INCIDENCE AND PREDICTORS OF TREATMENT FAILURE TO SECOND LINE ANTIRETROVIRAL TREATMENT IN A YOUNG PEOPLE LIVING WITH HIV CLINIC

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2015
DECLARATION

I hereby declare that all the work in this dissertation is original unless otherwise acknowledged and has not been submitted for another degree in this or any other university or institution of higher learning, or published in any form.

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DEDICATION

This work is dedicated to all the young people living with HIV/AIDS particularly those at Baylor-Uganda. May you be filled with the courage, strength and the Grace from God who sees us through every storm knowing that there is hope beyond the scourge.
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<table>
<thead>
<tr>
<th>ACRONYM</th>
<th>EXPLANATION</th>
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<tr>
<td>3TC</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>ABC</td>
<td>Abacavir</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reactions</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>Zidovudine</td>
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<td>Combination Antiretroviral therapy</td>
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<tr>
<td>ddl</td>
<td>Didanosine</td>
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<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
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<td>Human Immunodeficiency Virus</td>
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<tr>
<td>LPV/r</td>
<td>Lopinavir/ritonavir</td>
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<tr>
<td>MOH</td>
<td>Ministry Of Health Uganda</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor</td>
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<tr>
<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>PIs</td>
<td>Protease Inhibitors</td>
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<tr>
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<td>People Living with HIV/AIDS</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>YPLHIV</td>
<td>Young people’s living with HIV/AIDS</td>
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</tbody>
</table>
SECOND-LINE ART TREATMENT was defined as the regimen among young people living with HIV (YPLHIV) consisting of two nucleoside reverse-transcriptase inhibitors (NRTIs) and a ritonavir-boosted protease inhibitor (PI).

According to [1], among adults and adolescents, the following sequence of second-line NRTI options is recommended:

i. After failure on a TDF + 3TC (or FTC) based first-line regimen, AZT + 3TC should be used as the NRTI backbone in second-line regimens.

ii. After failure on an AZT or d4T + 3TC-based first-line regimen, TDF + 3TC (or FTC) should be used as the NRTI backbone in second-line regimens.

iii. Heat-stable fixed-dose combinations ATV/r and LPV/r are the preferred boosted PI options for second-line ART.

According to this study treatment failure was defined as 2 consecutive viral load measurements >1,000 copies/ml [1]

YOUNG PEOPLE LIVING WITH HIV (YPLHIV); Study participants aged 15-24 years.
ABSTRACT

**Background:** Second line (PI) based regimens are still very expensive in most developing nations yet will be needed soon by the high number of people on ART due to treatment failure. We asked whether socio-demographic, laboratory and treatment data can be used to estimate the incidence of treatment failure on second line based regimens and to predict treatment failure in a young people living with HIV clinic at Baylor-Uganda.

**Methods:** A retrospective cohort study was carried out on 298 medical records of young people living with HIV receiving second line care and treatment at Baylor-Uganda between the period 2010 and 2013.

**Results:** During the follow up time of 12 (5-49.0) months, there were 65 (21.8%) primary endpoints (treatment failure). The incidence rate was 18.2 (14.3-23.2) per 100 person years and the predictors that were associated with second line treatment failure were duration on ART medication of 1-2 years (HR=3.485, p=0.009), duration on ART of 3-4 years (HR=4.186, p=0.000), duration on ART of > 5years (HR=7.418, p=0.000), viral load > 1000 cp/ml (HR=3.933, p=0.000) and adherence levels < 95% (HR=2.775, p=0.001).

**Conclusion:** A relatively high rate of treatment failure was reported from a clinical setup among young people living with HIV/AIDS in Kampala Uganda. Elevated viral load count, poor adherence and duration on ART were the predictors identified to second line treatment failure.
CHAPTER ONE

1.0 Introduction

1.1 Background

The Human Immunodeficiency Virus (HIV) epidemic continues to be a major challenge to global health [2]. Globally, an estimated 35.3 million people were living with HIV in 2012 [3] with approximately 20% of all HIV positive people and 40% of incident infections found in the sub-Saharan Africa amongst the young people [4]. In Uganda, the HIV prevalence is at 7.3% among 15-49 year olds and among young people living with HIV at 3.7% [5].

The advent of antiretroviral therapy (ART) has resulted into people with HIV living long and healthy lives through continued access to treatment. Patients are typically treated with two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) when initiated on ART. For the most part, ART is safe and effective in suppressing the ability of HIV to multiply [6, 7] and in preventing other opportunistic infections as well as death.

However under some circumstances, ART fails to suppress HIV replication necessitating switch to second line regimens. Second line regimens consist of mainly two NRTIs and a ritonavir-boosted protease inhibitor (PI) [3]. The switch to 2nd line regimens implies that options for treatment are decreasing and therefore it is critical that patients thrive as long as possible on this regimen as third line/salvage options are very limited and require expert decision especially in developing countries. Issues and complications of second-line failure were addressed in WHO treatment guidelines of 2009 with a recommendation for third-line regimens suggested [8]. However, because third-line regimens are costly and not readily available, second-line treatment still remains the last therapeutic option available for majority of the patients in these settings.

The World Health Organization together with other international agencies like PEPFAR and partner states have over the years devoted significant public and private resources to combat HIV
through universal access to ART [9]. Most countries currently provide guidelines for the use of second-line regimens, and the extensive use of ART has resulted into increasing numbers of patients receiving second-line therapy [10].

A growing number of HIV-infected patients in resource-constrained settings are now on 2nd line ART yet little is still known about outcomes in such patients. Most of these patients are failing on second line with studies reporting failure rates of 22% at 6 months, 27% at 24 months, and 38% at 36 months depicting an increasing trend with time while on second line [7].

Treatment failure is routinely monitored clinically together with immunologic or virologic laboratory tests such as CD4, viral load testing and resistance profiling. However these tests are not readily available thus very costly and only carried out in a limited number of reference laboratories. This study explored laboratory, treatment and socio-demographic factors as predictors of second line treatment failure.

Treatment failure issues amongst the young people living with HIV/AIDS revolve around time of initiation of 2nd line, type of regimen prescribed, long term adverse drug reactions (ADRs), disclosure, unsatisfactory adherence, low baseline CD4 and resistance which have not been greatly explored. The predictors of second line treatment failure were reported as decreased adherence and low CD4 cell count [11] among young people.

