 1994). Not all individual in a given state make transitions, thus, the retention of a prior state at a specified period constitute a *survival*. Survival describes the probability that the episode duration of a given HIV state is equal to the initial state of observation. The individuals who fail to make transitions are the *survivors*. That is, the number of cohort members who survive all causes of decrement before the end of a certain age interval.

It is important to make clear and correct definition of states to enable proper model specification (Blossfeld & Rohwer, 2002). The collection of all possible states yields *state spaces*. For the case of this study, there are five (5) state spaces (N, A, B, C and D) as indicated in Figure 1. Henceforth, the change of states or transition between states is subject to chance probability. The probability that is associated with the different state transitions is the *transition possibilities* in event history analysis.

The probability to make transition is influenced by a number of factors which may be biodemographic and socioeconomic. *Demographic and socioeconomic factors* relate to stratification in society based on, age, gender, social class, educational attainment, literacy, occupational status, and residence type, time of initial therapy, counselling and therapy adherence status. These population-specific differences in the presence of disease and health outcomes represent *health disparity* (Carter-Pokras & Baquet 2002). Differences in transition rates, morbidity, mortality rates and expectation of life is the basis for examining health disparity in this study.

Morbidity denotes the incidence or the prevalence of disease (ill health) in a population (Weeks, 2005). That is, the frequency of transition at a given point in time/ age to a higher HIV/AIDS infection stage/state. On the other hand, *mortality* is the pattern or the occurrence of death in a population (Weeks, 2005). In this study mortality is represented by the transitions from any given HIV/AIDS infection state to death (N, A, B or C to D), or the incidence of transition to death (Mamun, 2003).

The average expected number of years of life remaining at a given age constitutes *life expectancy* (expectation of life). The ratio of the person years spent or expected to be lived in each HIV infection state to number of survivors at each specific age interval (Mamun, 2003). The sum total of life expectancy from each HIV infection stage arises to *total life expectancy* on the lifecourse of HIV infection. Hence, the ratio of stage specific life expectancy to total life expectancy derives us to what is termed as the *proportion of remaining lifetime,* in other words, the proportion of expectation of life in a given HIV/AIDS state.

Summarizing the whole individual's HIV infection event history up to and into a single measure (life expectancy) constitutes *HIV/AIDS lifecourse*. For this study, a series of different HIV/AIDS infection events, transitions, life expectancy and cofactors describes the HIV/AIDS lifecourse.

2.10 Summary of the Chapter

This chapter has presented the literature and theoretical concepts on HIV/AIDS and lifecourse perspective respectively. Literature on HIV/AIDS shapes the understanding of the time exposure and experience of the epidemic on global scale and in the study area (Uganda). Discussion to different factors documented by different authors to affect HIV infection progression. The theoretical framework serves to understand the lifecourse perspective in which the study situates its self. The lifecourse perspective has described how socioeconomic and demographic factors interact to shape one's lifetime experience. The chapter also integrates socioeconomic and demographic factors into the principles of the lifecourse perspective. A conceptual model for HIV infection progression is described and concepts that arises thereof are give operational definitions for measurement in analysis (Chapter four).

Chapter Three: Materials and Methods

3.1 Introduction

This chapter presents a detailed description of the research design; in addition, it describes the data used in this study, the steps and the set of methods employed in the analysis. It comprises of several subsections that goes deeper explaining the procedures and assumptions undertaken during this research process of the study.

3.2 Design and Methods

The study takes on a retrospective cohort design. It is a quantitative research design with statistical measures to estimate and describe the expectation of life in each HIV stage and establish the demographic and socioeconomic factors that contribute to differences in transition rates from one stage to another. The study utilizes event-history analysis procedures: Kaplan Meier and the Cox proportional hazard model to estimate exposure time, transition probabilities and the relative risk to event respectively.

3.3 Data Source

The study uses data (clinical data) from Mildmay Uganda. Mildmay Uganda offers a holistic centre-based approach to HIV/AIDS care and treatment at Mildmay Centre since 1998, now to over 21,000 persons living with HIV/AIDS. In addition, it offers care and treatment at various outreach clinics in urban and rural communities (Mildmay, 2010). Thus, the Mildmay Uganda's long term and extensive scope of HIV/AIDS care and treatment in Uganda offer a rich data for this study approach than any other source in Uganda.

HIV/AIDS care and treatment entails adherence and close monitoring of patients especially Children on Antiretroviral therapy to enable full benefits of HIV Treatment. In this regards, Mildmay Centre maintain a patients records/ database (Biodata, clinical, appointment schedules, etc.) on a routine basis. It is from this database that the study extracted the variables of interest to construct a sub-database to provide answers to the study objectives.

The study comprised of children under age 15 years on HIV/AIDS care and treatment at Mildmay Uganda. The study accessed clinical data of these children from Mildmay Uganda main hospital database. From the database, the study recruited a "cohort" of children of known HIV/AIDS status within an age range of 0- 14 years to examine their HIV/AIDS disease life history from the time of identification to age 15 years or death. The year 2000 was the base year for recruiting the study subjects. Henceforth, the study followed the HIV/AIDS life history of these children in a retrospective manner between the periods January 2000 to December 2010.

Arriving at the study sample, the study subjected all children undergoing HIV/AIDS care and treatment in the base year to a selection criterion. This selection criterion considered:

- Children under HIV/AIDS care and treatment at Mildmay Uganda,
- Children aged 0- 14 years in the years 2000 to 2010,
- Children of confirmed or recorded HIV infection status,
- And children whose date or age at initial HIV infection confirmation is available.

This selection criterion minimized the number of right censored cases on one hand and increased the depth of data on study subjects on the other hand. Hence, the whole operation will accumulate data of longitudinal nature on patients' socio-demographic data and clinical assessment on initial visit and successive referral visits and death reports. From this, the study constructs its database for subsequent analyses.

3.4 Methods of Data Analysis

The study employed two techniques of data analysis: Kaplan Meier Event History analysis procedures and the Cox proportional hazard model to estimate and describe transition, exposure time, expectation and influencing cofactors. The study dropped the earlier proposal to use Multistate Life Table (MSLT) to classify and describe HIV/AIDS transition lifecourse at a given distinct stage due to data limitations.

3.5 Kaplan Meier and Cox Proportional Hazard Model

The study specified Kaplan Meier survival functions to describe event failure against event time/ age that is, the survival function and the hazard. In addition, the study specified Cox proportional hazard models to analyze multiple covariates for their effect on survival in a given state. As input into the Cox regression model, the framework posits that demographic and socioeconomic factors as embedded in the five theme of the life course theory influence the rate of HIV/AIDS progression. The study considers; age, sex, education attainment, among others (covariates) as demographic and socioeconomic proxy indicators that influence HIV infection progression. Thus, the differences in demographic and socioeconomic factors constitute disparities in HIV/AIDS state transitions in CLWH. The basic Cox regression model specification (Blossfeld & Rohwer, 2002) has the form:

$$h(t) = h_0(t)e^{\beta_1 x_1} \quad \text{(i)}$$

Time here, refer to age of the study subject. Thus, the Multivariate Cox Proportional Hazard model takes the form of a hazard function at age t, h(t), as follows:

$$h(t) = h_0(t) * \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots + \beta_i X_i) \quad \text{(ii)}$$

Where, h(t) is the dependent variable, $h_0(t)$ is the baseline hazard function and β_1, β_2,…β_i are unknown regression coefficients, and the X_1, X_2… X_i, are the covariates.

The study specified four models for the hierarchical survival and survival to death as follows:

$$h(t) = h_N(t) * \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots + \beta_i X_i) \quad \text{(iii)}$$

Model survival from first to second stage (N→A)

$$h(t) = h_A(t) * \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots + \beta_i X_i) \quad \text{(iv)}$$

Model survival from second to third stage (A→B)

$$h(t) = h_B(t) * \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots + \beta_i X_i) \quad \text{(v)}$$

Model survival from third to fourth stage (B→C)

$$h(t) = h_D(t) * \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots + \beta_i X_i) \quad \text{(vi)}$$

Models survival from any one stage of HIV infection to death (N, A, B, C→D)

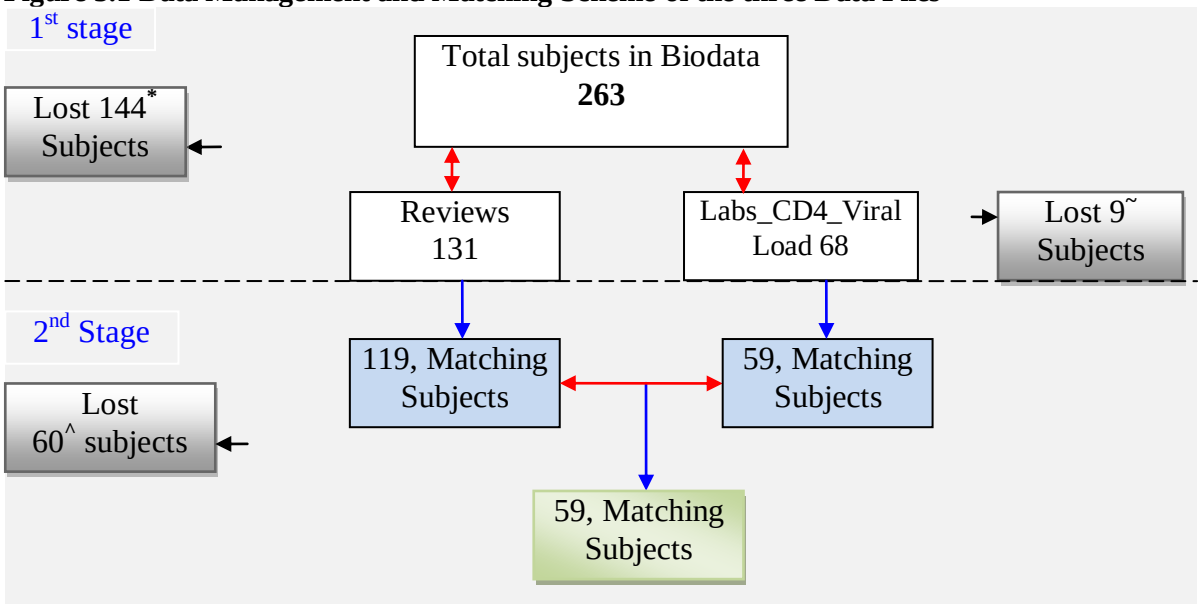
3.6 Ethical Considerations

The PRC, University of Groningen approved the study proposal, and Mildmay Uganda Research and Ethics Committee (MUREC) and then Uganda National Council for Science and Technology (UNCST) granted the permission to conduct the study. Consequently, the study ensured confidentiality of institutional data and anonymity of study subjects at all levels. In addition, the study replaced all personal identifying information with generalized coding and presentation of all results from the study is in aggregate form to ensure anonymity of subjects. Thus, the output of the study (as it follows in chapter four) constitutes: aggregates of demographic and socioeconomic characteristics of subjects, duration of stay in each HIV infection stage, transitional probabilities, Survival functions and Cox proportional hazard model estimates.

