Survival and factors influencing treatment outcomes of HIV infected children below 15 years on first-line HAART at Mbale hospital.

A dissertation presented to the Institute of Health Policy and Management in partial fulfilment of the requirements for the award of the degree of Masters of Science in Public Health

International Health Sciences University

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2010-MPH-RL-Feb-017

October 2012

Declaration

I hereby declare that this research report is my original work and has not been submitted to any institution for any award or published in any form and where the work of others has been included, due acknowledgement has been made.

Submitted by,

MUKUYE ANDREW …….

Approved by the supervisor,

MR AFAYO ROBERT …….

Dedication

This dissertation is dedicated to my wife and son for their invaluable support during this course.

Acknowledgements

I would like to convey my sincere thanks to all persons mentioned here-in for their input and support at all times that made this piece of work succeed.

First, i would like to thank my supervisor Mr. Afayo Robert for his time input into proposal development and preparation of this final dissertation.

Secondly i would like to thank all staff and support staff of Mbale Hospital ART clinic for allowing me to use the patient records and who made my work, especially of data collection easy.

Lastly special gratitude goes to all my class mates for they were always present and helpful during the entire course and development of this work.

I hope that the study findings will contribute to better management of HIV infected children in Mbale hospital and Uganda at large.

Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARVS	Antiretroviral drugs
efv or EFV	efaverenz
HAART	Highly active antiretroviral therapy
HIV	human immunodeficiency virus
JCRC	Joint Clinical Research Centre
MUAC	mid upper arm circumference
nvp or NVP	nevirapine
ul	microlitre

Operational definitions

Survival is the time in months from initiation of first-line HAART to switch to second-line HAART.

Loss to follow-up refers to any patient who has not showed up in the hospital three months or more from the last scheduled visit.

Transfer out means any patient who for one reason or the other leaves the hospital HIV/AIDS clinic for good.

Treatment outcomes refer to switch to second-line HAART, transfer out, loss to follow up or death of an HIV-infected child less than 15 years on first-line HAART.

Baseline refers to pre-HAART.

Abstract

Background: The Mbale regional referral hospital HIV care ART annual report for the year ending 31/12/2011 indicated that over 12% (49/401) of the children below 15 years that were on HAART were on second-line HAART and another 2% on first-line HAART had virologic failure and awaited switch to second-line HAART. Evidence from other settings in Uganda has shown more successful survival outcomes among children on first-line HAART but in Mbale hospital the outcomes are less successful.

Objective: To determine the survival and factors influencing the treatment outcomes of HIV-infected children under 15 years on first-line HAART at Mbale Hospital

Methods: A retrospective cohort design was used and records of 340 HIV-infected children under 15 years on first-line HAART at Mbale Hospital were abstracted. Analysis was based on the Kaplan Meier technique. Survivor function and hazard functions where two-sided log rank test for equality of survival functions and test for trend were done. The extended Cox proportional hazards model was used and covariates adjusted for.

Results: The overall survival was estimated to be 68.5%, CI= (52.8-79.9). The survival estimates at months; 12, 24 and 36 was; 100%, 95.8% (CI= 92.5-97.6) and 90.3% (CI= 85.4-93.7) respectively. After controlling for other factors, the factors influencing switch to second line HAART among HIV-infected children less than 15 years on first-line HAART were sex and baseline CD4 count.

Conclusions: The findings show that HIV-infected children on first-line HAART at Mbale Hospital have an overall survival that is lower compared to other settings. Being female and having a CD4 count greater than 200 cells/ul at initiation of first-line HAART increases survival. In HIV-infected children less than 15 years initiation on nevirapine-based first-line HAART is non inferior to initiation on efaverenz-based first-line HAART.

Recommendations: The communities should be sensitized to bring HIV-infected children early to the ART clinic so that they can be monitored and started on first-line HAART at CD4 counts above 200 cells/ul in order to improve these children's overall survival on first-line HAART. Male HIV-infected children should be monitored more closely before and after initiation of first-line HAART in order to improve their survival. The influence of baseline viral loads on survival of HIV-infected children on first-line HAART was not assessed in this study and would be an area for further research since studies in other settings have shown that high baseline viral loads are associated with increased chances of switching to second-line HAART.

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Chapter 1

Introduction

Introduction

There are over 33 million people living with HIV globally (over two thirds of these are in Sub-Saharan Africa) of which about 7.5% are children below 15 years (92% of these children are in sub-Saharan Africa). (UNAIDS, 2010) It is estimated that over 1.2 million people are living with HIV in Uganda, which number includes 150,000 children below 15 years. (UNAIDS, 2010)

It was reported that the number of people receiving antiretroviral therapy in Uganda in 2010 was 248,222 with 19854 of these being children below 15 years (WHO, 2011).The cumulative number of persons ever started on antiretroviral (ART) at Mbale hospital as of 31/12/2011 was 6619 and of these, 528 were children below 15 years. (Mbale hospital, 2011)

Antiretroviral therapy in children restores immune function, maintains maximal suppression of viral replication, reduces HIV-related morbidity and mortality, improves quality of life and prolongs survival. (Netsanet et al, 2009)

Several studies have documented the treatment outcomes of highly active antiretroviral therapy (HAART) in children in resource-poor settings. However, survival on first line highly active antiretroviral therapy (HAART) among HIV-infected children has not yet been well documented despite the fact that most paediatric HIV occurs in resource-limited countries. Studies have shown that HAART improves the survival of HIV- infected adults, but little is known about the extent to which HAART affects survival in paediatric HIV. Response to highly active antiretroviral treatment has been known to differ in age groups. (Andrew et al, 2011)

HIV disease takes a different course in children as opposed to the course it takes in adults because the virus attacks the immature thymus, which leads to a high HIV RNA viral load resulting into rapid death. It would

therefore be unfair to generalize results from studies of adults to HIV-infected paediatric populations. This means that the effect of HAART on survival should be documented specifically in children. (Andrew et al, 2011)

Survival in children on first line HAART remain poorly documented in resource-limited settings like Uganda. (Petros et al, 2010)

The Mbale regional referral hospital HIV/AIDS clinic is faced with an ever increasing number of HIV-infected children failing on first-line HAART regimens and requiring switch to second-line HAART regimens. Evidence from other settings in Uganda has shown more successful survival outcomes among children on first-line HAART but in Mbale hospital the outcomes are less successful.

There are limited data on the survival and factors influencing treatment outcomes of first-line HAART among HIV-infected children below 15 years in Mbale hospital and this study hoped to address this gap. The results of the study would help provide evidence to guide care and treatment practices and polices in Uganda.

It was a retrospective cohort study reviewing clinical and laboratory records of HIV-infected children below 15 years at the initiation of first-line HAART at Mbale hospital.

Background

The UNAIDS' AIDS epidemic update of 2008 estimated that "globally the numbers of children living with HIV increased from 1.5 million in 2001 to 2.5 million in 2007. However, estimated new infections among children declined from 460,000 in 2001 to 430,000 in 2007. Deaths due to AIDS among children had increased from 330,000 in 2001 to 360,000 in 2005, but had now begun to decline to an estimated 330,000 in 2007. Sub-Saharan Africa remained the most affected region in the global AIDS epidemic. More than two out of three (68%) adults and nearly 90% of children infected with HIV lived in this region, and more than three quarters (76%) AIDS deaths in 2007 occurred there." (UNAIDS, 2008)

“The Joint Clinical Research Centre in Uganda pioneered the use of antiretroviral therapy (ART) in sub-Saharan Africa. The antiretroviral drugs (ARVs) were initially imported and distributed to those patients who could afford to buy them. Joint initiatives between international organizations such as UNAIDS and private organizations such as the Joint Clinical Research Centre (JCRC) helped to reduce the cost of ARVs, making them accessible to many more people.” (Mugyenyi, 2001).