With the increasing evidence that the current clinical and immunological tools are not sufficient [12] to correctly identify early second line ART failure and the development of resistance to ART, there is need to critically study the predictors to 2nd line regimens for effective treatment care and management. Thus this study aimed to review medical records of the young people living with HIV to determine the incidence and predictors of treatment failure to second line therapy.
1.2 Problem Statement

There is limited data on second line outcomes among young people living with HIV/AIDS and yet the United Nations reports that young people are the fastest growing population of newly infected cases of HIV [13]. This is in line with the Uganda AIDS survey report that reports the HIV prevalence amongst the young people at 3.7%. Some of this high burden is attributed to mother to child transmission while the other is due to heterosexual transmission as seen in most sub-Saharan countries.

There is emerging concern of now young people who were perinataally infected with HIV and are fast transforming into adults [14]. This cohort of patients who were infected before development of their immune systems, and where subjected to ART at an early age do not have many treatment options available if they start failing on ART regimens. Similarly, the lifelong nature of ART treatment presents many challenges that need to be overcome if patients are to successfully remain on treatment and not bring about any treatment failure.

Furthermore, there are [9] reports that young people are at high risk of failing treatment and of transmission of the virus. Therefore, interventions need to be geared towards this group to enable them thrive on particular regimens for as long as possible by suppressing the virus. In addition the report also showed that the risk is more in urban settings and amongst those in socially marginalized groups which is in accordance with the Uganda AIDS survey indicator results [5].

Also, the current second line treatment options are difficult in ensuring long-term adherence due to pill burden, side effects, drug stock outs putting the compliance of these regimens in jeopardy especially in resource limited settings. Uganda just like other developing countries still faces challenges in diagnosing treatment failure due to lack of resources like the regular and reliable laboratory tests such as viral load testing, resistance profiling, and CD4 testing raising a need for other means to obtain this information for proper patient management.
Furthermore, intermittent interruptions of treatment due to drug unavailability, side-effects and toxicities are still major concerns in resource limited settings [15] thus second line ART especially among the young people living with HIV needs to be protected for as long as possible.

1.3 Justification

The Uganda HIV treatment guidelines for adolescents and adults recommend close monitoring and assessment of ART treatment for tolerance, side effects, efficacy of the medications every three months and also encourages patients to report any problem to the clinicians. In addition, they recommend certain laboratory investigations as the absolute minimum during the monitoring and assessment of ART. These laboratory investigations include full blood counts for anemia and other related complications, CD4 for efficacy of the regimens, liver and kidney function tests for monitoring toxicity among other tests [16]. Virological testing which has been shown as better at assessment for treatment failure compared to both clinical and immunological [17] is very costly and still being piloted as a national program by Ministry of Health Uganda at the Central Public Health Laboratories.

The rapid expansion of ART programs has come with growing concerns of high treatment failure rates especially amongst the young people with HIV with many needing third line regimens and salvage treatments or may need these regimens in the near future. These regimens have proven to be very expensive and not available in many facilities offering ART services.

Furthermore, young people living with HIV are faced with many challenges which complicate their ART treatment making their survival poor [18] and quality of life affecting the accelerating progress towards an AIDS free generation by 2015. However, they have also demonstrated capability to learn and support other young people in the care and management of the HIV epidemic. Thus, their involvement is crucial in the design of any interventions targeting any predictors to 2nd line ART treatment.

There is need to review patient medical records to see how well clinical/laboratory factors and socio-demographic factors relate to treatment failure on second line regimens with the increasing
evidence that the current clinical and immunological monitoring tools are not sufficient to identify early enough patients who are failing on 2\textsuperscript{nd} line regimens since routine virological testing is not readily available which is vital in identifying treatment failures.

Thus the study will provide information to understand the predictors and time to treatment failure on second line among young people living with HIV in order to both limit its occurrence and forecast the need for treatment options beyond second-line for longer-term effectiveness.
1.4 Conceptual Frame Work

**Clinical/laboratory factors**
- \(CD_4, CD_8,\) WHO stage,
- Neutrophils, Lymphocytes
- co-infection (TB)

**Viral factors**
- Viral load count,
- Duration on ART, Viral resistance

**Socio-demographic factors**
- School, number of siblings,
- household income, parents

**Drug related factors**
- ADR, experience on ART,
- Regimen type

**Treatment interruption**
- Loss to follow up, poor Adherence

**Host Factors**
- Age, Gender, Mode of transmission, Ethnicity

**Increased hospital stay-strain of health resources**

**Increased mortality and morbidity**

**Salvage treatments, high pill burden, restrictions to treatment, drug resistance**

**Figure 1**: Conceptual framework showing the potential predictors of 2\(^{nd}\) line treatment failure among young people living with HIV/AIDS and its consequences.
1.5 Scope of the Conceptual Frame Work

The conceptual framework outlines the potential predictors of second line ART treatment failure as well as its outcome. In this study, the predictors studied were age, sex, CD$_4$ cell count, CD$_8$ cell count, CD$_4$:CD$_8$, viral load, Duration on ART, WHO clinical stage, lymphocytes cell count, absolute Neutrophil count and adherence to ART medication.

1.6 Research Questions

- What is the incidence rate of second line treatment failure among young people living with HIV/AIDS at Baylor-Uganda?

- What are the predictors of treatment failure among young people living with HIV/AIDS at Baylor-Uganda?

1.7 Study Objectives

1.7.1 General Objectives

- To determine the incidence rate and predictors of treatment failure to 2$^{nd}$ line HAART among young people living with HIV at Baylor-Uganda.

1.7.2 Specific Objectives

- To determine the incidence rate of second line treatment failure among young people living with HIV/AIDS at Baylor-Uganda.

- To determine the predictors of treatment failure to second line antiretroviral therapy among young people living with HIV/AIDS at Baylor-Uganda.
CHAPTER TWO

2.0 Literature Review

2.1 Overview of 2nd line HAART

Second line regimens are indicated for patients who are forced to discontinue their initial regimens as a consequence of treatment failure which may be due to prolonged development of drug resistant mutations, unsuppressed viral load or severe toxicity. Treatment failure of the initial HAART regimen happens because the patient’s virus strain has developed resistance to one or more of the ARV medication due to sub optimal adherence however, this can also happen in patients with good adherence [11].