3.7 Dataset and Data Management Scheme

The dataset received contained three separate data-files (MS. Excel worksheets), Biodata, Review and Labs_CD4_Viral load dataset. Biodata set contain data on patients' background characteristics such as, sex, ages, date at registration, and information on immunization completion, parental characteristic HIV status and survival. On the other hand, Review dataset contain data on patients' health records on each date of clinical check up. These data include BMI, complications and diagnosis, treatment, WHO HIV stage and treatment tracks. The Labs_CD4_Viral load dataset contains data on the type of HIV test taken and result of the test on each date taken. All the three dataset have a unique identifying code for each patient, to identify a patient in all the files.

Figure 3.1 Data Management and Matching Scheme of the three Data Files



*Subjects lost from Bio-dataset file due to lack of data on review (Review dataset).
~ Subject lost from Labs_CD4_Viralload dataset due to lack of Biodata (Biodata file).
^Subject lost from Bio-dataset due to lack of data on Laboratory CD4 count or viral load.

Figure 3.1 shows the datasets and data processing scheme of this study. All the data files put together contained 263 subjects (children) based on the unique Patient Identification Number (PTIDNO). That is, Biodata file (base file) contained 263 subjects/ records, Review dataset had 131 and Labs_CD4_Viral Load had 68 subjects/ records. The base dataset (Biodata) originally contained 275 subjects, but the extra 12 records were duplicate subjects/ records.

The study matched the three datasets at two stages. At the first (above the dotted line), Biodata and Review datasets were matched based on patient identification numbers (PTIDNO). At this stage, 144 subjects were lost form the Biodata, as they were not contained in the review dataset. In addition, nine (9) subjects were lost from the Labs_CD4 dataset for they were not contained in Review dataset. Thus, at first stage of data matching, there were 119 matching subjects i.e. having data on Biodata and Review.

At second stage (below the dote line), the Labs_CD4 dataset was matched to the 119 subject prior matched datasets (from Biodata and Review). At this stage, 60 subjects were lost due to lack of data on Labs_CD4 and viral load. As a result, the operation matched only 59 (21%) subjects/ children from all the three datasets. That is, 59 children had all the data (disregard missing cases) on biodata, reviews and Labs_CD4_viral load. Otherwise, the data processing

scheme (Figure 3.1) indicates that there is loss of records on children between administrative, clinical/ diagnosis and laboratory. Estimates of this study emerge from the 59 children who had records in the three datasets.

3.8 Data Limitations

Data quality is an important aspect of research as it enhances its credibility, potential use to inform policy and reliability of conclusion thereof. Poor quality control in implementation and maintenance of the database can compromise medical record data quality. Irregularities in recording and updating clinical data are a potential source of data loss that greatly undermines this data source.

Indeed, the primary objective of this study was highly affected by the quality of data availed. The data had a lot of missing cases primarily resulting from poor record keeping procedures and coordination system. The fact that 80% of the subjects registered in care in the year 2000 missed clinical records, resulted in an insufficient sample to implement the Multi State Lifetable (MSLT) analysis technique as earlier proposed.

Beside, the progressive clinical data, which was available for the 20% subjects, also was incomplete, having had missing cases. As a result, it was impossible to estimate the effect of some factors thereby making a number of assumptions in order to impute the missing cases.

3.9 Summary of the Chapter

This chapter described the material and methods used in this paper. It specified the study type and design as well as the methods of analysis. The description of the scope of observation, inclusion and exclusion criteria of subjects gives the retrospective clinical data frame. The chapter has presented clearly the ethical considerations of the study, the datasets and its management scheme as well as some limitation that came with the data.

Chapter Four: Study Findings

4.1 Introduction

This chapter examines the HIV/AIDS progression among children following WHO (2007a) immunological staging of established HIV infection. HIV infection constitutes four distinct stages, which are immunologically and clinically determined (WHO, 2007) as earlier described in Table 1 of Chapter two, Operationalization of concepts. In the wake of ART, PLWH experiences reduced morbidity and mortality (USAID, 2010; Schneider et al., 2005), though this information is scanty (CDC, 2006). This chapter attempts to address this information gap by estimating; transition rates, exposure time and ascertain cofactors associated with HIV/AIDS progression among children living with HIV/AIDS.

4.2 Descriptive Results

This subsection presents the distribution and summaries of the data variables used in the study. In event history analysis, running Kaplan-Meier curves for categorical predictors provides insight into the shape of the survival function, whether groups are proportional or not. In addition, comparing survival functions across groups of factors help to select covariates to include in the final model.

Table 4.1 below presents the description of study subject by demographic and social characteristics. This provides an overview of what the subjects constitutes, thereby easing explanation of estimates in subsequent subsections.

Table 4.1 Background Characteristics to Children under HIV/AIDS Care and Treatment (n=59)

Characteristics		Frequency	Percent
Sex	Male	29	49.2
	Female	30	50.8
Age at registration	0- 4	21	35.6
	5- 8	26	44.1
	9-12	12	20.3
Caregiver	Aunts	21	35.6
	Grand Parent	8	13.6
	Mother/Father	16	27.1
	Others Relatives	14	23.7
Religion Affiliation	Catholic	30	50.8
	Protestant/Pentecostal	24	40.7
	Muslim	5	8.5
Birth Weight	Low (<=3 kg)	21	35.6
	Normal (>3 kg)	38	64.4
Mother's Survival	Alive	40	67.8
	Dead	19	32.2
Father's Survival	Alive	48	81.4
	Dead	11	18.6
Schooling	Not schooling	16	27.1
	Schooling	43	72.9

The descriptive characteristics of the study subjects (Table 4.1) indicate that 51% were females. The age distribution of children at registration ranged from 1- 12 years, where ages 5

-8 had the highest frequency (44%). Age at registration denotes the age at which a child was tested and confirmed to be HIV positive, and then a10 year and 4 months retrospective follow-up period data collection.

Aunts are the main (36%) caregivers to children in care at Mildmay Uganda, and the care from grandparents is evident (14%). In addition, the care given to children living with HIV (CLWH) from persons of distant relation is substantially (24%) availed. These included charity organizations, orphanage homes and individual philanthropies. Caregivers are very important persons for a child's compliance and social support on course of treatment (Biadgilign, et. al., 2009). Religion is an important element in psychological development and attitudes towards health utilization (Antai, 2009). Religious affiliation among persons living with HIV/AIDS as regards inculcates hope and comfort among them. It is indicated that, 51% of the children or their caregivers were affiliated to Catholic belief, followed by Protestants or Pentecostal belief (41%) and 8% affiliated to Muslim belief.

Birth weight is a vital indicator of child health risks and development (Mosley & Chen, 1984) child born with low birth weight have a high risk of childhood mortality (64%). It is indicated that majority of the children were born with normal birth weight. In addition parental survival especially of the mother is important for a child's survival as well (Little et al., 2007; Ronsmans, et al., 2010). Data indicate that 32% and 19% of the children had lost their biological mother and father respectively. Over 72% of the children had started schooling at the time of registration for HIV/AIDS care and treatment at Mildmay Uganda.

4.3 Duration Lived with HIV Infection in each HIV Stage

The duration of observation denotes that period between the time of registration for care and treatment at Mildmay Uganda and closer of observation April 2011. The study assumed that all subjected under study to occupy HIV infection stage I (Asymptomatic) at the time of registration. This led to specification of the event as the transition from Asymptomatic to Mildly asymptomatic or HIV infection stage II as the first transition.

Table 4.2 Duration of Exposure and Proportion of Remaining Lifetime in each Infection Stage

Estimates	Stage I	Stage II	Stage III	Stage IV
No. of Children	59	46	30	20
Person Months	3523	788	435	362
Exp Duration (months)	60	17	15	18
Exp Duration (years)	5.0	1.4	1.2	1.5
Prop of remaining lifetime	0.69	0.15	0.09	0.07

Table 4.2 summarizes the duration or exposure time of HIV infection for children under study at each HIV infection stage. The study constituted 59 children and these contributed 3,523 person months (5 years on average) in HIV infection stage I (Asymptomatic). At the time of the study 46 children were observed to have managed to transit to HIV infection stage II (Mildly asymptomatic). This means 13 children died or censored before transiting to mildly asymptomatic stage. The 46 children in stage II contributed 788 person months of exposure time to HIV infection.

Consequently, as the number of children progressing to a high HIV infection stage reduces, the total exposure time also reduces. The duration of stay in HIV infection stage III (Moderately asymptomatic) totals to 435 person months (1.2 years), a 6% less duration in

stage II. The estimate of the duration of exposure to severely asymptomatic stage is 362 person months (1.5 years). The data thus, indicates a total 87 months (7.2 years) of a life history of HIV infection among children in the study. A sum of 5 years is the expectation of life with Asymptomatic HIV infection stage before transiting to mildly asymptomatic stage. On the other hand, children are expects to live for one and half years with severely asymptomatic HIV infection.

Furthermore, the proportion of the remaining lifetime expectation at a given HIV infection stage indicates an inverse relationship with HIV infection stage. That is, the proportion of remaining lifetime to be lived at each stage of HIV infection decreases drastically with progressive amplification of the infection. Much (69%) of the expected lifetime on the lifecourse of HIV infection is gained with Asymptomatic HIV infection. On the other hand, only a third of the total HIV infection lifetime is the expectation of life with mildly asymptomatic, moderately asymptomatic and severely asymptomatic HIV infection stages all together. This indicates an increasingly short expectation of life and great probability of HIV infection progression once a child progresses from asymptomatic stage.

4.4 Transition Probabilities from each HIV Infection Stage

The numbers of subjects present in a given HIV infection stages are at risk of making a transition at each point in time (month), these subjects constitute a risk set. That is, the number of children observed before the time in question and up to and after this the particular observation time. This also includes all those who have experienced the event or censored exactly at this particular time point. Thus, the risk set is the total number of children exposed to risk of HIV infection transition, and those children who survives a transition at a given point in time builds up a survivor function. Therefore, computation of transition probabilities as the residue of the survivor functions from one.