Gill et al. noted that “ARV medications became more widely available in Uganda in 2004 when the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund) and the US President's Emergency Plan for AIDS Relief (PEPFAR) came in to support the provision of ART for people with AIDS. These two agencies provided unprecedented multilateral support and enabled the scaling up of access to ART” (2005).

“In June 2004, the Government of Uganda implemented an ARV programme in one national referral hospital (Mulago), in all 11 regional referral hospitals and 11 district hospitals, providing ARVs to 2700 patients. At the time of this study, the Uganda Government, under the National Strategic Framework for Expansion of HIV/AIDS Care and Support - 2001/2-2006/7 was providing ARVs through 140 accredited sites. Most of these were district hospitals and health centre IVs (rural health units offering primary health care, usually staffed by one doctor, one clinical officer, three nurses and three midwives). By September 2005, 14 300 patients were accessing ARVs through these Government facilities.” (WHO, 2006)

The number of children receiving antiretroviral therapy (ART) is increasing significantly, yet “at the end of 2010 only 23 percent of the 2.02 million children in need of ART in low- and middle-income countries were receiving it.”(WHO, 2011)

Banerjee et al noted that “in resource-limited countries, use of highly active antiretroviral therapy (HAART) in HIV-infected children is still poorly documented in terms of impact on survival.” (2010)

A study by Bill et al showed that “the 10-year survival rates for children born with HIV who receive highly active antiretroviral therapy was more than double those for children who do not.” (Kieryn, 2011)

A prospective cohort study by Philippa et al(2010) about growth, immune and viral responses in HIV infected African children receiving highly active antiretroviral therapy showed that "nadir CD4 cell % [OR 6.97 95% CI (2.6 -18.6)], age [OR 4.6 95% CI (1.14 -19.1)] and WHO clinical stage [OR 3.5 95%CI (1.05 -12.7)] were associated with successful treatment outcome."

Therefore, this study aimed to determine the survival and factors associated with survival among HIV-infected children less than 15 years on first-line HAART in Mbale hospital.

Problem statement

The Mbale regional referral hospital HIV care ART annual report for the year ending 31/12/2011 indicated that over 12% (49/401) of the children below 15 years that were on HAART were on second-line HAART. Viral load results for children who had been on first-line HAART for at least six months at Mbale regional referral hospital HIV clinic indicated that over 2% had viral loads above 5000 copies/ul which showed virological failure and were thus supposed to be switched to second-line HAART.

The Mbale regional referral hospital HIV/AIDS clinic is faced with an ever increasing number of HIV-infected children failing on first-line HAART regimens and requiring switch to second-line HAART regimens.

Second-line HAART regimens are very expensive and tend to have more side effects compared to first-line regimens. Failure among children on second-line HAART regimens at Mbale regional referral hospital HIV/AIDS clinic is higher compared to first-line regimens and so, the need to keep HIV-infected children on first-line HAART regimens for as long as possible cannot be over emphasized.

Evidence from other settings in Uganda has shown more successful survival outcomes among children on first-line HAART but in Mbale hospital the outcomes are less successful.

To this end, this study was aimed at assessing the survival and factors influencing treatment outcomes of HIV-infected children below 15 years on first-line HAART at Mbale hospital so as to provide evidence to guide care and treatment practices and polices of HIV-infected children in Uganda.

General objective

To determine the survival and factors influencing the treatment outcomes of HIV-infected children under 15 years on first-line HAART at Mbale Hospital

Specific objectives

1. To determine the survival of HIV-infected children under 15 years on first-line HAART at Mbale Hospital.
2. To determine the sociodemographic factors associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital.
3. To determine the immunological factors associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital.
4. To determine the hematological factors associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital.
5. To determine the drug related factors associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital.

Research questions

1. What is the survival of HIV-infected children less than 15 years on first-line HAART at Mbale Hospital?
2. What sociodemographic factors are associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital?

3. What immunological factors are associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital?
4. What haematological factors are associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital?
5. What drug related factors are associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital?

Significance

Survival in children on first line HAART remain poorly documented in resource-limited settings like Uganda. Most of the studies and clinical trials on the efficacy of highly active antiretroviral therapy (HAART) have been conducted in adult populations.

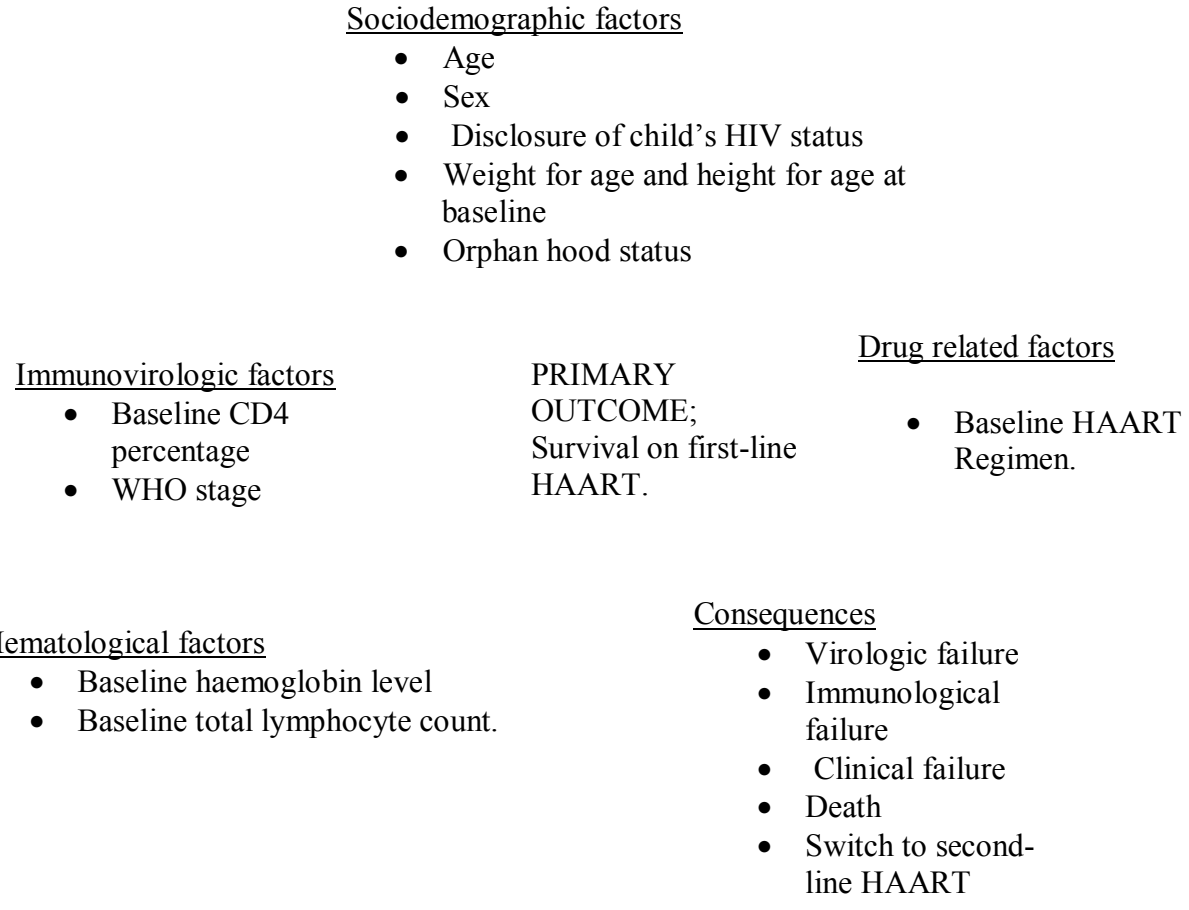
The few studies on survival among HIV-infected children on HAART have been conducted in urban centres (like Mulago Hospital) that are relatively well facilitated compared to rural settings like Mbale Hospital. It would be important to conduct similar studies in rural setting like Mbale hospital to see how they compare with those of urban centres like Mulago and enable the development of effective care so as to improve treatment outcomes.

