PREDICTORS OF THE FIRST LINE TREATMENT FAILURE IN HIV INFECTED CHILDREN WHO ARE ON SECOND LINE ART TREATMENT IN TANZANIA

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by

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A Dissertation Submitted in (Partial) Fulfilment of the Requirement for the Degree of Master of Sciences (Applied Epidemiology) of Muhimbili University of Health and Allied Sciences
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CERTIFICATION

The undersigned certify that they have read and hereby recommend for examination by the Muhimbili University of Health and Allied Sciences a dissertation entitled*:* **Predictors of First line ART Treatment Failure in HIV Infected Children on Second-Line ART Treatment in Tanzania**, in (partial) fulfilment of the requirement for the degree of Master of Science in Applied Epidemiology of the Muhimbili University of Health and Allied Sciences.

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Prof. Innocent Semali
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Date_____

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Date_____

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I, **Daudi S. Jorojick**, declare that this dissertation is my original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

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DEDICATION

This dissertation is dedicated to my beloved wife, Nurueneza N. Hombo, who has been a source of support and inspiration throughout this study. I also dedicate it to all NACP staff for providing my study with data sets, mentorship, and directives me with devotedly and enthusiastically.

ABSTRACT

Background: Global efforts towards achieving child HIV control include high level adherence to ART. However despite that, reports in Tanzania have reported that ART treatment failure in children ranged from 25.4% to 40%.Treatment failure and delay in switching to the second-line regimen are of significant concerns in the treatment of Human Immunodeficiency Virus (HIV) infected children in a resource-limited setting such as Tanzania. Tanzania HIV treatment and care electronic register at National AIDS Control Program had enrolled 43337 HIV positive children on treatment and care among whom 3669 had experienced first line ART treatment failure thus had been switched to second ART treatment line during the period 2016 to 2018.

Objective: to determine the predictors of the first-line treatment failure in HIV infected children receiving the Second-Line Antiretroviral Therapy (ART) in Tanzania.

Methods: this study was un-matched case-control which extracted data from the Care and Treatment Centers (CTC3) macro database, an electronic database at Tanzania National AIDS Control Program (NACP). The study used 3669 cases and 3669 controls. Cases were 0-15 years old children with HIV who had been switched from the first-line ART to currently the second-line ART in CTC3 in Tanzania between2016 and 2018. The control group composed0-15 years HIV infected children who had remained on the first-line ART during the study period, and who were in the CTC3 register during the same period. A prepared format was used to extract social demographic and disease profiles of the cases and controls. Unconditional logistic regression for unpaired data was used to assess the first-line ART treatment failure predictors at p-value ≤ 0.05 significant level.

Results: the study established that cases had a lower proportion of males (46.4%) than controls (50.4), which was significant difference at ($p<0.01$). Age groups, ART adherence, and WHO staging were also significant variables different between cases and controls. Furthermore, health facility ownership and health facility type distribution were also found to be significantly different between cases and controls. In the multivariate analysis, being

0-4 years showed a higher likelihood of treatment failure by 60 % compared to being older(AOR:1.59;95%CI:1.42,1.78). Similarly, treatment failure in female children was lesser than in male children(AOR:0.88;95%CI:0.81,0.96).Other significant predictor were poor ART adherence(AOR:2.15;95%CI:1.79,2.57), private health facilities (AOR:1.52;95CI:1.08,2.15), dispensaries and health centers (AOR:0.44;95%CI:0.39,0.50) and AOR:0.60;95%CI:0.54,0.66) respectively.