Resistance due to first line regimens containing 3TC and NNRTIs generally involve replacing the NNRTI with a PI while for regimens containing either AZT or d4T, the second line regimen includes a nucleoside backbone of ABC and If ABC is not available d4T or AZT may be used in the second line regimens.

2.2 Description of treatment failure

Failure of HAART is diagnosed clinically together with immunological or virological criteria. Virological failure usually occurs earliest, followed by immunological failure and lastly clinical failure [9]. According to [9], clinical failure among young people living with HIV/AIDS and adults is defined as a new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage IV) after six months of effective treatment; Immunological failure among young people with HIV and adults is defined as a CD4 cell count falling below the baseline or persistent CD4 levels below 100 cells/mm³ and virological failure is defined as 2 consecutive viral load measurements >1,000 copies/ml and both taken after 24 weeks on ART [1].
2.3 Management of 2\textsuperscript{nd} line treatment failure

A high proportion of patients about 21.8% fail virologically within the first six months after initiating second line, this failure is mainly attributed to suboptimal adherence [19]. The current WHO guidelines [1] recommend that patients failing virologically be subject to adherence support intervention after which a second viral load should be done in order to quantity the number of proportion of virological failures due to non-adherence and also assess the effectiveness of adherence interventions. However not all second line virological failures are due to poor adherence [19] and access to third line regimens is becoming a growing concern for patients failing on second line therapy.

2.4 Incidence of 2\textsuperscript{nd} line treatment failure

Various studies have reported different levels of incidence of 2\textsuperscript{nd} line treatment failure among young people living with HIV. Pujades-Rodriguez [20] reported the incidence of 18.8% from a multi cohort study of 632 patients, older than 14 year olds receiving second-line therapy for more than 6 months in 27 ART programs in Africa and Asia between January 2001 and October 2008. Similarly, Reynolds J. Steven [21] reported an incidence of 19.5% from a cohort study done in Rakai district, Uganda among sixty-five patients who had failed first-line ART and started on second-line regimen.

Further on, Olwale [19] in a systematic and meta-analysis review on the treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings. In this review comprising of 5812 citations, 19 reported second-line failure rates in 2035 patients. The virological failure rate was 21.8% at six months among adult patients.

In another prospective multicenter data analysis study by Mary-Ann Davies [22], a pooled analysis of routine individual data from children who initiated ART in seven South Africa treatment programs found the three year probability of virologic failure among 5485 children at 19.3% (95\%CI: 17.6–21.1).
Results from another prospective cohort study among 1469 HIV positive patients in Europe reported that 20% of patients did not achieve suppression after six months of initiation on second line therapy [23].

From the above, it is apparent that the incidence of second line treatment failure is less similar irrespective of geographical area. However, most of these studies reporting treatment failure were carried out in both children and adults living with HIV/AIDS.

### 2.5 Predictors of 2\textsuperscript{nd} line treatment failure amongst young people living with HIV

A systematic and meta-analysis done by [19] reported the predictors of 2\textsuperscript{nd} line treatment failure as duration of exposure to previous (first line) drug regimens and poor adherence.

A case control study among HIV positive patients on ART [24] at a tertiary referral center identified 39 patients with treatment failure as missed clinic appointments (OR=13.1, 95% CI: 2.8-61.1), multiple previous cART (OR=4.2, 95% CI:1.2-15.3), Hepatitis C infection (OR=8.6, 95% CI: 1.9-38.7), older age at HIV diagnosis (OR=1.1, 95% CI: 1.0-1.2) and CD\textsubscript{4} cell count at virological failure (OR=0.7, 95% CI: 0.5-0.9).

In addition, a retrospective study [25] between 2003 and 2008. Among the 195 participants on to second-line ART. The predictors of 2\textsuperscript{nd} line treatment failure were: weight in the lowest quartile for sex, CD\textsubscript{4} cell count ≤ 100 and adherence <90% at baseline.

A retrospective longitudinal analysis [26] among 829 patients in the Massachusetts General Hospital HIV Outpatient Clinic in the USA, reported: poor adherence (HR= 3.44; 95% CI: 2.34 -5.05), absolute neutrophil count <1000/mm\textsuperscript{3} (HR =2.90, 95% CI: 1.26 - 6.69), baseline viral load (HR = 2.69, 95% CI: 1.78 to 4.07), viral load at <12 months (HR=1.64, 95% CI: 1.10 to 2.45), CD\textsubscript{4} count <200 cells/mm\textsuperscript{3} (HR= 1.90, 95% CI: 1.31 to 2.76), nucleoside-only regimen (HR = 1.75, 95% CI: 1.08 to 2.82), prior virologic failure (HR = 1.70, 95% CI: 1.22 to 2.39) and ≥1 missed visit in the prior year (HR = 1.56, 95% CI: 1.13 to 2.16) as the predictors of treatment failure.
In a prospective multicenter data analysis study [27], the predictors for treatment failure were the use of NVP (aHR: 1.77, 95%CI: 1.11–2.83), RTV (aHR: 2.39; 95%CI: 1.57–3.64) and PMTCT exposure (aHR: 1.40; 95%CI: 1.02–1.92). This study may have an effect on the cohort of patients who were perinatally infected with HIV.

Further on, a retrospective study [28] among 817 HIV infected military beneficiaries found that elevated total CD$_8$ counts were associated with greater risk of future virologic failure.

Most of the studies on predictors of second line treatment failure have been done in adults and children implying that we don’t know if these predictors are the same in the young people living with HIV who are now considered as a high risk group.
CHAPTER THREE

3.0 Methodology

3.1 Study Design

A retrospective cohort study based on secondary medical data of young people living with HIV/AIDS receiving second line care and treatment.

3.2 Study Setting

The study was conducted at Baylor College of Medicine Children’s foundation-Uganda which is a national not-for profit organization operating a clinical center of excellence at Mulago Hospital in Kampala offering care and treatment to HIV infected patients and also serving as a national reference and referral center for pediatric HIV. It is staffed by infectious diseases specialists and physicians who follow the Uganda HIV treatment guidelines in the daily patient management and care.