This study therefore aimed to determine the survival and factors influencing treatment outcomes of HIV-infected children below 15 years on first-line HAART at Mbale hospital so as to provide evidence to guide care and treatment practices and polices of HIV-infected children in Uganda.

Conceptual framework

This conceptual framework shows the factors that influence survival among HIV-infected children below 15 years treated with first-line HAART at Mbale hospital. These antecedent factors have been grouped into; Socio-demographic factors, immunological factors, haematological factors and drug-related factors that will be assessed for their impact on the survival and factors associated with treatment outcomes among HIV-infected children below 15 years treated with first-line HAART at Mbale hospital.

Figure 1: Factors influencing survival on first-line HAART.



Chapter 2

Literature review

Survival of HIV-infected children

There have been several studies and clinical trials conducted to find out the efficacy of highly active antiretroviral therapy (HAART) in adult HIV-infected populations. The clinical efficacy of HAART in children and adolescents has not been well documented in resource-limited settings (RLS) which share the highest burden of paediatric HIV and where less than 5% of the HIV-positive children have access to HAART. (UNICEF, 2005)

Several studies have documented the treatment outcomes of highly active antiretroviral therapy (HAART) in children in resource-poor settings. However, survival on first line highly active antiretroviral therapy (HAART) among HIV-infected children has not yet been well documented despite the fact that most paediatric HIV occurs in resource-limited countries. Studies have shown that HAART improves the survival of HIV- infected adults, but little is known about the extent to which HAART affects survival in paediatric HIV. Response to highly active antiretroviral treatment has been known to vary in age groups. (Andrew et al, 2011)

HIV disease takes a different course in children as opposed to the course it takes in adults because the virus attacks an immature thymus, which leads to a high HIV RNA viral load resulting into rapid death. It would therefore be unfair to generalize results from studies of adults to HIV-infected paediatric populations. This means that the effect of HAART on survival should be documented specifically in children. (Andrew et al, 2011)

A study in Taiwan by Fang et al (2006) that looked at the life expectancy of newly-diagnosed HIV patients in the era of highly active antiretroviral therapy found out that the 5-year survival rate was six in every ten patients who had already developed AIDS at diagnosis (AIDS group), and nine in every ten in those who had not (non-AIDS group). When extrapolation was done, it yielded an expected mean survival time of about

eleven years after diagnosis for the AIDS group, and about twenty two years after diagnosis for the non-AIDS group.

A prospective analysis of 111 African HIV-infected children treated with highly active antiretroviral therapy and getting regular laboratory monitoring showed that the three year survival among these children was over ninety percent. Due to transmitted resistance mutations in 15% of the children that were evaluated, five of the children had first line HAART failure. Virologic failure occurred in 40% of the treated children despite the fact that all of them had immunologic success. Only eleven of the children failing first-line HAART were switched to second line HAART. (Kekitiinwa, A., et al, 2011) Close to ten percent of the children switched to second line HAART and this was lower than that of 12% at Mbale regional referral hospital ART clinic. This study seems to indicate that not all the children experiencing virologic failure are actually switched to the much needed second line HAART and they end up accumulating more mutations on a failing regimen.

A study by Andrew et al at TASO Masaka, Uganda about the five year survival of Paediatric HIV clients found that 243(91.4%) HIV-infected children were surviving after five years. (2010)

Factors influencing survival of HIV-infected children

A study in South Africa showed that lower weight-for-age Z-score and CD4% <10% were significantly associated with decreased survival. (Brian et al, 2011) A study by Kiweewa et al (2011) in Uganda found that duration on first line HAART was the only independent predictor of treatment failure and subsequent switch to second line HAART regimens.

Another study on the survival of HIV-infected children from the Asia-Pacific region found that HIV-infected children with a lower CD4 percentage, WHO clinical stage 4, and lower baseline weight-for-age Z score had decreased survival. (Lumbiganon et al, 2011)

A study by Torsak, B., et al (2011) on virologic and immunologic failure after first-line Non Nucleoside Reverse Transcriptase Inhibitor-based highly active antiretroviral therapy among HIV-infected children in Thailand had the following findings. In univariate Cox's regression to identify the predictors of virologic

failure and subsequent switch to second line HAART, gender, pre-HAART age, nadir CD percentage, CDC clinical class, base line HAART regimen and pre-HAART viral load were not found to be predictors. Since at univariate analysis these factors were not statistically significant, a multivariate model was not developed. In this study, NNRTI-based HAART showed significant improvement of virologic, clinical and immunologic outcomes and the regimens were non inferior to each other. Nearly all of virologic failure occurred in the first twelve months after initiation of Highly Active Antiretroviral therapy. Just like has been found in many other studies, immunologic failure as a monitoring tool for treatment failure and subsequent switch to second line HAART could not be relied on due to its low sensitivity.

A study that looked at switching after first-line antiretroviral therapy failure in resource constrained settings showed that the statistically significant predictors of switch to second line HAART included lower nadir CD4 count, being female, and remaining on antiretroviral therapy for a longer period of time. Age, WHO clinical stage, HAART regimen used, and classes of anti-retroviral drugs available at the clinic did not predict switch to second-line HAART. (International Epidemiological Databases to Evaluate AIDS, 2009)

A study by Collins et al (2010)about long-term survival among HIV-infected children receiving highly active antiretroviral therapy in Thailand showed that with age less than twelve months, a low CD4 cell percentage, and a low weight-for-height z score at HAART initiation, the survival was low. The chances of survival among infants less than twelve months at baseline was eight in ten at twelve months and seven in ten at sixty months of HAART, compared with ninety five point seven percent and ninety four point eight percent respectively, among children older than twelve months. Pre-HAART wasting and a low nadir CD4 percentage were significantly associated with decreased survival among older children but not among infants.

Leonardo, P., et al (2008) in their study found that lower nadir CD4 cell count and earlier calendar year at baseline were strong predictors of switch to second line HAART while Mohammed, I., D., et al (2008) found that nevirapine-based HAART, a nadir CD4 <150 cells/mm^3, treatment interruptions, and previous antiretroviral drugs for prevention of mother to child transmission predicted switch to second line HAART.

Immunologic factors

One prospective cohort study found that the pre-HAART WHO clinical stage and the nadir CD4 cell percentage had a strong association with a favourable treatment outcome. The chances of a successful treatment outcome were much higher among children with CD4 cells percentages greater than ten and WHO stage 1 and 2 at HAART initiation compared to those children with a CD4 cell percentage less than ten and WHO stage 3. (Philippa et al, 2010) The study in Lesotho by Niklaus, D., L., et al (2012) found that adherence levels less than ninety five percent and nadir CD4 cell counts less than one hundred cells per micro litre were the strongly associated with virologic failure and subsequent switch to second line HAART.