Figure 4.1 Transition Probabilities from each HIV Infection Stage

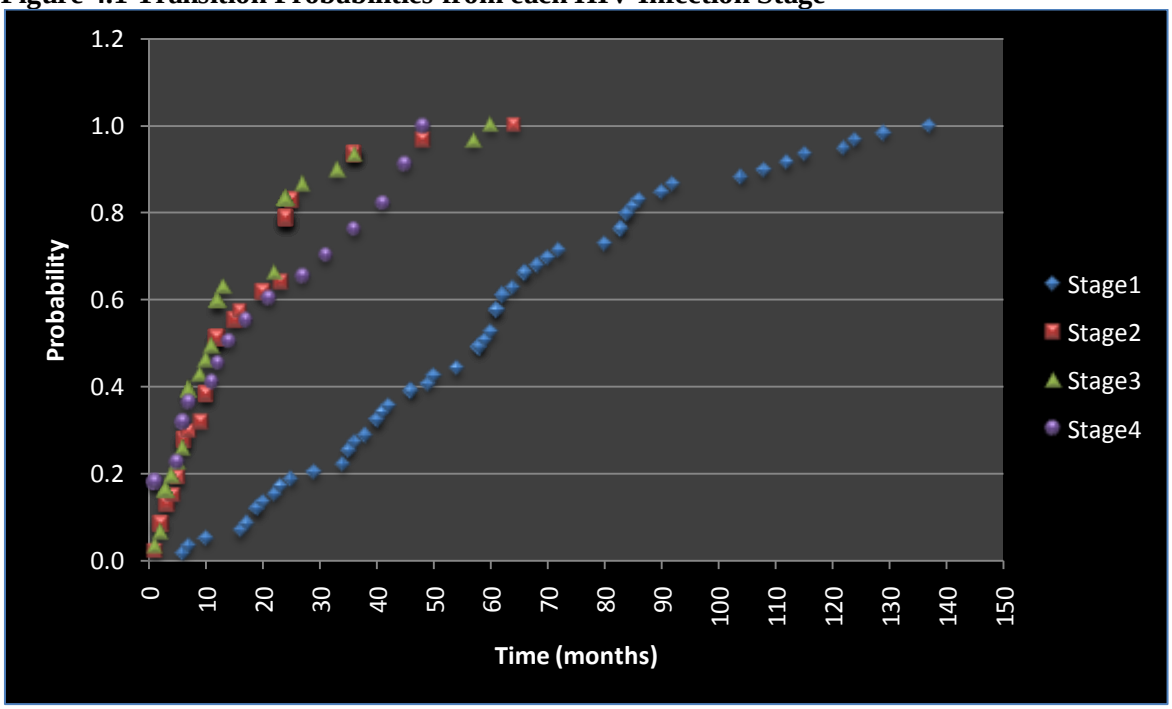


Figure 4.1 summarizes the transition probabilities of the four HIV infection stages for the period of 140 months of observation window. It can be seen that the transition probabilities in Asymptomatic HIV infection (Stage I) are markedly distinct from the other three stages. That

is, the probabilities for children living with HIV infection stage I to progress to a higher HIV infection stage are lower at all times than those of higher HIV infection stages. For example, at a duration of 60 months, the transition probability for HIV infection stage I is half that of stage II and III. In addition, there is no distinct pattern in transition probabilities in stages II (mildly asymptomatic) and stage III (moderately asymptomatic).

4.5 Survival Function for HIV Infection Stages

Survival function depicts the probability that a subject will survive beyond a specified time. It represents the cumulative proportion of subjects surviving (not progressing) up to a specified point in time. Figure 4.2 up to figure 4.5 presents the survival function for each of the four HIV infection stages observed in this study.

Figure 4.2 Survival Function for the Asymptomatic Stage

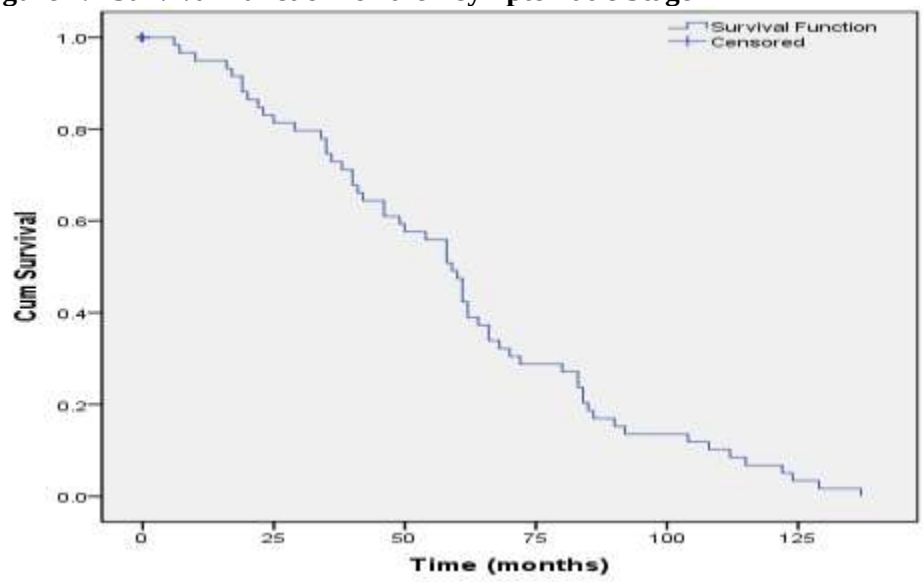
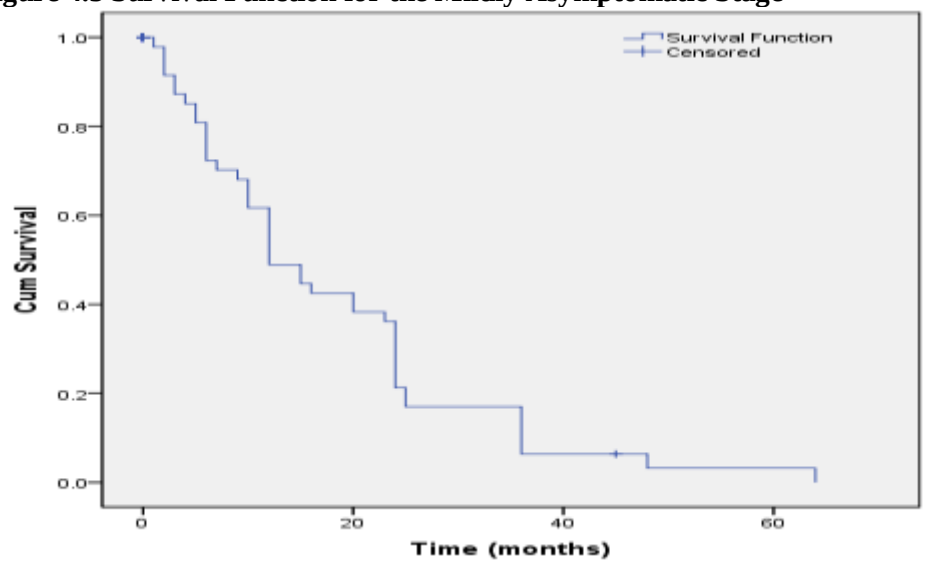


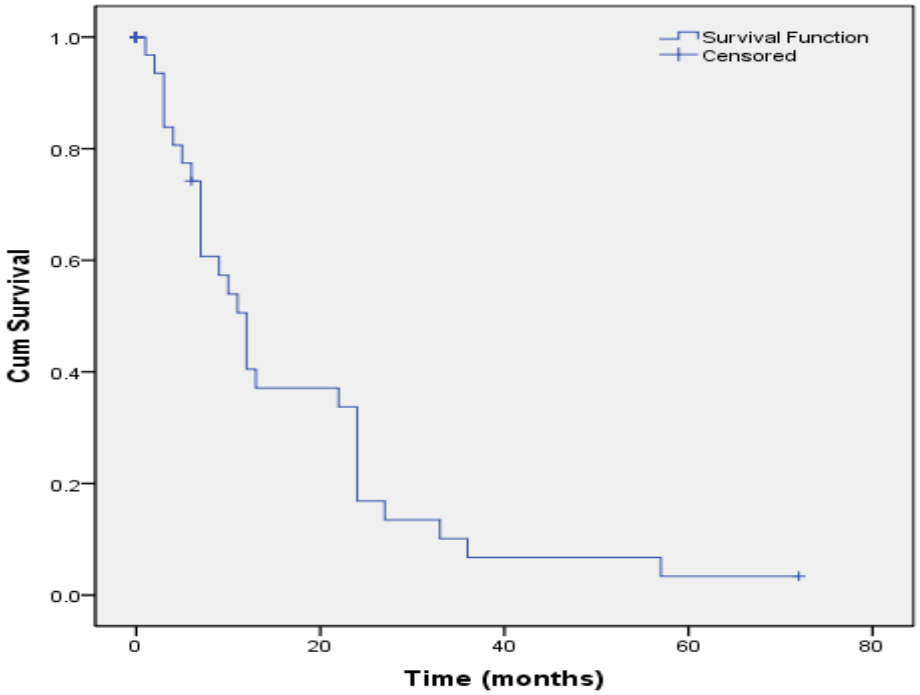
Figure 4.2 depicts the cumulative survival function for children in HIV/AIDS infection stage. The curve suggests a relatively slow transition rate at all ages. The figure shows that at 59 months of living with HIV infection stage I, half of the children transit to a higher HIV infection stage II (Mildly asymptomatic).

Figure 4.3 Survival Function for the Mildly Asymptomatic Stage



For stage II (Mildly asymptomatic), the cumulative survival function describes a fast transition rate (Figure 4.3), there is quick exit from stage II after the period of 21 months. In this stage, there was one death observed after a period of 42 months. Furthermore, half of children progressed to the next HIV infection stage III or death after 12 months as also indicated in the mean survival time estimate (Table 4.3).

Figure 4.4 Survival Function for the Moderately Asymptomatic Stage



Survival probability with moderately asymptomatic HIV infection (Figure 4.4) indicates that there is a faster progression to a higher HIV infection stage in the first 18 months than in the months there after. At the fifth and 72nd month of this stage, two children are censored or dead. After 12 months of observation in HIV infection stage III, half of the children progresses to another HIV infection stage or dies.