Baylor Uganda offers HIV care and treatment to over 2000 HIV infected and affected children, young people living with HIV/AIDS and adults at the Clinical center of Excellence at Mulago Hospital. As of December 2013, 450 young people were on second line regimens at the site.

Every newly enrolled patient at Baylor-Uganda clinical center of excellence is retested and the baseline laboratories also performed. These patients are then initiated on the respective regimens i.e. first line, second line and in few instances on third line regimens basing on the national guidelines and through clinical expert opinions. The patient’s residence details are also taken for follow up purposes through home visits in their respective zones as demarcated by the organization.

The Baylor-Uganda certified college of American pathologist laboratory carries out the internal and external testing of the clinic patient samples for tests such as complete blood count, clinical chemistry, CD4 cell count among other investigations. In addition, the clinical team places a lot
of emphasis on continuous patient education which is done daily by the experts specialized in HIV management and care.

Further on, Baylor-Uganda uses an electronic monitoring record system alongside paper based manual system for the tracking of patient care, treatment and decision making by the clinicians which has proved very helpful in record management. This medical data is verified, cleaned and quality controlled on a daily basis by the data department with monthly and quarterly reports generated for the concerned stakeholders where monitoring indicators such as no of corrected reports, number of missing visits, number of missing tests, number of errors made among other indicators are followed up using the root cause analysis approach.

3.3 Study Participants

3.3.1 Target Population

HIV infected young people living with HIV receiving second line care and treatment from Baylor-Uganda, Clinical Centre of Excellence Mulago between January 2010 and December 2013.

3.3.2 Accessible Population

HIV infected young people living with HIV receiving second line care and treatment from Baylor-Uganda between January 2010 and December 2013.

3.3.3 Study Population

All HIV infected young people living with HIV receiving second line care and treatment from Baylor-Uganda who fulfill the eligibility criteria.
3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

- HIV infected young people living with HIVs aged 15-24 years on second line therapy.
- Receiving care from Baylor-Uganda.
- With at least 2 Viral load result after initiation on second line.

3.4.2 Exclusion Criteria

Young people living with HIV/AIDS whose medical records are missing data on key variables such as Adherence, CD4, Viral load at or within the visit windows of baseline, week 24 and week 48 visits.

3.5 Sampling Procedure

All young people living with HIV receiving second line care and treatment at Baylor-Uganda were included in this study for the period January 2010-December 2013.

3.6 Sample Size Determination

To determine an appropriate sample size that can be used to establish the incidence of treatment failure among young people living with HIV at Baylor-Uganda, the Kish Leslie formula was used.

\[ N = \frac{Z^2pq}{d^2} \]

\( Z = \) level of confidence.
p= incidence of second line treatment failure was reported at 0.195 in Uganda [21].

N=total number of participants.

d=precision 5% (0.05).

p=proportion of study population with treatment failure.

Z=critical value at 95% level of confidence=1.96.

Submitting the values into the formula, the minimum number of subjects required to determine the incidence was 241.

**Sample size for analytical objective**

To determine the predictors of treatment failure to second line antiretroviral therapy among young people living with HIV.

Sample size for the analytical objective was estimated using survival analysis calculations [29].

A study by Pujades-Rodríguez [30] reported IRR of 3.14 for adherence. In this case we’ll assume a 5% level of significance, the use of a two-sided test in the analysis and 0.8 power for estimated sample size.

The required number of events is calculated from:

\[ E = e_t + e_c \]

Where \( e_t = \) events in group of young people living with HIVs with low adherence.

\( e_c = \) events in group of young people living with HIVs with high adherence.

Using

\[ e_c = \frac{(Z_\alpha + Z_\beta)^2}{Q^2(1+Q\Delta)/(1-\Delta)} \]

where
\[ Z_\alpha = \text{critical value at 95\% level of confidence} = 1.96. \]

\[ Z_\beta = \text{critical value at 80\% power} = 0.84. \]

\[ Q = \text{ratio of proportion of young people living with HIV/AIDS with high adherence} = 1. \]

\[ \Delta = \text{incident risk ratio from previous study} = 3.14 \ [30]. \]

This gives \( e_c = 29 \)

\[ e_t = Q e_c = 29 \]

\[ E = e_t + e_c = 58 \]

Sample size;

\[ N_{\text{total}} = \frac{(1+Q) E}{(1-\pi_c) + Q (1-\pi_T)} \]

Where \( \pi_c = \text{cumulative survival at 1 year for young people living with HIVs with good adherence}. \)

\[ = \exp (-\lambda t) \]

\( t = \text{time of interest} = 1 \text{ year}, \)

\( \lambda = \text{hazard rate for young people living with HIVs with good adherence} = 383.5 \text{ per 1000 person years} \ [31]. \)

\[ = 0.68 \]

Where \( \pi_t = \text{cumulative survival at 1 year for young people living with HIVs with poor adherence} \)

\[ = \exp (-\lambda t) \]

\( t = \text{time of interest} = 1 \text{ year}, \)

\( \lambda = \text{hazard rate for young people living with HIVs with good adherence} = 176.0 \text{ per 1000 person years} \ [31]. \)

\[ = 0.839 \]
\[
N_{\text{total}} = \frac{((1+0.5)\times 58)}{((1-0.68) + (1-0.839))} = 180
\]

A sample size of 180 was the minimum required to establish the predictors of treatment failure to second line antiretroviral therapy in a young people living with HIV clinic.

Therefore a sample size of 241 was the minimum to achieve the study objectives, however all the data set was used.

3.7 Variables

3.7.1 Dependent Variable

The primary outcome variable was virological failure defined as 2 consecutive viral load measurements >1,000 copies/ml [1] from the time of initiation on second line ART regimen.

3.7.2 Independent Variables

Socio demographic factors: age, sex.
Clinical factors: WHO clinical stage, duration on ART
Immunological factors: CD$_4$, CD$_8$, neutrophil count, lymphocytes count, CD$_4$:CD$_8$.
Adherence: adherence was assessed as the number of pill balances returned to the clinic from the previous visit. For this study adherence was categorized as either good or bad; good adherence was reported as $\geq$ 95% levels and poor adherence as < 95%.