Another study by Shearer, W., T., et al (2000) that evaluated the immune survival factors in HIV-1 infected children found that those who survived longer had higher serum IgG levels ,CD19+/CD20+, CD4+, CD8+ , and B-cell counts and, but lower serum IgM and IgA levels than those who had lower survival. Blood haemoglobin levels and serum albumin were lower, but serum HIV-1 RNA levels and LDH were higher in the nonsurvivors compared to survivors. In univariate analysis, significant predictors of survival included baseline HIV-1 RNA, CD8+ and CD4+ cell counts, haemoglobin, IgG, albumin and LDH. In multivariable analysis, low nadir CD4+ count, albumin levels, IgG, and low baseline viral load were important predictors of poor survival. CD4+ cell count and serum IgG level were identified as independent predictors of survival. Both serum albumin levels and baseline viral load predicted survival.

A similar study found that Indian HIV-infected children who had a nadir CD4 percentage greater than or equal to twenty had significantly higher survival as compared to children who had 14% or less.(Rajasekaran et al, 2009) Sara et al (2011) found that baseline predictors of switching to second-line HAART included lower CD4 cell counts.

A study by Chandy, S., et al (2011) on consequences of treatment switching and the predictors in South Indian patients on HAART found that those who had more symptoms and with a lower nadir CD4 cell count were

more likely to switch to second line HAART but higher baseline viral loads were not predictors of treatment switching, and just a few of those with treatment failure were switched to second-line HAART.

Socio-demographic factors

Eduardo et al (2004) found that age less than two years, stunted growth, low mid upper arm circumference, low haemoglobin levels, and water shortage in the house predicted lower survival. In models with time-varying covariates, both stunted growth and wasting in the preceding month were statistically significant predictors and were independently associated with decreased survival.

A study by Heye et al (2012) on the predictors of treatment failure and time to detection and switching in Ethiopia found that HIV-infected children who were less than thirty six months old were more prone to treatment failure.The CHIPS study by Kate lee (2006) about the wide disparity in switch to second-line therapy in HIV infected children found that older children switched sooner than younger children.A study by Paton et al(2006) on the impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy found that under nutrition at HAART initiation was significantly associated with poor survival.

Ntambwe **(2010) in a study among Ugandan children found that** with regard to outcomes of highly active antiretroviral treatment, a nadir CD4 percentage less than fifteen predicted very poor survival more so if HAART was started at a late clinical stage. When the father's HIV status was not known, survival was low compared to when the status was known. Children who had either both parents or a father alive had better survival.

The impact of disclosure on the survival of HIV-infected children shows conflicting results. Some studies have shown that disclosure helps the children adjust to their illness leading to better survival; however, stress levels may increase after disclosure with resultant poor adherence, treatment failure and subsequent switch to second line highly active antiretroviral therapy. There has been no conclusive evidence from previous studies about the impact of disclosure on survival on first line HAART among HIV-infected children less than fifteen years. (New York State Department of Health AIDS Institute, 2009)

Drug related factors

Nevirapine based first line HAART was found to be non inferior to efaverenz based first line HAART in a study by Lapphra et al (2008) among HIV-infected Thai children for both the ARV- experienced and the ARV-naïve but a cohort study by Keiser et al(2002) showed that compared to nevirapine, efavirenz patients had a longer time to treatment failure and subsequent switch to second-line HAART.

A study by Nachega, J., B., et al (2008) found that in a multivariate analysis, patients on efaverenz had a lesser risk of virologic failure, regimen discontinuation and death.

Adherence to HAART is critical to the survival of HIV/AIDS infected people.A number of impediments to successful adherence such as high pill burden and foul-testing medications have been identified in paediatric HIV literature as predictors of decreased survival. (Michele, 2011)

A study by Carina, c., et al (2009) looking at the reasons for early switch to second line HAART in the Caribbean and Latin America found that nevirapine-based HAART and AIDS at HAART initiation were associated with a higher risk of switch to second line HAART compared to Efaverenz-based regimens.

Haematological factors

Dalton et al (2010) in a study on the predictors of mortality in HIV-1 infected children on antiretroviral therapy in Kenya found that low baseline haemoglobin was significantly associated with decreased survival. A study by Anastos et al (2004) found that a low pre-HAART total lymphocyte count was associated with decreased survival. Similarly, a study by Brinkhof et al (2005) found that a low baseline absolute lymphocyte count was a strong predictor of decreased survival.

The studies above carried out in different settings found the factors associated with survival among HIV-infected children less than 15 years on first-line HAART to include: age, sex, disclosure of child's HIV status, body mass index (BMI), orphan hood status, mid upper arm circumference, baseline viral load, WHO stage, baseline haemoglobin level, nadir baseline total lymphocyte count, duration on first line HAART regimen and

baseline HAART Regimen. The findings from these studies concurred on some predictors of switch to second line HAART but disagreed on others.

Chapter 3

Methodology

Introduction

This chapter is arranged into the following sections namely: Study design; Study setting; Sources of data; Study population; Eligibility criteria; Sample size calculation; Sampling procedures; Study variables; Data collection techniques; Data collection tools; Plan for data analysis; Quality control issues; Plan for dissemination; Ethical issues; and limitations of the study

Study design

This was a retrospective cohort study conducted at Mbale regional referral hospital, Eastern Uganda among HIV-infected children less than 15 years at the time of initiation of first-line HAART enrolled from February 2004 to July 2011 followed to July 2012.

Study setting:

On the 1/10/2010 the three HIV/AIDS clinics (all based in Mbale regional referral hospital) namely paediatric HIV/AIDS clinic, infectious disease clinic and JCRC Mbale HIV/AIDS clinic were merged together to form one HIV/AIDS clinic. The patients receiving HAART from Mbale regional referral hospital come from several districts in Eastern Uganda.

The cumulative number of persons ever started on antiretroviral (ART) at Mbale hospital as of 31/12/2011 was 6619 and of these, 528 were children below 15 years. (Mbale hospital, 2011)

Sources of data:

Data was abstracted from clinical and laboratory case report forms in the files of HIV-infected children less than 15 years at the time of initiation of first-line HAART at Mbale hospital.

Population

Target population: All HIV infected patients in Eastern Uganda.

Accessible Population**:** All HIV-infected children on HAART at Mbale Hospital from 2004 to 2012.

Study population**:** HIV-infected children less than 15 years at the time of initiation of first-line HAART at Mbale hospital between 2004 and 2012 who will meet the inclusion criteria.

Eligibility criteria

Inclusion criteria

- Children less than 15 years of age at initiation of first-line HAART were included.
- The children should have been on HAART for at least 12 months prior to data abstraction.
- The first-line HAART regimen at initiation was either niverapine based or efaverenz based.

Exclusion criteria

- HIV-infected children whose data was not available or not clear for review.

Sample size calculation

Sample size

$n = \frac{(Z\,\alpha/2 + Z\beta)^2}{(b-\delta)^2\, p1p2d} =$ 340 HIV-infected children below 15 years on first-line HAART.