Figure 4.5 Survival Function for the Severely Asymptomatic Stage

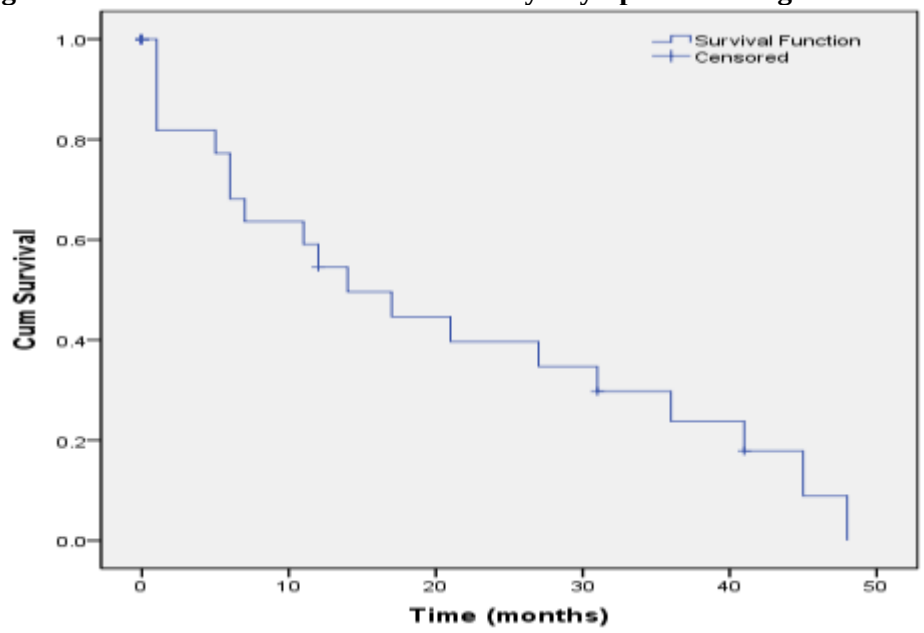


Figure 4.5 presents the cumulative survival function for children surviving with severely asymptomatic HIV/AIDS infection and describes a steeper survival rate. A few subjects were censored, meaning that more of the children were right censured by the study date. Nevertheless, after 14 months living with severely asymptomatic HIV infection 50% of the children make a transition to death.

4.5.1 Mean and Median Survival Time with HIV/AIDS Infection

This describes the survival of children on the lifecourse of HIV/AIDS infection. That is, survival with Asymptomatic HIV infection (stage I) up through severely asymptomatic HIV infection (stage IV). Table 4.3 presents the Mean and Median survival times (person months) for children living with HIV infection stage I to stage IV of HIV infection with standard errors and their confidence intervals at 95%.

Table 4.3 Means and Medians Survival Time (months) in each of the four HIV Infection Stages

	Mean				Median			
			95% C.I				95% C.I	
Stages	Estimate	Std. Error	Lower	Upper	Estimate	Std. Error	Lower	Upper
Stage I	59.7	4.3	51.4	68.1	59.0	3.4	52.4	65.6
Stage II	18.0	2.1	13.8	22.1	12.0	2.1	7.8	16.2
Stage III	16.9	2.9	11.1	22.6	12.0	1.6	8.9	15.1
Stage IV	20.7	3.8	13.3	28.0	14.0	4.5	5.3	22.7

The estimate of the median time of survival in Asymptomatic is 59 person months, indicating that after 59 months half of the children experience changes in HIV infection to mildly asymptomatic. Table 4.3 further shows that children living with HIV on average spend 60 person months in asymptomatic stage.

For mildly asymptomatic HIV infection stage, the median survival time is 12 person months. That is, after 12 months of living with mildly asymptomatic HIV infection, 50% of the children progressed to a higher HIV infection stage (Moderately asymptomatic stage). In addition, a period of 18 months on average is lived with mildly asymptomatic HIV infection stage.

With moderately asymptomatic HIV infection stage, children survive with the infection (Moderately Asymptomatic) for 12 person months before progressing to a higher HIV infection rate. Hence, at 12 months of living with moderately asymptomatic HIV infection, half of the children change their HIV infection stage to a higher one. However, estimates shows that children on average survive moderately asymptomatic HIV infection stage for 17 months.

The median survival time with severely asymptomatic HIV infection stage indicates that 50% of children survive the infection for 14 person months. On average, children survive severely asymptomatic HIV/AIDS infection stage for 21 person months before transiting to an absorbing state.

4.5.2 Survival Function Comparisons by Children's Characteristics

Estimates of survival functions employ Kaplan Meier procedure, which is, run with a comparison by all independent variables. The literature in chapter two (section 2.6) was the basis for selection of independent variables to estimate their effect on HIV infection progression. These factors include, age, sex, genetics, viral load, HIV-subtype, co-infection, social support, education, nutrition, maternal health, among others. However, there is data limitation to explore the effect of all factors cited in section 2.6 of this study. Thus, analysis in

this study is limited to the variables presented in Table 4.1 background characteristics of the children under study.

Table 4.4 Comparison of Survival Curves by Children Characteristics

		Asymp. Sig. (2-sided) Pearson Chi^2			
Variables	df	Stage I	Stage II	Stage III	Stage IV
Sex [Male, Female]	1	0.991	0.960	0.256	0.551
Age group [0-4, 5-8, 9-12]	2	0.037	0.183	0.520	0.642
Caregiver [Aunts, Grand Parent, Parents, Others Relatives]	3	0.064	0.150	0.056	0.193
Religion [Catholic, Protestants, Muslims]	2	0.084	0.775	0.035	0.555
Birth Weight [Low, Normal]	1	0.196	0.428	0.650	0.589
Mother's Survival [Dead, Alive]	1	0.076	0.292	0.379	0.585
Father's Survival [Dead, Alive]	1	0.154	0.282	0.101	0.885
Child School Status [Yes, No]	1	0.692	0.397	0.242	0.250

The study examined whether there is a difference in survival curves of groups of independent variables based on a log-rank test. That is, stratification of survival functions by groups (indicated in brackets) on independent variables (background characteristics) of children under study.

Sex is an important predictor of health and as regards HIV infection progression; females have been found to have an elevated risk of HIV progression (Rodriguez et al., 2010). In this study however, the survival curves of girls and boys were not different for HIV infection progression in all stages of HIV infection. Age is also a major factor determining HIV infection progression, with infants having a higher rate of HIV infection progression than old children do (Blanche et al., 1997). Results in Table 4.5 indicate a significant difference in ages of children on HIV infection progression in stage I; the differences disappear with progress to a higher HIV infection stage.

Caregiver are important persons to children on treatment, they give them comfort and support they need to comply with lifelong treatment of HIV/AIDS treatment. They help them deal with adherence and stigma associated with the infection and routine medication. Table 4.4 indicates that there is significant difference between caregiver in HIV infection stage I and stage III. Likewise, differences in survival curves based on religion show a similar pattern to that of caregivers. Religion offers a similar psychological support to patients as caregivers does, it instils a sense of belongingness and self-esteem.

Many studies have depicted birth weight to be a strong predictor of child's health and survival. Children of low birth weight have a heightened risk of childhood illnesses and succumbing to infant mortality (UBOS & Macro Int Inc, 2006). However, results show no significant differences in survival probabilities between children born of low birth weight and those born of normal weight.

Parental survival especially of a mother is very crucial for the health and survival of her young ones. Table 4.4 indicates that the survival probabilities of children living with HIV infection are not difference for those who lost their mothers or fathers for all the four stages of HIV infection. In addition, there is no difference in survival curves for children living with HIV infection whether they were going to school or not.

4.6 Risk Factors for HIV Infection Progression

This section examines the effect of each independent variable on HIV infection progression. To achieve this through both bivariate and multivariate Cox regression model specification. Relative risk (RR), the ratio of the exponent to the reference category in a specified factor was the basis for estimation of the effect of the risk factors on HIV infection progression. Relative risk is thus the measure of the likely effect of risk factors on HIV infection progression among children who received HIV/AIDS care and treatment.

4.6.1 Bivariate Analysis of Risk Factors

A first step in the analysis of risk factors is to estimate the estimation of the relative risk for each factor individually. Table 4.5 below presents bivariate results of risk factors and Asymptomatic HIV infection progression from a Cox proportional hazard model.

Table 4.5 Relative Risk of HIV Infection Progression from Stage I (Bivariate Results)

Risk Factors		B	SE	Sig.	Exp(B)	95% CI for Exp(B)		-2 LL
						Lower	Upper	
Sex	Male	0.003	0.265	0.991	1.003	0.507	1.984	370.3
Caregiver				0.052				361.8*
	Grand parents	-0.727	0.447	0.104	0.483	0.201	1.161	
	Mother/father	0.203	0.335	0.545	1.225	0.635	2.363	
	Other persons	0.601	0.353	0.089	1.824	0.912	3.645	
Religion				0.058				364.5*
	Pentecostals	-0.589	0.293	0.044	0.555	0.312	0.985	
	Moslems	0.394	0.488	0.420	1.482	0.570	3.858	
BW	Low	-0.365	0.287	0.203	0.694	0.331	1.454	368.6
Mother	Living	0.454	0.345	0.189	1.574	0.647	3.832	368.4
Father	Living	0.491	0.298	0.099	1.634	0.758	3.521	367.4
Age at registration				0.034				364.2*
	0-4	-0.700	0.381	0.067	0.497	0.186	1.326	
	5-8	-0.965	0.373	0.010	0.381	0.146	0.994	

*p-value<0.05

Table 4.5 indicates that being a boy is not strong risk factor to HIV infection progression from stage I compared to girls. The relative risk for boys living with HIV to progression from Asymptomatic to a higher HIV infection stage is unitary (RR=1.00, CI: 0.51-1.98) to that of girls. Care giving depicts a significant predictor of HIV infection progression from Stage I. Note that, children receiving care from their grandparents have a low hazard rate to progress from Asymptomatic that is 48% of that of children receiving care from their Aunts (RR=0.48, CI: 0.20-1.16). However, children under care of their parents (mother/father) and those having care form other persons have higher hazards of progression from Asymptomatic HIV infections (RR=1.23, CI: 0.64- 2.36) and (RR=1.82, CI: 0.91- 3.65) respectively.

A significant effect of Religion on HIV infection progression is also evident. The relative risk for children affiliated to Pentecostal to progression from Asymptomatic is significantly low (RR=0.56, CI: 0.31-0.99) and not significantly high for Muslims (RR=1.48, CI: 0.57-3.86) of that of Catholics at $p<0.05$. Birth weight, survival of mother or father reveals no significant effect on child's HIV infection progression from Asymptomatic to a higher Infection stage.