3.8 Data Collection and Management

3.8.1 Data Collection

Data was collected from the point when second line treatment was initiated at Baylor-Uganda, the time points studied were: week 0 (with a window interval of 8 weeks before the start of the second line treatment), week 24 (window interval of weeks 18–30) and week 48 (> week 36) where more than one laboratory result was available, the one closest to the particular time point was used. Trained data collection research assistants obtained information from the electronic
management record system using the pre-tested coded data extraction forms because of the different window intervals for the study participants as the data was or may not have been specific at the exact established time points.

Descriptive information i.e. socio demographic, clinical and laboratory factors was collected on the study participants at the time points required in this study.

3.8.2 Data Management

3.8.2.1 Data Processing

The principal investigator cross checked all the filled data extraction forms for purposes of ensuring both correctness and completeness, the research assistants entered the certified data into EPI data v 3.1 for export to STATA v .12 for analysis. Safe storage of the forms was ensured for subsequent analysis and reference purposes.

3.8.2.2 Data Analysis

Descriptive statistics were used to characterize the socio-demographic, clinical and laboratory variables at baseline in form of percentages and medians. Kaplan-Meier estimates were used to describe time-to-event distributions for virological failure. The endpoint was treatment failure measured from the time of initiation on second line treatment at Baylor-Uganda to two consecutive viral load measurements > 1000copies/ml. Censoring was done at transfer to another facility, loss to follow up and at end of study period i.e. December 2013.

The incidence rate of treatment failure was determined by dividing the number of events (treatment failure) that occurred during the duration of the study by the person years of observation contributed by the total cohort per unit time.

To determine the possible predictors, a cox proportional hazard model was used. Predictors that were significant at p=0.2 were considered for multivariate analysis. In the multivariate analysis, the predictors were assessed for interaction using the chunk test by comparing the -2log
likelihoods of the reduced and full models. Confounding was assessed for the predictors at a percentage of greater than 10%.

3.9 Quality Control

The data extraction tool was pre tested to ensure applicability and any necessary adjustments were made. At least 20 data filled forms were randomly assessed for accuracy and completeness prior to certification of the lot and there was onsite verification of the data collected.

3.10 Ethical Considerations

Approval to conduct this research was obtained from the Clinical Epidemiology unit, School of Medicine Research ethics committee of Makerere University Kampala, Uganda National council of Science and Technology and the Baylor-Uganda Research Ethical committee.

A waiver of consent was applied for from the research ethics committee since the study was to utilize secondary data. All information obtained was processed in anonymity with the patient identification numbers being transformed into codes that where subsequently used throughout the process of data collection and analysis.

3.12 Dissemination of findings

Study finding will be disseminated to the clinical epidemiology unit and school of graduate studies. One copy will be sent to Makerere University Albert Cook library and Baylor-Uganda. Attempts will be made to ensure that findings are peer reviewed and disseminated to scientific community for publication.
CHAPTER FOUR

4.0 RESULTS

4.1 STUDY SUBJECTS

The study consisted of young people living with HIV/AIDS on second line ART treatment at Baylor-Uganda between 1st Jan 2010 and 31st Dec 2013. A total of 441 young people’s records were retrieved during this period. Of the 441 records, 298 (67.6%) had at least 2 HIV RNA measurements (Figure 1).

![Study Profile Diagram]

Figure 2: Study profile of young people living with HIV/AIDS on second line ART treatment at Baylor-Uganda between 1st January 2010 and 31st December 2013.
4.2 DESCRIPTIVE DATA

4.2.1 Baseline characteristics of participants

Table 1 summarizes the baseline characteristics of the study participants. Of the 298 participants 50.7% were males. The median age of the young people living with HIV/AIDS in the study was 17.7 years (IQR 15.0-23.9). About sixty nine percent (68.8%) of the young people living with HIV/AIDS were WHO clinical stage III/IV and 85.6% reported good adherence levels of ≥95%. Approximately twenty eight percentage (27.9%) had a CD$_4$ cell count of <200 cells/µl as shown in the table below.
Table 1: Baseline characteristics of young people living with HIV on second line ART treatment at Baylor-Uganda between 1\textsuperscript{st} January 2010 and 31\textsuperscript{st} December 2013.

<table>
<thead>
<tr>
<th>Characteristic at baseline, n=298</th>
<th>Summary statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>151 (50.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>147 (49.3%)</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>17.7 (15-23.9)</td>
</tr>
<tr>
<td>Duration on ART</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>136 (45.6)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>22 (7.9)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>104 (34.9)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>36 (12.1)</td>
</tr>
<tr>
<td>WHO stage n (%)</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>93 (31.2)</td>
</tr>
<tr>
<td>III/IV</td>
<td>205 (68.8)</td>
</tr>
<tr>
<td>Adherence (a) n (%)</td>
<td></td>
</tr>
<tr>
<td>≥95</td>
<td>255 (85.6)</td>
</tr>
<tr>
<td>&lt;95</td>
<td>41 (13.8)</td>
</tr>
<tr>
<td>(CD_4) (cells/mm(^3)), n (%)</td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>215 (72.1)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>83 (27.9)</td>
</tr>
<tr>
<td>Viral load (b) (cp/ml), n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>118 (39.6)</td>
</tr>
<tr>
<td>≥1000</td>
<td>136 (45.6)</td>
</tr>
<tr>
<td>Status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>273 (91.6)</td>
</tr>
<tr>
<td>Dead</td>
<td>14 (4.7)</td>
</tr>
<tr>
<td>Transferred out</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td>Loss to follow up</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Neutrophil count (x10(^5)cells/(\mu)l), median IQR</td>
<td>2 (1-17)</td>
</tr>
<tr>
<td>Lymphocyte count (cells/(\mu)l), median IQR</td>
<td>1482 (201-4755)</td>
</tr>
<tr>
<td>(CD_8) (cells/(\mu)l), median IQR</td>
<td>978 (160-4091)</td>
</tr>
<tr>
<td>(CD_4):(CD_8), median IQR</td>
<td>0.34 (0.1-3.2)</td>
</tr>
</tbody>
</table>
a) 2 participants missing information at baseline.

b) 44 participants missing information at baseline.