Where, δ is the superiority margin of efaverenz versus niverapine based first-line HAART = 54% =0.54(The HIV-CAUSAL Collaboration, 2012)

b is the hazard ratio of niverapine versus efaverenz based first-line HAART [95%CI] = 1.5(Charles, B., Hicks, 2012)

Assuming that sample size will be evenly distributed between the two groups (p1 = p2 = 0.50).

d = patients who will experience switch to second-line HAART after virologic failure (>5000copies/ml) =0.1(Roos et al, 2010)

$Z_{\beta \text{ is}}$ the power of the study corresponding to 80% (0.8416)

$Z_{\alpha/2 \text{ is}}$ the Standard normal value corresponding to 95% confidence interval (1.96)

Sampling technique

Selection of the study patient records/charts (files) was done at Mbale hospital records department by members of the research team which comprised of two trained research assistants who were intern-doctors at Mbale hospital, two members of staff of Mbale hospital records department and the principal investigator. Data was abstracted into the standardized data extraction form

Study variables

Independent variables

Sociodemographic factors

- Age
- Sex
- Disclosure of child's HIV status
- Weight for age at baseline
- Height for age
- Orphan hood status

Immunological factors

- Baseline CD4 percentage
- WHO stage

Drug related factors

- Baseline HAART Regimen status.
  - Niverapine
  - Efaverenz

Haematological factors

- Baseline haemoglobin level
- Baseline total lymphocyte count.

Outcome variable

- Survival time

Survival time was measured as time from initiation of first-line HAART to time to switch to second-line HAART and was determined by subtracting the date of initiation on first-line HAART from the date of switch to second-line HAART. Patients who did not experience the event (switch) by the end of the study or by the time of loss to follow-up, transfer out or death were considered censored.

Patients were censored at the date of the last visit if they were lost to follow-up, at the date of transfer out or death.

In order to obtain information of clients who were lost to follow-up, both their telephone contacts and those of their relatives were searched from their case report forms and they were contacted.

Data Collection techniques

All patients' medical records that met the eligibility criteria were abstracted into a pre-tested data abstraction form. Data was collected by two trained research assistants who were intern-doctors at Mbale hospital, two members of staff of Mbale hospital records department and the principal investigator.

Data Collection tools

A specially designed data abstraction form was used to collect data.

Plan for data analysis

All data was checked for completeness, sorted, coded and entered into the computer using SPSS version 16 package and the raw data was securely stored to maintain confidentiality. Data was exported to STATA version 9.0 software package for analysis.

The Kaplan Meier technique was used. Univariate analysis involved use of summary statistics like frequencies, mean, and median survival. The probability of survival of HIV-infected children on the different first-line HAART regimens i.e. niverapine based and efeverens based first-line HAART regimens was estimated using the Kaplan-Meier method.

The survivor function; median survival time, and hazard functions; hazard ratios with their confidence intervals were determined. Tests (two sided log rank test and log rank test for trend) for equality of survival functions was done. Bivariate, multivariate level and the Cox proportional /regression hazard analysis were done and covariates adjusted for.

Quality Control Issues

The research assistants were trained to ensure that they collect accurate data. The data abstraction form was pre-tested to ensure that it was able to collect data on all the variables.I ensured that the dates in the patients' files matched with those on the laboratory result forms. Two members of staff of Mbale hospital records department picked the files to avoid any bias. Double entry of data was done.

Plan for dissemination

The findings were presented and a hard copy availed to International Health Sciences University and Mbale hospital staff.

Ethical Issues

Ethical clearance was obtained from Mbale regional referral hospital ethical committee and permission was obtained from Mbale hospital authorities to conduct the study. Confidentiality of data was ensured by identifying study subjects using codes and unauthorized persons did not have access to the collected data.

Chapter 4

Data presentation, analysis and interpretation

Descriptive analysis

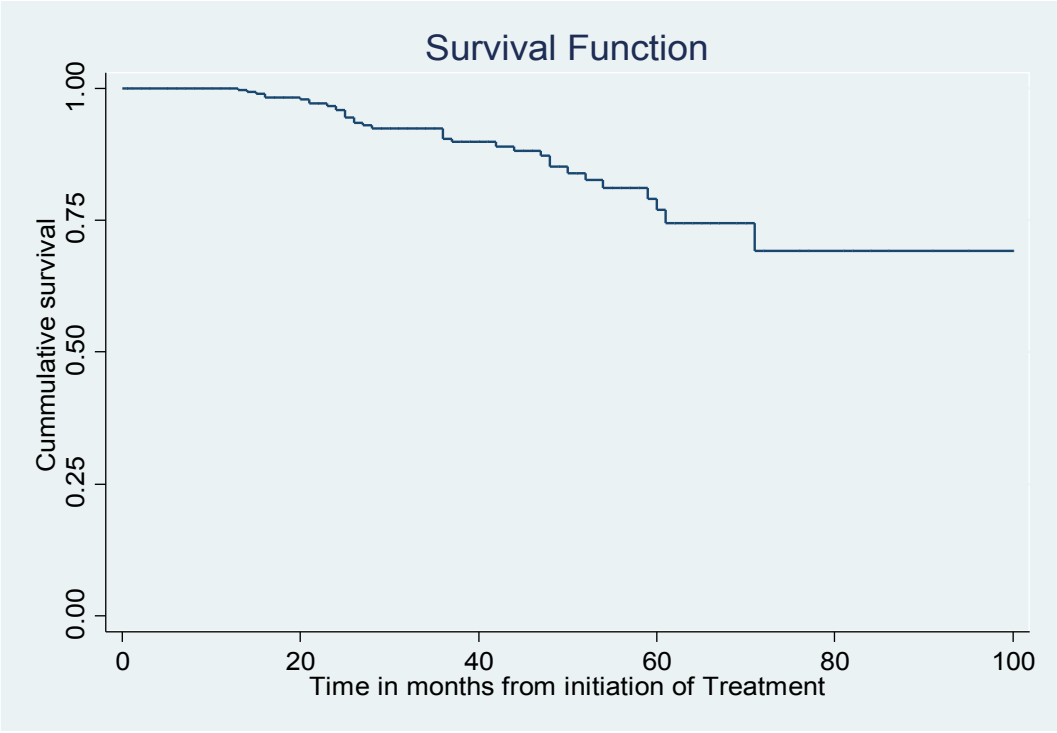
We studied 340 patients who contributed a total of 11478 months (956.5 patient years) of follow-up. We observed 34 switches (failures), giving an overall failure rate of 355.5 per 10000 patient-years. 59.4% (202/340) of the children studied were less than or equal to five years of age. There were 180 female and 160 male HIV-infected children on fist line HAART. The sample size was evenly distributed between the nevirapine and efaverenz groups i.e. 170 HIV-infected children in each group. The rest of the descriptive analysis for the independent variables in this study is summarized in table 1 below.

Table 1: Characteristics of the HIV-infected children aged 15 years or less on first line HAART at Mbale ART Clinic.