Results shows that age at which children starts care and treatment of HIV/AIDS is a significant predictor of HIV infection progression among children. The hazard of children aged 5-8 years progressing from Asymptomatic is 38% (CI: 0.15-0.99) of that of children aged 9 and more years. The study notes that, age at registration remained the only significant predictor of HIV infection progression at all stages of HIV infection. It was observed that

with Mildly asymptomatic children age 0-4 and 5-8 have lower risk of HIV infection progression 21% (CI: 0.09-0.47) and 23% (CI: 0.10-0.52) respectively of that of children aged 9 years and over. For stage III ages 0-4 had (RR=0.30, CI: 0.11-0.81) and ages 5-8 (RR=0.28, CI: 0.10-0.76) compared that of ages 9 years and over. Likewise, with severely asymptomatic, children aged 0-4 and 5-8 have a 20% (CI: 0.05-0.80) and 26% (CI: 0.06-1.04) respectively HIV infection progression risk rate of those aged 9 years and over.

The -2 log likelihood (-2LL) ratio in Table 4.5 represents the improvement in the model fitting of the data when a covariate is added to an empty model. That is, the null hypothesis that regression coefficients for predictor variables are zero or equal that of an empty model. The -2LL for caregivers, religion and age at registration indicates that the regression coefficients are significantly different from zero. We accept the null hypothesis for the variables sex, birth weight and parental survival, for - 2 partial log-likelihood does not change significantly when they are added to a model.

4.6.2 Multivariate Analysis of Risk Factors

We examine the relative risk of HIV infection progression in the presence of multiple risk factors. At this level, we specify a multivariate model estimates with all covariates as listed in Table 4.1 above. Due to a small sample size, interaction of factors is not examined in this analysis.

Table 4.6 Relative Risk of HIV Infection Progression from Stage I (Multiple Factors)

Risk Factors	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Male [Female]†	-0.175	0.293	0.354	1	0.552	0.84	0.472	1.493
Caregiver [Aunts]†			7.817	3	0.050			
Grandparents	-1.063	0.542	3.850	1	0.050	0.345	0.119	0.999
Mother/father	0.278	0.388	0.512	1	0.474	1.320	0.617	2.827
Others relatives	0.490	0.408	1.444	1	0.229	1.632	0.734	3.629
Religion [Catholic]†			3.348	2	0.187			
Pentecostals	-0.608	.337	3.250	1	0.071	0.545	0.281	1.054
Moslems	0.038	.536	0.005	1	0.943	1.039	0.364	2.969
Mother living [Dead]†	0.968	0.625	2.399	1	0.121	2.633	0.773	8.962
Father living [Dead]†	0.774	0.455	2.892	1	0.089	2.169	0.889	5.295
Low birth weight [Normal]†	0.768	0.610	1.585	1	0.208	2.155	0.652	7.125
Age at registration [9-12]†			3.872	2	0.144			
0- 4	-0.208	0.433	0.230	1	0.632	0.813	0.348	1.898
5- 8	-0.768	0.450	2.911	1	0.088	0.464	0.192	1.121

†Reference category

Table 4.6 above presents a general model of the relative risk of HIV infection progression in the first stage of HIV infection (Asymptomatic). The estimation entered all variables examined in univariate analysis into one model to establish the relative risk in presence of other variables. The model was specified and fitted the data significantly (-2LL 345.5, p=0.010). The resultant estimates indicate that sex of a child remain an insignificant (RR=0.84, CI: 0.47- 1.49) predictor of HIV infection progression. Care giving is depicted a significant predictor of HIV infection progression, children receiving care from their grandparents have a significant low hazard rate (RR=0.35, CI: 0.12-0.99) to progress to a higher HIV infection stage relative to those receiving care from their Aunts. For religion,

father's survival status and age at initiation of HIV/AIDS care and treatment, the effect on HIV infection progression is significant at 90% confidence interval. However, the survival status of mother and birth weight there was no observable significant effect on HIV infection progression.

4.6.3 Refined Model Specification

The model presented in Table 4.6 contains all the predictor variables but we have seen that some of the variables are not good predictor of HIV infection progression in the analysis. In order to predict well the HIV infection progression, we specify a simpler model by eliminating extraneous covariates in the model; this reduces standard errors of the coefficients and improves prediction. To achieve this, we specify the model in Table 4.6 again by introducing in Stepwise variable selection method to improved model fitting. As a result, basing variable entry selection on the significance of score statistic (0.05), and removal based on the probability of likelihood-ratio statistic (0.10). A similar procedure for HIV infection stages II up to stage IV is applied. This procedure improves the model fitting (-2 log likelihood) and proper interpretation of the model estimates, thus the models are estimated with only covariates that significantly predict HIV infection progression at each Stage.

Table 4.7 Relative Risk of HIV Infection Progression at all Stages (Refined for Multiple Factors)

		B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)		
								Lower	Upper	-2 LL
Stage I	Caregiver [Aunt]†			12.340	3	0.006				360.1*
	Grandparents	-1.282	0.514	6.224	1	0.013	0.277	0.101	0.760	
	Mother/father	0.117	0.336	0.122	1	0.727	1.124	0.582	2.170	
	Others persons	0.679	0.354	3.683	1	0.055	1.972	0.986	3.945	
	Father [surviving]†	1.065	0.412	6.676	1	0.010	2.902	1.293	6.510	
Stage II	Age at reg. [9- 12]†			15.515	2	0.000				549.7*
	0- 4	-1.585	0.426	13.833	1	0.000	0.205	0.089	0.472	
	5- 8	-1.486	0.419	12.543	1	0.000	0.226	0.099	0.515	
Stage III	Caregiver [Aunt]†			3.813	3	0.282				428.2*
	Grandparents	-1.826	1.033	3.125	1	0.077	0.161	0.021	1.219	
	Mother/Father	0.049	0.387	0.016	1	0.899	1.050	0.492	2.245	
	Others persons	-0.356	0.475	0.561	1	0.454	0.701	0.276	1.778	
	Age at reg. [9- 12]†			6.988	2	0.030				
	0- 4	-1.272	0.535	5.652	1	0.017	0.280	0.098	0.800	
	5- 8	-1.398	0.545	6.588	1	0.010	0.247	0.085	0.719	
Stage IV	Age at reg. [9- 12]†			5.395	2	0.067				110.6*
	0- 4	-1.662	0.719	5.34	1	0.021	0.190	0.046	0.777	
	5- 8	-1.196	0.712	2.82	1	0.093	0.302	0.075	1.221	

†Reference category, Age at reg. - age registration into care and treatment, *P <0.05

For the first stage, backward stepwise selection method, only two covariates qualifies through the selection criterion father's survival and caregiver. Children with surviving fathers have a significantly higher hazard rate of HIV infection progression than those who lost their fathers (RR=2.90, CI: 1.29-6.51). In addition, Caregiving to children living with HIV/AIDS remains a significant predictor of HIV infection progression at stage I. Children receiving care from their grandparents have a significantly lower hazard rate of HIV infection progression (RR=0.28, CI: 0.10-0.76) compared to children receiving care from their Aunts. Receiving

care from biological parents is indifferent relative to receiving care from Aunts, while receiving care from other relatives/ persons is only significant relative to receiving from Aunt at $p<0.10$ significance level.

For Mildly asymptomatic (stage II), the model result indicates that age of children at enrolment into HIV/AIDS care and treatment is the only significant predictor of HIV infection progression at Stage II. That is, the risk of HIV infection progression is heavily dependent on time of initiation of treatment. Children who started care and treatment at ages 0-4 and 5-8 years had 21% (CI: 0.09- 0.27) and 23% (CI: 0.10-0.52) respectively lower risk of HIV infection progression relative to those who started care and treatment at ages 9-12 years.

At moderately asymptomatic (Stage III), the model retains two variables caregiver and age at initiation of HIV/AIDS care and treatment. The model indicates that caregiver significantly improves model fitting though it is not a strong predictor of HIV infection progression at this stage. It is again observed that children who receive care from grandparents have a lower relative risk of progression than those receiving care from their Aunts ($p<0.10$). Furthermore, age at initiation of HIV/AIDS care and treatment remained an important predictor of HIV infection progression. The model indicate that children who were initiated in care at ages of 0-4 and 5-8 years had a significantly lower risk of HIV infection progression (RR=0.28, CI: 0.10-0.80) and (RR=0.25, CI: 0.09-0.72) respectively than those initiated at nine and more years.

For severely asymptomatic (Stage IV), only age at initiation into HIV/AIDS care and treatment passed the criterion. Likewise, the model indicates that the older the age at initiation into HIV/AIDS care and treatment the higher the relative risk of HIV infection severity. This ranged from 19% (CI: 0.05-0.78) for children aged 0-4 and 30% (CI: 0.08-1.22) for children aged 5-8 years at the time when initiated in HIV/AIDS care and treatment relative to children initiated to care age 9 years and older.

Chapter Five: Discussion, Conclusion and Recommendations

5.1 Introduction

This Chapter presents a summary of the paper through a discussion of the findings, Conclusions and Recommendations. The arguments herein relate to the study objectives, and first present a recap of the study objective.

The study aimed at examining HIV/AIDS progression among children, by modelling the life course of HIV/AIDS and associated factors following WHO (2007a) immunological staging of established HIV infection. The study objective was split-up into four research questions in order to provide answers in a logical manner. The four research questions set to establish (i) the expected duration of stay in each HIV state. (ii) The proportion of the remaining lifetime spent in a given HIV stage. (iii) the transition probabilities from a given HIV state to another, and (iv) demographic and socioeconomic factors that affect differences in HIV/AIDS progression among children living with HIV infection in Uganda. The basic assumption of the study that HIV infection progression is unidirectional that is, disregarding reversal in HIV infection stages.

5.2 Summary of Results

The ultimate period of observation for the 59 children in the study was 11.4 years, contributing 5,108 person months on the HIV infection lifecourse. Over half (55%) of the total HIV infection lifetime is lived with Asymptomatic stage. Indeed, the duration of exposure to HIV infection contributed in each HIV infection stage decreases with progressive amplification in the HIV infection. Furthermore, a half of children with HIV infection stage I survive 59 months before making a progression to a higher stage as opposed to 12 months in stage II and stage III.

Furthermore, Table 4.2 indicates that children with asymptomatic HIV infection (Stage I) are expected to survive on HIV infection lifecourse for a longer span of time than those in advanced stages. That is children occupying asymptomatic HIV infection stage are expected to survive about 70% of the expectation duration of HIV infection exposure time. There is increasingly short expectation of life and great probability of HIV infection progression once a child progresses from asymptomatic HIV infection stage.