4.3 Treatment Failure Analysis (Primary Endpoint)

4.3.1 Incidence of second line Treatment Failure

A total of 298 subjects were followed up in the study and the median follow up time was 12 (5-49.0) months. During this period, there were 65 (21.8%) treatment failures. The incidence rate was 18.2 (14.3-23.2) per 100 person years.

4.3.2 Assessment of Factors Predictive of Treatment Failure

The outcome variable was treatment failure, while the predictor variables were; age, sex, CD₄ count, viral Load, Duration on ART, neutrophil count, lymphocyte count, CD₈ count, adherence on ART regimen, WHO clinical stage at baseline, CD₄:CD₈.

4.3.2.1 Univariate Analysis

In the univariate analysis, the predictors associated with second line treatment failure were duration on ART medication of 1-2 years (HR=3.414, p=0.014), duration on ART of 3-4 years (HR=4.004, p=0.000), duration on ART of > 5 years (HR=7.475, p=0.000), viral load > 1000 cp/ml (HR=3.582, p=0.002) and adherence levels < 95% (HR=3.582, p=0.002) at baseline. The results for univariate analysis are summarized in the table below.
Table 2: Univariate Analysis for Treatment Failure.

<table>
<thead>
<tr>
<th></th>
<th>Treatment failure (N=298)</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>36 (12.1)</td>
<td>1</td>
<td>0.793</td>
<td>0.455-1.382</td>
</tr>
<tr>
<td>Males</td>
<td>29 (9.7)</td>
<td>0.793</td>
<td>0.455-1.382</td>
<td>0.413</td>
</tr>
<tr>
<td><strong>Age median, (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.7 (15-23.9)</td>
<td>0.933</td>
<td>0.812-1.073</td>
<td>0.331</td>
</tr>
<tr>
<td><strong>Duration on ART, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>35 (11.7)</td>
<td>1</td>
<td>3.414</td>
<td>1.286-9.063</td>
</tr>
<tr>
<td>1-2 years</td>
<td>7 (2.3)</td>
<td>4.004</td>
<td>1.926-8.321</td>
<td>0.000</td>
</tr>
<tr>
<td>3-4 years</td>
<td>17 (5.7)</td>
<td>7.475</td>
<td>2.738-20.408</td>
<td>0.000</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>6 (2.0)</td>
<td>1</td>
<td>3.08</td>
<td>1.625-5.838</td>
</tr>
<tr>
<td><strong>WHO stage, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>18 (6.0)</td>
<td>1</td>
<td>0.947</td>
<td>0.500-1.793</td>
</tr>
<tr>
<td>III/IV</td>
<td>47 (15.8)</td>
<td>0.947</td>
<td>0.500-1.793</td>
<td>0.868</td>
</tr>
<tr>
<td><strong>Adherence, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 95</td>
<td>22 (7.4)</td>
<td>3.08</td>
<td>1.625-5.838</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;95</td>
<td>43 (14.4)</td>
<td>3.08</td>
<td>1.625-5.838</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Viral load (cp/ml)†, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>9 (3.0)</td>
<td>3.582</td>
<td>1.595-8.045</td>
<td>0.002</td>
</tr>
<tr>
<td>≥1000</td>
<td>52 (17.4)</td>
<td>3.582</td>
<td>1.595-8.045</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>CD4 cells, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>37 (12.4)</td>
<td>1</td>
<td>0.662</td>
<td>0.302-1.450</td>
</tr>
<tr>
<td>&lt;200</td>
<td>28 (9.4)</td>
<td>0.662</td>
<td>0.302-1.450</td>
<td>0.303</td>
</tr>
<tr>
<td><strong>Neutrophils, x10³, median (IQR)</strong></td>
<td>2 (1-7)</td>
<td>0.955</td>
<td>0.757-1.204</td>
<td>0.695</td>
</tr>
<tr>
<td><strong>Lymphocyte count, median (IQR)</strong></td>
<td>1503 (377-4755)</td>
<td>1</td>
<td>0.998-1.001</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>CD6 cells, median (IQR)</strong></td>
<td>1003 (195-4091)</td>
<td>1.001</td>
<td>1.000-1.003</td>
<td>0.249</td>
</tr>
<tr>
<td><strong>CD4:CD8, median (IQR)</strong></td>
<td>0.2 (0.0-1.3)</td>
<td>0.377</td>
<td>0.409-3.450</td>
<td>0.389</td>
</tr>
</tbody>
</table>

† 4 participants missing baseline viral load
The significant predictors as well as those with P<=0.25 were then subjected to multivariate cox PH distribution model to identify the independent predictors of second line treatment failure.

4.3.2.2 Multivariate Cox PH distribution analysis.

Adjusted Hazard Ratios were compared for the young people living with HIV/AIDS on second line after adjusting for interaction and confounding.

The factors that were associated with second line treatment failure at multivariate analysis were duration on ART medication of 1-2 years (HR=3.485, p=0.009), duration on ART of 3-4 years (HR=4.186, p=0.000), duration on ART of > 5 years (HR=7.418, p=0.000), viral load > 1000 cp/ml (HR=3.933, p=0.000) and adherence levels < 95% (HR=2.775, p=0.001). The results of the multivariate analysis are summarized in the table below.
Table 3: Multivariate Analysis for Treatment Failure.

<table>
<thead>
<tr>
<th></th>
<th>multivariate cox PH model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment failure (N=298)</td>
</tr>
<tr>
<td>Adherence, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥ 95</td>
<td>43 (14.4)</td>
</tr>
<tr>
<td>&lt;95</td>
<td>22 (7.4)</td>
</tr>
<tr>
<td>Duration on ART, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>35 (11.7)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>17 (5.7)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Viral load (cp/ml)†, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>9 (3.0)</td>
</tr>
<tr>
<td>≥1000</td>
<td>52 (17.4)</td>
</tr>
<tr>
<td>Lymphocytes count, median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1503 (377-4755)</td>
</tr>
<tr>
<td>CD₈ cells, median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1003 (195-4091)</td>
</tr>
</tbody>
</table>
4.4 Assessment of selection bias on participants excluded from the study

A total of 143 participants of the eligible subjects were excluded from the study as shown previously in figure 2. We compared this excluded group with those included in the study on the basis of the baseline predictors as shown in the table below.