Variable	frequency	percentage
Age at initiation of first line HAART		
≤5 years	202	59.4
>5 years	138	40.6
Sex		
Male	160	47.0
Female	180	53.0
Disclosure		
Yes	31	9.1
No	56	16.5
NA	253	74.4
ART status		
Nevirapine	170	50.0
Efaverenz	170	50.0
Baseline CD4 count		
≤200	69	22.4
>200	239	77.6
Baseline Cd4 percent		
≤13.95	141	45.8
>13.95	167	54.2
Baseline Haemoglobin level		
≤10.7 g/dl	147	52.7
>10.7 g/dl	132	47.3
Baseline Lymphocyte level		
≤3.55 g/dl	139	49.5
>3.55 g/dl	142	50.5
Baseline BMI		
≤15.39 Kg/m^2	230	67.7
>15.39 Kg/m^2	110	32.3
Orphan-hood		
Both alive	201	59.1
Mother alive	24	7.1
Father alive	31	9.1
Both dead	84	24.7
WHO stage at initiation of first line HAART		
Stage 1	1	0.3
Stage 2	29	8.5
Stage 3	225	66.2

Stage 4	85	25.0

Figure 2: Survival function for HIV infected children treated with first line HAART



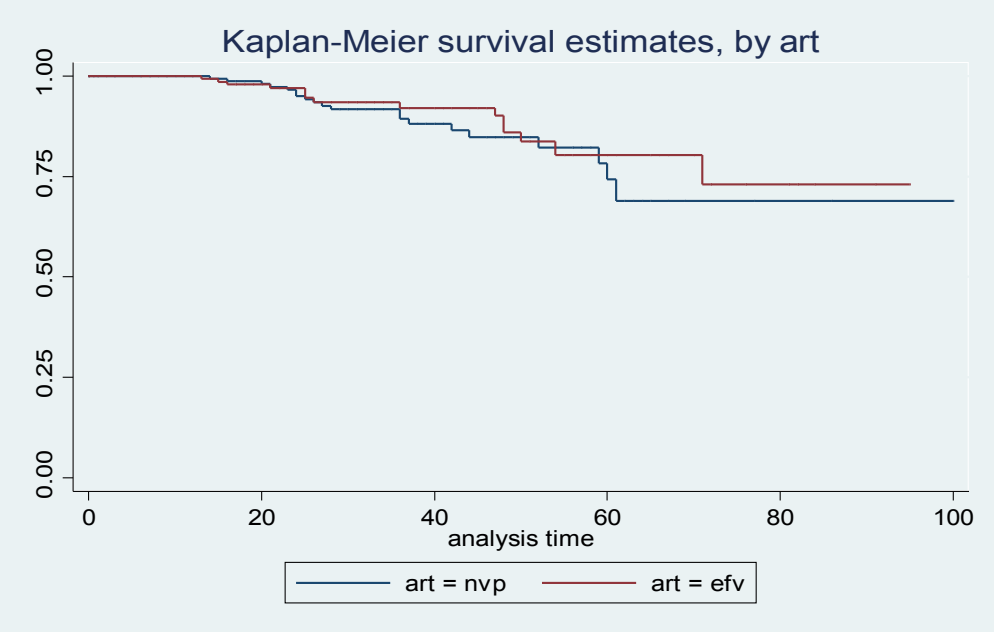
The overall probability of survival after initiation of first-line Anti-retroviral therapy was estimated by Kaplan Meier method. The overall survival was estimated to be 68.5%, CI= (52.8-79.9). The survival estimates at months; 12, 24 and 36 was; 100%, 95.8% (CI= 92.5-97.6) and 90.3% (CI= 85.4-93.7) respectively as shown in figure 2 above.

Bivariate Analysis

Table 2: The survival estimates at 12, 24 and 36 months for HIV infected children on first line treatment are shown below:

Treatment Regimen	12 months	24 months	36 months
Nevirapine based combination	100%	94.9% (CI=89.7-97.6)	89.2% (CI=81.8-93.7)
Efaverenz based combination	100%	96.9% (CI=91.9-98.8)	91.9 (CI=84.0-95.9)

Figure 3: Kaplan Meir survival estimates of HIV infected children receiving Efaverenz and Niverapine at Mbale ART Clinic.



Kaplan Meier Survival curves were constructed for comparison of survival patterns of patients on Nevirapine (nvp) and Efaverenz (efv). The survival times for patients put on Niverapine at baseline was almost the same as for patients put on Efaverenz. Median survival could not be determined because the probability of survival was higher than 50% among patients on both Nevirapine and Efaverenz. Patients on Efaverenz (Survival time mean = 83, 95%CI=76-90) had slightly superior survival compared to Nevirapine (Survival time mean = 82, 95%CI=75-89) patients but the difference was not statistically significant (log rank test p<0.4653) (Figure 3).

The survival for both those on nevirapine and efaverenz based HAART was 100% in the first 12 months. However, survival differences were observed after 24 months and 36 months. In general, patients on Efaverenz based HAART had slightly better survival than those on Nevirapine based HAART after 24 months and 36 months as shown in table 2 above.

Patients who had CD4 count more than 200 cells/ul were less likely ($p<0.001$) to be switched to second line therapy than those with CD4 less than 200 cells/ul. Patients with median CD4 percent greater than 13.95 were less likely (0.041) to be switched to second line combination than those with median CD4 percent less than 13.95. Other socio-demographic and clinical characteristics were not significantly associated with hazards of switch (**Table 3**).

Table 3: Hazard ratio (HR) for Switch to Second line HAART among 340 HIV patients age 15 years or less receiving Nevirapine and Efaverenz

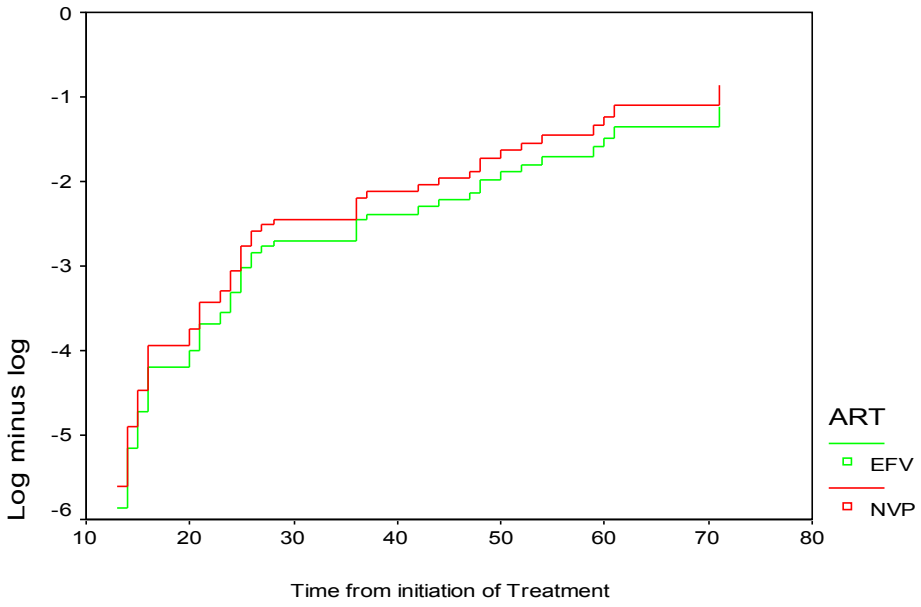
Variable	Number Switched	HR	Logrank p-value
Age			
≤5 years	19	1	
>5 years	15	1.35	0.392
Sex			
Male	20	1	
Female	14	0.56	0.093
Disclosure			
Yes	2	1	
No	6	1.42	
NA	26	0.98	0.737
ART status			
Nevirapine	20	1	
Efaverenz	14	0.77	0.465
CD4 count			
≤200	17	1	
>200	11	0.20	<0.001
Cd4 percent			
≤13.95	16	1	
>13.95	5	0.38	0.041
Hemoglobin level			
≤10.7 g/dl	10	1	
>10.7 g/dl	11	1.55	0.320
Lymphocyte level			
≤3.55 g/dl	14	1	
>3.55 g/dl	7	0.47	0.096

BMI			
≤15.39 Kg/m^2	17	1	
>15.39 Kg/m^2	10	0.68	0.329
Orphan-hood			
Both alive	19	1	
Mother alive	2	0.93	
Father alive	3	2.46	
Both dead	10	1.23	0.606
WHO stage			
Stage 1	0	1	
Stage 2	3	0.72	
Stage 3	18	0.91	
Stage 4	13	1.61	0.396

Testing the Proportionality assumption using the log minus log against survival time

Prior to fitting the final model, the assumption of proportionality of hazard between Nevirapine and Efaverenz categories was verified (tested) using log minus log plot. The lines in these plots were parallel, an indication that the variables did not violate the proportionality assumption (**Figure 4**).