The probabilities for children living with HIV infection stage I to progress to a higher HIV infection stage are lower at all times than those of higher HIV infection stages (Figure 4.1). Indeed, at about two years of exposure time, the transition probabilities in stage I are three times lower than in stage II up to stage IV. Nevertheless, transition probabilities from stage II, Stage III and Stage IV are high and show a mixed pattern in the initial periods. Transition probabilities in Stage II to stage IV have a faster rate in the initial phases than in last phases of these stages

The study found no significant differences in sex of a child, birth-weight and mother's survival on children's HIV infection progression. On the other hand, age at initiation of HIV/AIDS care and treatment has a profound effect on HIV infection progression at each stage of HIV infection. In addition, caregivers, father's survival and religious affiliation influence a child's lifetime exposure to HIV infection. Early ages at initiation of HIV/AIDS care, Protestants/ Pentecostals and death of a father are associated with low risk of HIV infection progression relative to old ages and Catholics respectively.

5.3 Discussion

With the advent of antiretroviral therapy and HIV/AIDS care and treatment, persons living with HIV infection live a good healthy life with a near-normal lifespan of those without the infection. However, this is dependent on timely and appropriate use of antiretroviral therapy, that is, proper adherence to treatment (WHO, 2007a). When persons living with HIV/AIDS enrol in care, routine monitoring helps in examine the effect of the infection and or the effectiveness of the treatment for appropriate treatment and care.

The levels of viral load, CD4 cell count or CD4 cell percent present per cubic millilitre of blood sample help to assess the effectiveness of treatment. Viral load helps to determine the number of HIV virus present in the blood, while the CD4 measure gives indication on the health of the immune system. Any of these tests provides a basis to start on ART and or decision to change and boost the therapy. However, these tests are also dependent on biological and social factors. For example, normal CD4 count or normal CD4 percent vary according to age of the person (WHO, 2007a) as illustrated in chapter two Table 2.1 of this study.

The variation in the viral load, CD4 count or CD4 percent at different points in time of HIV infection check-up constitutes a change in the stage or degree of the HIV infection. These HIV infection stages are hierarchical. However, with HIV/AIDS care and treatment (ART) persons living with the infection are expected to live a near normal life, sustain a stage for a long time or even reverse the stage of infection. This is true especially in absence of treatment complications, proper adherence to treatment and absence of other HIV infection influencing factors (co-factors) that hampers the effectiveness of the therapy or facilitates the HIV virus mutation. In this study, we assumed that all children at initial observation were in Asymptomatic HIV infection stage (Stage I). Given that the study sought to estimate progression (not retrogression) probability from one stage to another, a few cases of reversal in HIV infection staging are not considered.

5.3.1 Expected Duration of Stay in each HIV State

The estimation of the expected duration of exposure to HIV infection revealed that children spend on average over seven years on the lifecourse of HIV infection. However, the stage specific duration of exposure contributed in each HIV infection stage decreases with progressive intensification of HIV infection. This phenomenon is evident from Lawn (2004) study, where he observed that the progressive impairment of the immune system and virulent opportunistic infections undermines the duration of exposure. Over half (55%) of the lifetime exposure to HIV infection is lived with Asymptomatic stage (Stage I) indicates that children live a healthier life with HIV infection stage I. Indeed, low or undetectable viral load, high number of CD4 count is the characteristics of asymptomatic stage (WHO, 2007a; NIH, 2010; CDC, 1994) and there are fewer chances of opportunistic infections.

On the other, less duration of exposure in higher HIV infection stages indicate that once a person progresses from Stage I, the chance to continue progression to severe HIV infection stage or even death increases. This echoes Braitstein et al. (2006) observation that progression and mortality is higher among advanced stages of HIV infection than in first or earlier stages. On average children, survive about 60 months with HIV infection Stage I before progressing to another infection stage. This is more than double the survival time for each of the other three stages, which further suggests that survival time with HIV infection is mostly within Stage I. This concurs with findings by Blanche et al. (1997) where over 65% of the children presented with minor symptoms after 6 years of follow-up.

5.3.2 Proportion of the Remaining Lifetime Spent in a Given HIV Stage

The expectation of life at each HIV infection stage revealed a great prospect of life for children occupying infection stage I. Children living with Asymptomatic HIV infection should expect to live about three quarter of the total lifecourse of HIV infection with Asymptomatic HIV infection stage. This in one way or the other resonates the earlier described duration of stay in each HIV infection stage where, much of the total HIV infection lifetime was observed to be spent in stage I. Certainly, the proportion of the remaining lifetime decreases systematically with progressive intensification of HIV infection. Indicating that, the prospect of life is lost or reduces with advanced HIV infection stages. The results suggested that children occupying HIV infection Stage I have more chances to live longer than those who have progressed to higher infection stages, Braitstein et al. (2006) has similar results. In fact, the onset of AIDS (Severely asymptomatic stage) is associated with short survival duration, Feachem (2001) and Braitstein et al. (2006) have similar observation. The severely impaired immune system gives way for numerous opportunistic infections which eventually succumbs the body to fatality as observed by WHO (2007a).

5.3.3 Transition Probabilities from HIV Stages

The study estimated transition probabilities for HIV infection progression from a low stage to a high stage of infection. Results from this have shown risk of making a transition to differ at all time point (Figure 4.1) this is reflecting on findings of Zwahlen & Egger (2006) where median survival time is shown to differ between patient groups. The fact that the probability for a child to progress from Asymptomatic HIV infection stage is low at all time points compared to Stages II up to Stage IV is indicative of a healthy living. Certainly, low morbidity and opportunistic infections as well as high CD4 count and low viral load characterized asymptomatic HIV infection stage compared to other stages (Gona et al., 2006). This translates to Zwahlen & Egger (2006) conclusion that low CD4 lymphocytes and high viral load effect faster HIV infection progression. Nevertheless, the transition probabilities increases directly with increasing duration of survival with HIV infection Stage I; this suggests a gradual decline in the immune system with time.

Transition probabilities in Stage II to stage IV have a faster rate in the initial phases than in last phases of these stages. Transition probabilities are high and faster in these three stages (mildly, moderate and severely asymptomatic) than in asymptomatic stage. There similar results from a number of studies (Lawn, 2004; Morgan, 2002) especially for stage IV, where rates of infection progression are high. The fluctuations in the transition probabilities among stages II up to stage IV are suggestive of drug interruptions or treatment failures. Treatment failure is fatal to the health of a PLWH and in many cases; it is a result of non-adherence to therapy (MoH, 2009). Non-adherence to therapy results into viral drug resistance/ treatment failure (Klimas et al., 2008; MoH, 2009) that facilitate rapid viral replication hence, sudden HIV infection progression.

5.3.4 Co-factors for Differences in HIV/AIDS Progression

For the factors linked to HIV infection progression, the study found that sex of a child is independent of the duration spent in a given HIV infection stage. This is in conformity to the findings in a number of studies (Zwahlen & Egger, 2006; Dennis, 1998; Liu et al., 2004) that have not found a sex effect on HIV infection progression. Though some studies have found an elevated risk of HIV infection progression among females (Rodriguez et al., 2010), this is attributed to the lower viral set point for females (Dennis, 1998; Liu et al., 2004; Liu et al., 2004) than in males.

The effect of age on HIV infection progression is evident at each stage of HIV infection. Young ages at initiation of HIV/AIDS care and treatment is associated with lower risk of HIV infection progression than older ages. Zwahlen & Egger (2006) makes similar observation where they state that younger ages are associated with longer survival time on HIV infection lifecourse. Therefore, younger age initiation to HIV/AIDS care and treatment helps to build a strong immune system with consistent T-cells as opposed to children who start care and treatment at later ages when the immune system is already frail. In fact, WHO (2008) and Abraham et al. (2003) have recorded that initiation of HIV/AIDS care and treatment at infant ages boosts the immune system that suppressed viral replication abilities.

The effect of grandparents as caregiver on the risk of HIV infection progression is apparent in this study. The UN (2008) has acknowledged the worker of grandparents especially the grandmother in giving care to children living with HIV/AIDS. Though the coming of ART assumes that PLWH live a normal life and can fend for themselves (WHO, 2007a), this is not entirely true for children and adult at certain circumstances. The lifelong treatment for HIV infection may spark stress and depressive condition, which is detrimental to the wellbeing of a person (Ironson et al., 2008). In addition, children need social support, comfort and reminders to adhere to the treatment and to deal with stigma in daily life. The strong grandparents' effect associated with HIV infection progression is consistently with a number of literatures that have indicated a great role and burden that grandmothers have rendered in care to their grandchildren living with HIV/AIDS (UN, 2008).
In addition, PLWH needs social support, not only from immediate caregivers, religious institution are some of these sources of support. The study has some evidence suggesting a strong religious affiliation effect on HIV infection progression. Nguyen (2005) notes the religious effect on HIV infection where he acknowledges the importance of counselling for psychological challenges and stigma religious institutions offers. This linkage of social support and care giving to PLWH is also evident in the Uganda National HIV & AIDS Strategic Plan 2007/8 – 2011/12 (UAC, 2007) that advocates for a multifaceted approach to HIV/AIDS care and treatment. However, the low risk of HIV infection progression among Protestants/Pentecostals relative to Catholics is hard to digest here. It is unlikely that the polarized views on some HIV/AIDS prevention campaigns (condom use) that Catholic Church is stringent on can affect treatment. Indeed, the Catholic Church is more liberal when it comes to offering holistic care, counselling services (Prince et al., 2009). In addition, there many initiative that offers social support and instil positive living among PLWH through the Catholic Church (Mubanda, 2011). Thus, the correlation observed here needs further investigation with a bigger sample size than one used in this analysis for conclusive statements.

The absence of a significant effect of birth-weight on HIV infection progression is not in conformity with findings from other studies. For example, Wei et al. (2004) indicate that children of low birth-weight were two times at risk of infant mortality than those born of average weight. Indeed, birth weight is recorded as a strong predictor of child's health and survival (UBOS & Macro Int Inc, 2006), and low birth weight is associated with significant absence of certain micronutrients in the body which is a potent factor for HIV infection progression (Deschamps et al., 2000; Dennis, 1998). The absence effect of the effect of birth weight on HIV infection progression in this study might be a mask by the nutritional support offered to children with HIV/AIDS. ART recognizes nutritional support as a supplement to boost their nutritional status and immune system (Namulema et al., 2007).

The survival of the father negatively affects the health of a child living with HIV/AIDS. This is a critical observation since common observation cites the health and survival of a mother to be more important than that of a father (Little et al., 2007). The effect of paternal survival on a child's HIV infection is a new shift on this arena though it is unclear from this study how father's survival amplifies a child's HIV infection progression. Perhaps it is the dominant gender roles that men assume in African societies and men's ego to evade public sero-disclosure. For this matter, a father perhaps adamantly impinges the child's access and adherence to treatment. Nevertheless, this finding poses a debate beyond the methodology and data used in this study thus, a conclusive statement on this finding needs further investigation of a qualitative type of research.