As shown in the table below, the participants were identical in some of the characteristics but equally different in the ones that were shown to be predictive of the study outcome thus selection bias was minimum.
<table>
<thead>
<tr>
<th>Parameter at baseline</th>
<th>Enrolled (n=298), n (%)</th>
<th>Not Enrolled (n=143), n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>151 (50.7%)</td>
<td>72 (50.3)</td>
<td>0.913</td>
</tr>
<tr>
<td>Female</td>
<td>147 (49.3%)</td>
<td>71 (49.7)</td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>17.7 (15-23.9)</td>
<td>17.4 (15-23.9)</td>
<td>0.527</td>
</tr>
<tr>
<td>Duration on ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>136 (45.6)</td>
<td>24 (16.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>1-2 years</td>
<td>22 (7.9)</td>
<td>16 (11.8)</td>
<td></td>
</tr>
<tr>
<td>3-4 years</td>
<td>104 (34.9)</td>
<td>86 (60.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>36 (12.1)</td>
<td>17 (11.9)</td>
<td></td>
</tr>
<tr>
<td>WHO stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>93 (31.2)</td>
<td>47 (32.9)</td>
<td>0.573</td>
</tr>
<tr>
<td>III/IV</td>
<td>205 (68.8)</td>
<td>96 (67.1)</td>
<td></td>
</tr>
<tr>
<td>Viral load, (cp/ml), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>118 (39.6)</td>
<td>2 (15.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>≥1000</td>
<td>136 (45.6)</td>
<td>96 (67.1)</td>
<td></td>
</tr>
<tr>
<td>Adherence n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95</td>
<td>255 (85.6)</td>
<td>111 (77.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>&lt;95</td>
<td>41 (13.8)</td>
<td>27 (18.9)</td>
<td></td>
</tr>
<tr>
<td>CD4 (cells/mm3), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>215 (72.1)</td>
<td>85 (59.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>&lt;200</td>
<td>83 (27.9)</td>
<td>48 (33.6)</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count (x10³cells/µl), median (IQR)</td>
<td>2 (1-17)</td>
<td>2 (1-7)</td>
<td>0.975</td>
</tr>
<tr>
<td>Lymph# (cells/µl),median (IQR)</td>
<td>1482 (201-4755)</td>
<td>1426 (84-5095)</td>
<td>0.388</td>
</tr>
<tr>
<td>CD8 (cells/mm3), median (IQR)</td>
<td>978 (160-4091)</td>
<td>991 (59-2959)</td>
<td>0.811</td>
</tr>
<tr>
<td>CD₄:CD₈, median IQR</td>
<td>0.34 (0.1-3.2)</td>
<td>0.27(0.01-2.0)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
CHAPTER FIVE

5.0 DISCUSSION

In this study we queried retrospective medical data of young people living with HIV on second line regimens for the incidence and the predictors of second line treatment failure.

5.1 Incidence of second line treatment failure

During the study period, there were 65 (21.8%) primary endpoints (treatment failure). The incidence rate was 18.2 (14.3-23.2) per 100 person years. These results are likely to be an underestimate of incidence because some eligible young people living with HIV were not included due to missing data on 2nd viral loads. These young people were more likely to have high viral load counts which has been found to be associated with treatment failure in this study.

These findings are synonymous with those reported from similar settings [30], [7], [32] showing rates of 15.6-38.3 per 100 person years. However these results are still higher than those observed in resource rich settings [33] where virological testing is readily available. The lack of alternative treatment options is likely to impede clinician’s decisions on treatment modification in resource limited settings resulting into the high incidence rates on regimens. In this case our results may only be a representation of the situation in resource limited settings.

5.3 Predictors of second line treatment failure

In agreement with other studies is the identification of poor adherence as a predictor of treatment failure [20], [34], [35]. This may reflect a success of adherence interventions as an early warning indicator in treatment monitoring programs identifying treatment failure in settings where viral load and resistance testing still remains unavailable. These results are also synonymous with those from studies done in resource limited settings that demonstrate high levels of adherence among persons on ART as compared to their counterparts in resource rich settings. However,
adherence still remains difficult to measure and among the young people, it still poses several barriers like fear of disclosure status, large number of pills required, forgetfulness, drug supply, cost of ART limited financial resources country health ministries and drug related toxicities that need to be addressed for effective treatment outcomes.

Contrary to previous findings [36], [32] is the lack of association between CD4 count of less than 200 cells/µl and treatment failure. However, this is in line with other studies [37], [38] which have shown CD4 cell count as having a poor sensitivity and lower positive predictive value for identifying virological failure in adults with treatment failure. Studies have also reported that CD4 cell count initially remains elevated in patients who fail to maintain and achieve undetectable plasma viral load while receiving PI based regimens [39]. This further stresses the need for viral load testing for treatment monitoring, but in an era of constrained resources this is not quite feasible and may subsequently lead to inadequate treatment monitoring. Therefore CD4 testing still remains an important strategy in HIV care.

As with other findings [21], [19], our findings also showed that an elevated viral load measurement is associated with an increased risk of treatment failure. This is possibly due to the development of resistant viral variant strains to ART medication that confer resistance to ART medication due to the possibility of a higher proportion of baseline resistance to the NRTI drug class which may lead to sub optimal treatment response due to cross resistance. This further highlights the need for routine viral load measurements in clinical treatment in resource limited settings where there is also a growing need to correctly distinguish between treatment failure and non-adherence on ART.

Our findings also showed that there was an association between treatment failure and duration on ART with an increasing risk the longer a participant was on ART. This is synonymous with previous reports [40] [41]. A possible explanation would be that the participant is being maintained on a failing regimen thereby increasing the chances of having multiple drug mutations due to the absence of virological testing which is common in resource limited setting thereby limiting the effectiveness of future regimens options.
Similarly young people living with HIV initiating second line regimens at advanced WHO clinical stage had a 0.94 reduced risk of failing treatment. This was synonymous with a previous study [42] but was contrary to another study [43]. A possible explanation to this finding would be a modification in the behavioral activities particularly adherence once they were diagnosed as being in advanced stages of the disease. This finding further stresses that clinical staging is not associated treatment failure.

In tandem with findings from other studies is the lack of association between treatment failure and gender [32], [43]. Similarly, age was not associated with treatment failure which was synonymous with another study [44]. However, a protective effect was noted with increasing age. A possible explanation to this finding would be the better understanding of the importance and value of ART with age hence better treatment outcomes.