Figure 4: Log minus log survival against time at the initiation of First line HAART.



Testing for time dependence

Proportional hazard assumption was also tested using time dependent covariates. There were no significant covariates, an indication that the proportionality of hazard assumption was not violated. A model without time dependent covariates was fitted and used in subsequent analysis.

Multivariate analysis

The explanatory variables with p<0.2 at bivariate analysis were considered for multivariate analysis in order to fit the final model. These included Sex, CD4 count, CD4 percent, and Hemoglobin level and lymphocyte count. The model was fitted by including the main predictor (ART status), independent variables and interaction terms in the full model and reducing it by removing the product terms to assess whether there was interaction between variables and the main predictor (Chunk test). The difference between the log likelihood ratio for the full and reduced model was assessed using Chunk test. The test showed that there was no interaction. In this model CD4 percent and lymphocyte count were not significant and they were removed from the model and assessed for confounding but they were not confounders. Thus the final Cox proportional hazards regression model was given as h (t, x) = ho (t) exp (0.48ART+0.16CD4+0.39SEX). ART status was retained in the final model because it was the main predictor in this study.

The analysis showed that HIV positive children who were females and those with CD4 count more than 200 cells/ul were less likely to be switched to second line HAART than males (HR=0.39, 95%CI=0.179-0.359, P=0.017) and those with CD4 level less than 200 cells/ul (HR=0.16, 95%CI=0.076-0.359, P<0.001) respectively after controlling for other factors. These results are summarized in Table 4.

Table 4: Multiple Cox proportional hazard regression model for independent predictors of survival among 340 HIV patients aged 15 years or less at Mbale ART Clinic.

Variable	HR	95%CI	p-value
ART			
Nevirapine	1		
Efaverez	0.48	(0.216-1.056)	0.068
CD4 level			
≤200 counts/mm^3	1		
>200 counts/mm^3	0.16	(0.076-0.359)	<0.001
Sex			

Male	1		
Female	0.39	(0.179-0.359)	0.017

Chapter 5

Discussion

Survival of HIV-infected children under 15 years on first-line HAART at Mbale Hospital

The overall five year survival of HIV-infected children less than 15 years on first-line HAART at Mbale Hospital was estimated to be seven in every ten HIV-infected children. This survival is lower than that in other settings in Uganda. For example, a study by Andrew et al (2010) at TASO Masaka, Uganda about the five year survival of Paediatric HIV clients found that nine in every ten HIV-infected children were surviving after five years. This lower survival at Mbale Hospital compared to that at TASO Masaka is probably due to the fact that the HIV-infected children at Mbale Hospital were initiated on HAART at lower CD4+ counts compared to those at TASO Masaka. In Taiwan, Fang et al (2006) found an overall 5 year survival of seven in ten patients which is comparable to that found in this study. Therefore the survival of HIV-infected children less than 15 years on first-line HAART at Mbale Hospital could be improved by initiating them on first-line HAART at higher baseline CD4+ counts.

In this study, HIV- infected children on Efaverenz based first-line HAART had slightly superior survival compared to those on Nevirapine though the difference was not statistically significant. This means that either regimen is equally effective as a first-line HAART regimen in HIV-infected children.

These results were comparable to the findings of Lapphra et al (2008) in HIV-infected Thai children which found that the survival rates of children in the Nevirapine group were not different from those in the Efaverenz group.

Results from studies in Europe and the United States of America included in the HIV CASUAL collaboration (2012) showed that patients on efaverenz based first-line HAART had better survival compared to those on nevirapine based first-line HAART. This was because those on efaverenz based regimens were more adherent to treatment.

Factors associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital

The factors associated with survival among HIV-infected children less than 15 years on first-line HAART at Mbale Hospital were baseline HAART regimen, CD4 count and CD4 percentage plus sex.

Other **studies have found** factors associated with survival among HIV-infected children less than 15 years on first-line HAART from other settings to include: age, disclosure of child's HIV status, body mass index (BMI), orphan hood status, mid upper arm circumference, baseline viral load ,WHO stage, baseline haemoglobin level, baseline total lymphocyte count, and baseline HAART Regimen.

This study found that the level of CD4 count was significantly associated with survival. HIV positive children with CD4 count more than 200 cell/ul were less likely to be switched second line ART combination therapy than those with CD4 level less than 200 cells/ul. These results are comparable to findings in studies by Sara et al (2011) and Chandy, S., et al (2011) which found that baseline predictors of switching to second-line HAART included lower CD4 cell counts.

The difference is probably because at CD4 counts lower than 200 cells/ul, the body's immunity is severely compromised and the children may have co-infections like tuberculosis that require treatment. The increased pill burden reduces adherence to HAART and thus increases the chances of first-line HAART failure and subsequent switch to second-line HAART.

This therefore, reemphasizes the need to initiate children on first-line HAART at CD4 counts above 200 cells/ul. Currently in Uganda, any HIV positive person with a CD4 count below 350 cells/ul or HIV-infected children equal or less than 24 months are initiated on HAART.

This **study also showed that HIV infected children initiating HAART at higher CD4 percentages were less likely to switch to second line HAART at bivariate analysis but not at multivariate analysis. This finding was not in agreement with studies in other settings: Kate Lee (2006) in UK and Ireland, Brian et al (2011) in South Africa; Lumbiganon et al (2011) in the Asia- Pacific region; Philippa et al (2010) in Uganda; and Rajasekaran et al (2009) in India where low baseline CD4 percentages were associated with increased chances of switching to second line HAART.**

This is probably explained by the fact that the body's immunity is severely compromised and the children may have co-morbidities that require treatment. The increased pill burden reduces adherence to HAART and thus increases the chances of first-line HAART failure and subsequent switch to second-line HAART.

This study also found that survival on first-line HAART was significantly associated with the sex of the child. HIV positive children who were females were less likely to be switched second line ART combination therapy than males. These results are different from those in the International Epidemiological Databases to Evaluate AIDS (2009) where being female was associated with increased likelihood of switching to second-line HAART.

The CHIPS study by Kate lee (2006) about the wide disparity in switch to second-line therapy in HIV infected children found that sex was not independently associated with switch to second line HAART.

The reason why females are less likely to be switched to second line HAART is not clear. Male HIV infected children should therefore be monitored more closely in order to improve their survival on first-line HAART.

Age of the HIV-infected children in this study was not found to significantly influence survival on first-line HAART. This is in line with a study done by International Epidemiological Databases to Evaluate AIDS (2009). However, studies else where: Brian et al (2011) in South Africa; Collins et al (2010) in Thailand; and

Eduardo et al (2004) did find age to be a predictor of switch to second line HAART. The CHIPS study by Kate lee (2006) about the wide disparity in switch to second-line therapy in HIV infected children found that older children switched sooner than younger children. The low survival in children equal or less than 5 years can be explained by the fact that their immunity is still low and their adherence is more dependent on the caregivers compared to their older counterparts.