5.4 Conclusion and Recommendations

The duration of exposure to each distinct HIV infection stage differs from stage to stage and about three quarters of the lifetime lived with HIV infection is spent with asymptomatic HIV infection stage. Moreover, the progressive and amplification of the HIV viral infection undermines the duration of exposure time in each additional higher stage of HIV infection. The transition probability with Asymptomatic HIV infection stage is lower than that of higher infection stages at all time yet; there is an increasingly great probability of HIV infection progression once a child progresses from asymptomatic stage.

HIV infection progression is independent of sex of a child, however, age at starting care and treatment greatly affects exposure time at each stage of HIV infection. Certainly, later ages at initiation of HIV/AIDS care and treatment are associated with high risk of infection progression. Grandparents offer ample care to HIV infected children than other persons, and the role of region in offering social support is evident yet, paternal survival impinge on the of an HIV positive child.

Henceforth, to optimize survival time on HIV infection lifecourse, HIV/AIDS care and treatment (ART) should target to control and maintain HIV infection within asymptomatic levels yet initiating care on the earliest time possible. Adequate monitoring and management of the infection should prioritize early diagnosis through PMTCT and routine medical reviews. Empowering stakeholder in HIV/AIDS care and treatment, such as caregivers, religious institution with information will greatly improve their abilities to enhance the goals of HIV/AIDS care.

The study proposes further research into co-factors of HIV infection progression based on rich data and perhaps a different methodology encompassing qualitative research to conceptualize the effect of factors such as paternal survival on a child HIV infection lifecourse.

These findings have several limitations; the results accrue from a small sample of subjects coupled with several imputations for missing cases. Estimates would be more insightful from a bigger sample and complex analysis techniques for conclusive statements. Nonetheless, the study results tally with findings from other studies and provide good indications on disparities of HIV infection progression among children to stimulate pragmatic actions.

5.5 Study Translation into Existing Policies and Interventions

Describing the life history of HIV/AIDS provides insight into the National HIV/AIDS Strategic Plan (NSP) 2007/8- 2011/12 whose main goal is to *achieve universal access targets for HIV/AIDS prevention, care, treatment and social support by 2012* (UAC, 2007). There is a great urgency to rapidly scale up access to HIV/AIDS-related services to alleviate the debilitating impacts of the infection. This is in concomitant with Okero et al. (2003) conclusions and UNAIDS (2010) comments on the UN's 2006 adoption of the goal of universal access to ART.

Insight into HIV infection transition probabilities enhances the policy agenda of scaling-up and averting likely morbidity and mortality as well as sustaining of the current achievements. This informs policies into managing the increasing demand for ARVs/T that HIV infection progression rates attenuate.

The study advocates for continuous monitoring and evaluation, and other quality improvements aspects to ARVs adherence support, tolerance and side effects of the medications and efficacy of the treatment. This is evident in the NSP (UAC, 2007) but needs strengthening for effective monitoring of patients on ART to provide a pathway that promotes survival, reduce morbidity and improve the quality of life of PLWH.

The duration of survival with HIV infection, directly influences the course of ART; this comes with a financial need to maintain a lifelong treatment. The success of ART program requires constant, timely procurement and stocking of ARVs and related drugs/regimen (UAC, 2007; MoH, 2009; Okero et al., 2003). Thus, the expectation of life on the course of HIV infection is an insight to reinvigorated advocacy and mobilization of funds from development partners and local sources to strengthen and sustain universal access to ART programs.

Examining cofactors of HIV infection progression brings social inequalities and health disparities that make some population categories vulnerable to diseases stresses policy intervention on equitable access to ART. The need for equitable access to anti-retroviral treatment among all population subgroup is a major concern of the NSP. In addition, informed decision-making requires well thought research, which provides evidence for intervention. This study shed new research evidence to enrich effectiveness, efficiency and relevance of HIV and AIDS response for continuous improvement. The findings of the study incite decisions on early initiation of ART irrespective of the levels of viral load and CD4 count.

References

Abrams, E. J., Wiener, J., Carter, R., Kuhn, L., Palumbo, P., Nesheim, Lee, F., Vink, P. & Bulterys, M., (2003). 'Maternal health factors and early paediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children'. *AIDS, 17*(6), 867-77.

AHRQ (2001). *Diabetes Disparities among Racial and Ethnic Minorities, Fact Sheet*. Agency for Healthcare Research and Quality, 2101 East Jefferson Street, Rockville, MD 20852

Amy, F., Kotelchuck, M. & Adess, N. (2009). Policy Brief: A New Agenda For MCH Policy And Programs: Integrating a Life Course Perspective. Contra Costa Health Services. www.cchealth.org/groups/lifecourse

Antai, D. (2009). 'Faith and child survival: The role of religion in childhood immunization in Nigeria'. *Journal of Biosocial Science, 41*(1), 57-76.

Asser, S. M. & Swan, R. (1998). 'Child fatalities from religion-motivated medical neglect'. *Paediatrics* 101(4), 625–29.

AVERT (2011). http://www.avert.org/worldstats.htm. last visited February 4, 2011.

Ben- Shlomo, Y. & Kuh, D. (2002). 'A lifecourse approach to chronic disease epidemiology: Conceptual models, empirical challenges and interdisciplinary perspectives'. *Inter. Journal of epidemiology*, 31(2), 285-93.

Biadgilign, S., Deribew, A., Amberbir, A. & Deribe, K. (2009). 'Barriers and facilitators to antiretroviral medication adherence among HIV-infected paediatric patients in Ethiopia: A qualitative study'. *SAHARA J*. 6(4), 148-54

Blanche, S. (1997). 'Morbidity and mortality in European children vertically infected by HIV-1 the French paediatric HIV infection study group and European collaborative study'. *Journal of Acquired Immune Deficiency Syndromes, 14*(5), 442-450.

Blossfeld, H. & Rohwer, G. (2002), *Techniques of Event History Modeling: New Approach to Causal Analysis.* Lawrence Erlbaum Associates, Inc. Mahwah, New Jersey.

Bos, V., Kunst, A. E., Keij-Deerenberg, I. M., Garssen, J., & Mackenbach, J. P. (2004). 'Ethnic inequalities in age- and cause-specific mortality in the Netherlands'. *International Journal of Epidemiology, 33*(5), 1112-19.

Braitstein, P. Brinkhof, M.W., Dabis, F., Schechter, M., Boulle, A. & Miotti, P. (2006), 'Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low income and high-income countries'. *Lancet* 367 (9513), 817–824.

Caldwell, J. C. (1993). 'Health Transition: the Cultural, Social and Behavioural Determinants of Health in the Third World'. *Soc Sci Med* 36(2),125-135.

Carter-Pokras, O., and Baquet, C. (2002). 'What is a "health disparity"?'. Association of Schools of Public Health, *Public Health Reports*, 117(5), 426-434.

CDC (2006), HIV/AIDS Basics. Divisions of HIV/AIDS Prevention, National Centre for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. http://www.cdc.gov/hiv/resources/qa/definitions.htm. last visited on Feb 28, 2011.

CDC (2011), Health Disparities and Inequalities Report. United States, Centres for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Supplement / Vol. 60.

Centres for Disease Control and Prevention (1994), 'Revised classification system for HIV infected children (<13 years old)'. *MMWR*, 43(RR-12),1-10.

Del Amo, J., Del Romero, J., Barrasa, A., Pérez-Hoyos, S., Rodríguez, C., Díez, M., García, S., Soriano, V. & Castilla, J. (2002). 'Factors influencing HIV progression in a seroconverter cohort in Madrid from 1985 to 1999'. *Sexually Transmitted Infections, 78*(4), 255-260.

Dennis, H. O. (1998). Epidemiology of Disease Progression in HIV: HIV In-Site Knowledge

Base Chapter. University of California, San Francisco. http://hivinsite.ucsf.edu/InSite?page=kb-03-01-04 accessed on May 16, 2010.
Deschamps, M. M., Fitzgerald DW, Pape, J. W. & Johnson, W. D. (2000). 'HIV infection in Haiti: natural history and disease progression'. *AIDS*, 14(16), 2515-21.
Douek, D. C., Roederer, M. & Koup, R. A. (2009). 'Emerging concepts in the immunopathogenesis of AIDS'. *Annu. Rev. Med.* 60: 471–84.
Dyer, W.B., Ogg, G. S., Demoitie, M. A., Jin, X., Geczy, A. F., Rowland-Jones, S.L., McMichael, A. J., Nixon, D. F., & Sullivan, J. S. (1999). 'Strong human immunodeficiency virus (HIV)-specific cytotoxic T-lymphocytes activity in Sydney Blood Bank Cohort patients infected with nef-defective HIV-type 1'. *Journal of Virology* 73 (1), 436–443.
Elder, G. H. (1998). 'The Life course as developmental theory'. *Child Development*, 69 (1), 1-12.
Elder, G. H., Shanahan, M. J. & Clipp, E. C. (1994). 'When war comes to men's lives: Life-course patterns in family, work, and health'. *Psychology and Aging, 9*(1), 5-16.
Feachem, R. (2001). 'HAART-the need for strategically focused investments'. *Bull. World Health Organ* 79(12), 1152-3.
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* 296(3), 292-300.
Halfon, N., Russ, S. & Regalado, M. (2005). The Lifecourse Health Development Model: A guide to children's health care policy and practice. http://www.zerotothree.org. retrieved on Feb 28. 2011.
Hall, S., Holman, C. D., Sheiner, H. & Hendrie, D. (2004). 'The influence of socio-economic and locational disadvantage on survival after a diagnosis of lung or breast cancer in western Australia'. *Journal of Health Services Research and Policy 9*(2), 10-16.
Hutchison, E. D. (2007). *A Life Course Perspective*. CLC-45347.qxd 7/31/2007. http://www.corwin.com/upm-data/16295_Chapter_1.pdf accessed March, 2011.
Ironson, G., O'Cleirigh, C., Fletcher, M. A., Laurenceau, J. P., Balbin, E., Klimas, N., Schneiderman, N. & Solomon, G. (2005). 'Psychosocial factors predict CD4 and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment'. *Psychosomatic Medicine, 67*(6), 1013-21.
Joint United Nations Programme on HIV/AIDS (2006). Overview of the global AIDS epidemic. UNAIDS-2006 Report on the global AIDS epidemic. ISBN 9291734799. http://data.unaids.org/pub/GlobalReport/2006/2006_GR_CH02_en.pdf. retrieved on Feb 22, 2011.
Kaleebu. P, French .N, Mahe. C., Yirrell, D., Watera, C., Lyagoba, F., Nakiyingi, J., Rutebemberwa, A., Morgan, D., Weber, J., Gilks, C. & Whitworth, J. (2002). 'Effect of human immunodeficiency virus (HIV) type 1 envelope subtypes A and D on disease progression in a large cohort of HIV-1-positive persons in Uganda'. *Journal of Infectious Disease* 185 (9), 1244–50.
Kennedy, C. M., Kuhn, L. & Stein, Z. (2000). 'Vitamin A and HIV Infection: Disease Progression, Mortality, and Transmission'. *Nutrition Reviews*, 58(10), 291-303.
Kitahata, M. M., Van Rompaey, S. E., Dillingham, P. W., Koepsell, T. D., Deyo, R. A., & Dodge, W. (2003). 'Primary care delivery is associated with greater physician experience and improved survival among persons with AIDS'. *J Gen Intern Med*. 18(2), 95-103.
Klimas, N., Koneru, A. O., & Fletcher, M. A. (2008). 'Overview of HIV'. *Psychosomatic Medicine,* 70(5), 523-530.
Lawn, S. D. (2004). 'AIDS in Africa: the impact of co-infections on the pathogenesis of HIV-