The study findings also showed that there was no association between absolute neutrophil count and treatment failure. Our results however showed a protective effect with an elevated neutrophil count which was synonymous with a previous study [26]. A possible explanation of this would be the opportunistic infections resulting into low neutrophil count due to poor immune system resulting into high rates of treatment failure.

Our findings also showed that CD8 cell counts was not associated with treatment failure. Our results however showed a protective effect with an elevated CD8 count which was synonymous with a previous study [28]. Since CD8 cell serve as memory cells in the immune system, this finding has implication as a potential predictor for future treatment failure among virally suppressed individuals.

In line with the above, CD4:CD8 was not associated with treatment failure, this was synonymous with a previous study [45] which showed that there was no predictive value of the CD4:CD8 ratio for clinical outcomes. A possible explanation could be that among adults on ART, the CD4/CD8 ratio rarely reaches normal levels due to lymphocyte activation and subpopulation changes, interleukin effects, co-infections, and immunosenescence.
Furthermore, our results showed that total lymphocyte count was not associated with treatment failure but showed a protective effect with an elevated count this is possibly because lymphocytes play an important role in the immune system by helping fight off diseases especially among people living with HIV/AIDS who are immunocompromised.

Our study has strengths and limitations. A major strength of our study is its large cohort of young people living with HIV on second line treatment at the Baylor-Uganda facility that provided the sample size greater than required. Because of this, we were able to study outcomes of second line ART with laboratory and treatment data evaluated.

The study was done in a routine clinical setup that mimics the general situation in many resource limited settings. Many of the data variables obtained in such setting has been used for programmatic set ups where there is adequate treatment monitoring. However, this study was carried out in a clinical center of excellence where most of the services like drug supply, laboratory supplies, expert physicians and consultants are quite reliable which may be far more different from what is available in majority of the facilities offering similar services countywide.

This analysis also had a number of limitations. 143 (32.4%) of the young adults on second line regimens were excluded from the study because they had one viral load result within the study period. This could have resulted into an underestimate of the incidence of treatment failure on second line regimen. However, the sample size that was required to meet the study objectives was achieved.

The study utilized electronic medical records, although these are more reliable than paper charts, they are not as complete as clinical trial or research databases. Despite this limitation this study suggests that electronic medical records data collected as part of routine care can be used to identify patients at increased risk of failing on ART.

Adherence was measured in the study using medication possession ratios based on refill pattern which is an indirect measure of behavior. This method is not sensitive to adherence interruptions.
resulting from behaviors such as pill sharing or “pill dumping”. Despite this limitation, this method has been shown to be inexpensive and readily accessible monitoring tool associated with virologic outcome in sub-Saharan Africa [46].

Resistance testing was not explored in this study, although this was not done, prior studies have showed that, virologic failure of second-line ART was unlikely to have been from acquired PI-associated drug resistance mutations. A large randomized trial showed that failure among patients on boosted protease inhibitor regimens is rarely associated with emergence of new protease inhibitor mutations [47]. This is in line with results from a recent study in South Africa among patients failing lopinavir/ritonavir-containing second-line regimens that showed a very low prevalence of major lopinavir resistance mutations [48] suggesting that adherence not resistance is the primary cause in second-line ART failure in adults.

Random error in the study was addressed through using an adequate sample size for studying each objective in the study which was more than the minimum required in addition, all the young people living with HIV who were on second line regimens at the study site were considered for this study and where all studied.

Selection Bias was addressed through comparison of the young people who were excluded from the study with those who were enrolled in the study. In addition, all the young people living with HIV who were transferred to other health facilities or died during the study period were censored at the point when this happened.

Information Bias was addressed through assessment of at least 20 randomly filled data forms for accuracy and completeness before certification of any lot and through onsite verification of the data collected. There was no confounding in the data at multivariate analysis.
CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

In conclusion, we report a relatively high rate of treatment failure from a clinical setup among young people living with HIV/AIDS in Kampala Uganda. Elevated viral load count, poor adherence and duration on ART were the predictors identified to second line treatment failure.

6.2 RECOMMENDATIONS

From our study findings, we recommend viral load testing as part of routine ART clinical care especially among young adults who have been on second line regimens for more than three years in order to combat treatment failure for the success of ART especially in resource limited settings where cost is a major determinant upon which monitoring interventions are based. This is line with the findings of [49].

6.3 FUTURE RESEARCH

A proposed future study is a more rigorous prospective cohort study with possibility of doing resistance testing, drug–drug interaction particularly with TB drugs among the young living with HIV/AIDS.
REFERENCES


4. Carter M: *Young people (15 to 24 years) especially likely to drop out of HIV care*, 2013.


9. WHO: *Antiretroviral therapy for HIV infection in adults and adolescents*. Recommendations for a public health approach 2010


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APPENDIX

Appendix A: Data extraction form

Incidence and Predictors of treatment failure to second line Antiretroviral Treatment in a young people living with HIV Clinic

1.) Patient No. ..............................................................................................................

2.) Date of data extraction (dd/mm/yy). ........................................................................

Socio-demographic characteristic

3.) Age (yrs). ..............................................................................................................

4.) Sex
   a) Male
   b) female

Clinical factors

5.) Prior ART regimen ..................................................................................................

6.) Current ART Regimen ..........................................................................................

7.) WHO clinical stage
   a) I
   b) II
   c) III
   d) IV
8.) Adherence

1. Wk 0...........................................
2. Wk 24........................................
3. Wk 48........................................

9.) CD4 count (cells/ml)

   a) Wk 0...........................................
   b) Wk 24........................................
   c) Wk 48........................................

10.) CD8 count (cells/ml)

    a) Wk 0...........................................
    b) Wk 24........................................
    c) Wk 48........................................

11.) Neutrophils (cells/ml)

    a) Wk 0...........................................
    b) Wk 24........................................
    c) Wk 48........................................

12.) Lymphocyte count (cells/ml)

    a) Wk 0...........................................
    b) Wk 24........................................
    c) Wk 48........................................

13.) Viral Load count (copies/ml)

    a) Wk 0...........................................
    b) Wk 24........................................
    c) Wk 48........................................