This study showed that those with higher haemoglobin levels prior to first-line HAART initiation were less likely to switch to second line HAART but this relationship was not statistically significant. Similarly, Dalton et al (2010) in Kenya and Anastos et al (2004) seem to concur with the findings of this study. When HIV infected children start HAART at low baseline haemoglobin levels, some drugs like zidovudine decrease the levels further leading to anaemia and thus decreased survival.

Though not statistically significant, children with higher lymphocyte count were less likely to switch to second line HAART and this concurs with studies by Anastos et al (2004) and Brinkhof et al (2005). At high lymphocyte counts, the body is able to defend itself against any infections and this reduces the co-medications and pill burden, leading to good adherence and improved survival.

Survival on first-line HAART in this study could not be explained by body mass index although children with lower body mass indices were more likely to switch to second line HAART**.** However, studies by Brian et al (2011) in South Africa, Lumbiganon et al (2011) in the Asia- Pacific region, and Collins et al (2010) in Thailand found that switch to second line HAART was explained by body mass index. The difference in the results could probably be due to difference in study setting and study design.

Children in this study who had both parents were more likely to switch to second line than those who had lost both parents. This is different from findings in a study by Ntambwe (2010) **on the influence of parents' and caregivers' characteristics on the outcomes of antiretroviral treatment in Ugandan children which found that when both parents were alive, the children were less likely to switch to second line HAART.**

Clinical stage of HIV/AIDS was not found to predict survival on first-line HAART. A study on switching to second-line antiretroviral therapy in resource limited settings showed that Clinical stage did not predict

switching to second-line HAART. (International Epidemiological Databases to Evaluate AIDS, 2009) This concurred with our findings but a study in another setting showed conflicting results. A prospective cohort study on growth, immune and viral responses in HIV infected African children receiving highly active antiretroviral therapy found that children with WHO stage 1 and 2 were three times more likely to have a successful treatment outcome when compared to those children with WHO stage 3. (Philippa et al, 2010)

Methodological issues

The results from this study must be considered with caution. The results can only be generalized to HIV-infected children attending the ART clinic at Mbale Hospital.

Loss to follow-up might have led to information bias which was reduced by making phone calls to the HIV-infected children's next of kins to establish the vital status of these children. Missing information and lack of direct contextual information in the files to answer the study variables also led to information bias. This missing information like viral load and mid upper arm circumference was not assessed in this study.

The study design was a retrospective chart review of records that greatly reduced biases that may have resulted from differential misclassification of the predictor variables.

In view of the limitations and what was done to minimize them, we believe, these findings are internally and externally valid.

Chapter 6:

Conclusions and recommendations

Conclusions

The findings show that HIV-infected children on first-line HAART at Mbale Hospital have an overall survival that is lower compared to other settings.

In HIV-infected children less than 15 years initiation on nevirapine-based first-line HAART is non inferior to initiation on efaverenz-based first-line HAART.

Being female and having a CD4 count greater than 200 cells/ul at initiation of first-line HAART increases survival.

Recommendations

The communities should be sensitized to bring HIV-infected children early to the ART clinic so that they can be monitored and started on first-line HAART at CD4 counts above 200 cells/ul in order to improve these children's overall survival on first-line HAART.

Male HIV-infected children should be monitored more closely before and after initiation of first-line HAART in order to improve their survival.

The influence of baseline viral loads on survival of HIV-infected children on first-line HAART was not assessed in this study and would be an area for further research since studies in other settings have shown that high baseline viral loads are associated with increased chances of switching to second-line HAART.

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Appendices

Appendix 1: questionnaire

PART I: Sociodemographic factors

1. Unique identity number……..
2. Date of birth ……..(dd/mm/yyyy)
3. Age in years……
4. Sex 1. ☐ M 2. ☐ F
5. Disclosure of child's HIV status (not applicable for children below 8 years) 1. ☐ YES 2. ☐ NO 3. ☐ NA(NOT APPLICABLE)

6. Weight for age at baseline (**Gomez Classification:** The child's weight is compared to that of a normal child (50th percentile) of the same age. Percent of reference weight for age = ((patient weight) / (weight of normal child of same age)) * 100)

   1. ☐ 90-110%: normal 2. ☐ 75-89%: mild malnutrition 3.☐ 60-74%: moderate malnutrition 4. ☐ <60%: severe malnutrition 5.☐ Weight not measured

7. Height for age(stunting)(**Waterloo Classification:** percent height for age = ((height of patient) / (height of a normal child of the same age)) * 100)

   1. ☐ > 95%: normal 2. ☐ 90-95%: mild malnutrition 3.☐ 85-90%: moderate malnutrition 4. ☐ <85: severe malnutrition 5.☐ Height not measured

8. Orphan hood status

   1. ☐ Both alive 2. ☐ Mother alive 3. ☐ Father alive 4. ☐ Both dead

9. Mid upper arm circumference (Note: applicable for children between 1 and 5 years old.)

1. ☐ > 13.5: normal 2. ☐ 12.5-13.5: at risk 3.☐ 11-12.4 cm: moderate malnutrition 4. ☐ <11 cm: severe malnutrition 5.☐ Not applicable

PART II: Immunologic factors

10. Before first-line HAART was initiated, was the CD4 count done?

    1. ☐ Yes 2. ☐ No

11. If yes, what was this baseline CD4 count?……..cells/ul.

12. What was the baseline CD4 percentage?.....%

13. WHO clinical staging at initiation of first-line HAART.

    1. ☐ Stage 1 2. ☐ Stage 2 3. ☐ Stage 3 4. ☐ Stage 4

PART III: Drug related factors

14. Baseline HAART Regimen.

    1. ☐ Nevirapine based 2. ☐ Efaverenz based

PART IV: Haematological factors

15. Before first-line HAART was initiated, was the baseline haemoglobin estimation done?

    1. ☐ Yes 2. ☐ No

16. If yes, what was the baseline haemoglobin level?

    1. ☐ Normal> 10g/dL 2. ☐ Mild anemia 8.5 – 10.0 g/dL 3. ☐ Moderate anaemia 7.5 – 8.4 g/dL 4. ☐ Severe anaemia 6.50 – 7.4 g/dL 5. ☐ Life threatening anaemia < 6.5 g/dL

17. Before first-line HAART was initiated, was the baseline total lymphocyte count done?

    1. ☐ Yes 2. ☐ No

18. If yes, what was the baseline total lymphocyte count?

    1. ☐ Normal (> or =1500/ul) 2. ☐ Lymhocytopenia (<1500/ul)

PART V: Outcome variable

19. when was the client initiated on first-line HAART ?.....(dd/mm/yyyy)
20. Is the client still on first-line HAART?

    1. ☐ Yes 2. ☐ No

21. If yes, specify the date last seen (or lost to follow-up).....(dd/mm/yyyy)
22. If no, what was the date of switch to second-line HAART?.....(dd/mm/yyyy)
23. Survival time in months ……

24. Client's survival status.

1. ☐ Still in HIV clinic on first-line HAART 2. ☐ Switched to second-line HAART 3. ☐ Lost to follow-up 4. ☐ Transferred out 5. ☐ Dead.