1 infection'. *J. Infect. Dis.* 48(1), 1–12.
Lintje, H., Bos, V. & Kunst, A. E. (2007). 'Differences in cause-of-death patterns between the native Dutch and persons of Indonesian descent in the Netherlands'. *American Journal of Public Health, 97*(9), 1616-18.
Little, K., Thorne, C., Luo, C., Bunders, M., Ngongo, N., McDermott, P. & Newell, M. L. (2007). 'Disease progression in children with vertically-acquired HIV infection in sub-Saharan Africa: Reviewing the need for HIV treatment'. *Current HIV Research, 5*(2), 139-153.
Liu, K., Peters, V., Weedon, J., Thomas, P., & Dominguez, K. (2004). 'Sex differences in morbidity and mortality among children with perinatally acquired human immunodeficiency virus infection in New York city'. *Archives of Pediatrics and Adolescent Medicine, 158*(12), 1187-88.
Mamun, A. (2003). *Life history of cardiovascular disease and its risk factors*: multistate life table approach and application to the Framingham Heart Study. Population studies, Rozenberg Publishers, Amsterdam, the Netherlands.
Merete, O. (2006). 'The life course perspective: a challenge for public health research and prevention'. *European Journal of Public Health*, 16(3), 230.
Michael, N. L., Chang, G., Louie, L. G., Mascola, J. R., Dondero, D., Birx, D. L. & Sheppard, H. W. (1997). 'The role of viral phenotype and CCR-5 gene defects in HIV-1 transmission and disease progression'. *Nature Medicine, 3*(3), 338-40.
Mildmay (2010), Work in Uganda. http://www.mildmay.org/uganda/. Last visited on Feb 22, 2010.
Mockus, D. S., Coon, P. C., & Gardner, A. (2007). AIDS in Riverside County: Racial/Ethnic Differences in Reporting Source and Disease Progression. Riverside: Riverside County Department of Public Health, Epidemiology and Program Evaluation.
MoH (2004), *Nutritional Care and Support for People Living with HIV/AIDS in Uganda*: Guidelines for Service Providers. STD/AIDS Control Programme, Ministry of Health (MoH) Kampala- Uganda.
MoH (2009), *National Antiretroviral Treatment Guidelines for Adults, Adolescents, and Children*. 3rd Edition. STD/AIDS Control Programme, Ministry of Health (MoH) Kampala- Uganda.
Morgan, D. Mahe, C., Mayanja, B., Okongo, J. M., Lubega, R. & Whitworth, J. A. (2002). 'HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries?'. *AIDS* 16 (4), 597–632.
Morgan, D., Maude, G. H., Malamba, S. S., Okongo, M. J., Wagner, H., Mulder, D. W. & Whitworth, J. A. (1997). 'HIV-1 disease progression and AIDS-defining disorders in rural Uganda'. *Lancet 350*(9073), 245-50.
Mosley, W. H. & Chen, L. C. (1984), An analytic framework for the study of child survival in developing countries. *Population and Development Review* 10:25-45.
Mubanda, L. R. (2011). *From dying with dignity to living with rules: AIDS treatment & "holistic care" in Catholic organizations in Uganda*. Reprocentret – The copy centre of the Faculty of Social Sciences, University of Copenhagen, Denmark.
Namulema, E., Sparling, J. & Foster, H. D. (2007). 'Nutritional supplements can delay the progression of AIDS in HIV-infected patients: results from a double-blinded clinical trial at Mengo Hospital, Kampala, Uganda'. *J. Orthomol. Med*, 22(3), 129-36.
Newell, M., Coovadia, H., Cortina-Borja, M., Rollins, N., Gaillard, P., & Dabis, F. (2004). 'Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: A pooled analysis'. *Lancet, 364*(9441), 1236-43.
Nguyen, V. K. (2005). 'Antiretroviral globalism, biopolitics, and therapeutic citizenship'. In O. Aihwa, & S. J. Collier, *Global Assembalges-Technology, Politics and Ethics as*

Anthropological problems (pp. 124-144). Malden, MA: Blackwell Publishing.
Niessen, L. (2002). *Roads to Health: Multi-State Modeling of Population Health and Resource Use*. Rozenberg Publishers/Dutch University Press, Amsterdam
NIH (2010), HIV/AIDS. http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/Pages/factors.aspx. accessed on May 14, 2011.
NIH (2010). Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. Accessed (10 Feb, 2010)
Okero, F. A., Aceng, E., Madraa, E., Namagala, E & Serutoke, J. (2003), *Perspectives and practice in antiretroviral treatment scaling up antiretroviral therapy: experience in Uganda: case study*. WHO Library Cataloguing-in-Publication Data, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
Omran, A. R. (1998). 'The epidemiologic transition theory revisited thirty years later'. *World Health Statistics Quarterly, 51*(2-4), 99-119.
Page, L. C., Goldbaum, G., Kent, J. B. & Buskin, S. A. (2009). 'Access to Regular HIV Care and Disease Progression among Black African Immigrants'. *Journal of the National Medical Association* 101(12), 1230-36.
Parruti, G., Manzoli, L., Marani Toro, P., D'Amico, G., Rotolo, S., Graziani, V., Schioppa, F. Consorte, A. Alterio, L. Marani Toro, G. & Boyle, B.A. (2006). 'Long-term adherence to first-line highly active antiretroviral therapy in a hospital-based cohort: Predictors and impact on virologic response and relapse'. *AIDS Patient Care and STDs* 20(1), 48-57.
Preston, H. S., Heuveline, P. & Guillot, M. (2001), *Demography measuring and modelling population processes*. Blackwell publishers, Oxford UK.
Prince, R., Denis, P., & van Dijk, R. (2009). 'Introduction to Special Issue: Engaging Christianities: Negotiating HIV/AIDS, Health, and Social Relations in East and Southern Africa'. *Africa Today 56* (1), 4-18.
Rodríguez, Y. A., Ávila, J. P., Cardellá, V. K., Gómez, C. F., Gil, A. B., & Fernandez, T. T. (2010). 'Factors linked to rapid progression to aids in Cuban subjects'. *Revista Cubana De Medicina Tropical*, 62(2), 146-53.
Ronsmans, C., Chowdhury, M. E., Dasgupta, S.K., Ahmed, A. & Koblinsky, M. (2010). 'Effect of parent's death on child survival in rural Bangladesh:a cohort study'. *Lancet* 375: 2024–31
Schneider, M. F., Gange, S. J., Williams, C. M., Anastos, K., Greenblatt, R. M., Kingsley, L., Detels, R. & Munoz, A. (2005). 'Patterns of the hazard of death after AIDS through the evolution of antiretroviral therapy: 1984-2004'. *AIDS, 19*(17), 2009-18.
Serwadda, D., Mugerwa, R. D., Sewankambo, N. K., Lwegaba, A., Carswell, J. W., Kirya, G. B., Bayley, A. C., Downing, R. G., Tedder, R. S. & Clayden, S. A. (1985) 'Slim Disease: A New Disease in Uganda and its Association with HTLV-III Infection'. *Lancet* 2(8460):849-852
StatSoft, Inc. (2011), Electronic Statistics Textbook. Tulsa, OK: StatSoft. WEB: http://www.statsoft.com/textbook/, visited on June 6, 2011.
UAC (2007), *Moving Toward Universal Access: National HIV & AIDS Strategic Plan 2007/8 – 2011/12*. Uganda AIDS Commission, Republic of Uganda: Kampala, Uganda.
Uganda Bureau of Statistics (UBOS) & Macro International Inc. (2007). *Uganda Demographic and Health Survey 2006.* Calverton, Maryland, USA: UBOS and Macro International Inc.
UN (2008), Caregiving in the context of HIV/AIDS. United Nations -Division for the

Advancement of Women, Expert Group Meeting on "Equal sharing of responsibilities between women and men, including care-giving in the context of HIV/AIDS". United Nations' Office at Geneva. EGM/ESOR/2008/BP.4

UNAIDS (2010), Report on the Global AIDS Epidemic: http://www.unaids.org/GlobalReport/Global_report.htm. last visited February 4, 2011.

UNAIDS. (2008) Report on the Global AIDS Epidemic. http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp. Retrieved Feb 21, 2011.

Weeks, J. R. (2005). *Population. An introduction to concepts and issues*. Ninth edition, Wadsworth Publishing, Belmont.

Wei, R., Msamanga, G. I., Spiegelman, D., Hertzmark, E., Baylin, A., Manji, K. & Fawzi, W. W. (2004). 'Association between low birth weight and infant mortality in children born to human immunodeficiency virus 1-infected mothers in Tanzania'. *Pediatr Infect Dis J* 23(6), 530-5

WHO (2007a), *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children*. WHO Press, World Health Organization, Geneva, Switzerland.

WHO (2007b). *Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector*. World Health Organization, Geneva, Switzerland.

WHO (2008). Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group Meeting. WHO Antiretroviral Therapy for Infants and Children 2008. WHO Headquarters, Geneva, Switzerland. Retrieved on Feb 28. 2011.

WHO (2009), Women and health: today's evidence tomorrow's agenda. WHO Headquarters, Geneva, Switzerland. Retrieved on Feb 28. 2011.

Zwahlen M, Egger M (2006) (PDF). *Progression and mortality of untreated HIV-positive individuals living in resource-limited settings: update of literature review and evidence synthesis*. UNAIDS Obligation HQ/05/422204. http://data.unaids.org/pub/Periodical/2006/zwahlen_unaids_hq_05_422204_2007_en.pdf. Retrieved April 24, 2011