Conclusion: predictors of the first line ART treatment failure and consequent switch to the second line ART included patients' sex, age group, and ART adherence. Health system predictors included health facility type and health facility ownership. Consequently, health managers and providers need to adopt policies and actions that mitigate against the identified significant predictors. Moreover, more research on how predictors mediate the effects is recommended to inform an effective method to institute real time-based interventions.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

ABBREVIATION/ACRONYMS

ADR	Acquired Drug Resistance
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Treatment
ARV	Antiretroviral
ATV/r	Boosted atazanavir
CDC	Centers for Disease Control and Prevention
CTC	Care and Treatment Centre
DRM	Drug Resistance Mutation
EFV	Efavirenz
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
HSHSP	Health Sector HIV Strategic Plan
MOHCDGEC	Ministry of Health Community Development Gender Elderly and Children
NNRTI	Non-Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
TFELP	Tanzania Field Epidemiology and Laboratory Training Program
TLD	Tenofovir Lamivudine and Delutegravir
TLE	Tenofovir, Lamivudine and Efavirenz

DEFINITION OF KEY TERMS

Adherence: this refers to the extent to which a client's behaviour coincides with the prescribed regimen as agreed upon through a shared decision-making process between the client and the health care provider, evidenced by the follow-up card. A combination of tools is used to assess patient medication adherence. Based on the remaining pill count, clinicians can consider good, fair, and poor compliance, and it can perform better when combined with self-reported adherence. We consider good, fair, and poor adherence if the percentage of missed dose is <95%, 85–94%, and < 85% respectively. [2]

Clinical failure: is a new or recurrent clinical event indicating advanced or severe immune deficiency (WHO clinical stage 3 and 4 clinical conditions except for T.B.) after six months of effective treatment [1]

Immunological failure: persistent (at least 2 CD4 measurements) CD4 levels below 200cells/mm for children younger than five years, and CD4 levels below 100 cells/mm for older than five years; recognized as developing or returning to the following age-related immunological thresholds after at least six months on ART, in a treatment-adherent child [2]

Reliability: reliability in this study refers to the accuracy and consistency of the variable's measurement.

Validity: validity in this study refers to the extent to which an instrument measures what it purports to measure

Virological failure: this refers to a viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test. [3]

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background Information

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome(HIV/AIDS) is still a significant public health problem globally. By the year 2020, about 36.7 million people were living with HIV/AIDS in the world, out of which, 2.1 million were children (below 15 years old). Reports showed that 70% (1.5million) most children infected with HIV were living in sub-Saharan African countries [4]. Eastern and southern Africa, in particular, were the regions which were most affected by the HIV epidemic: accounting for 45% of the world's HIV infections. Reports show that AIDS-related illnesses had claimed lives of about 32 million people since its start in the 1980's to the year 2020[4].In Tanzania, the average prevalence of HIV was 4.7in 2018. Approximately 142000 children under the age of 15 years were infected with HIV, with an estimated 3200 AIDS-related child deaths annually. The prevalence nonetheless varied by region in Tanzania[6]. The highest prevalence was observed in Njombe Region (14.8%), whereas, the lowest prevalence was seen in Lindi and Pemba regions (0.3 [7]. Currently, it is estimated that 79% of people, including children with HIV, know their status.

Approximately, 50% of HIV-infected children die before the age of two, and one-third of those who survive past the age of two, die before at the age of five[5]Fortunately, the treatment of HIV infection has tremendously improved since the advent of potent combination therapy (ART). ART dramatically reduces HIV-associated morbidity and mortality and transforms HIV disease into a chronic manageable condition [10]. By 2018, 23.3 million people who were living with HIV were receiving ART globally [11]. In 2014, 48% of children in 21 priority countries (aged 0-14) living with HIV were receiving ART [9].

The only challenge facing the treatment is ART failure. This occurs when the therapy or strategies used fail to combat the disease in individual cases or series. ART Treatment failure can be virologic, immunologic, and/or clinical [20], [21] [47]. Virological failure

can be detected when the plasma viral load is above 1000 copies/ml in two consecutive measurements with a good adherence within three months and on ART at least six months. Moreover, immunological failure is defined as a fall in CD4 cell count to baseline (or below) or a 50% reduction from on treatment peak value or presence of persistent CD4 cell count below 100 cells/mm[12].

Factors identified as contributors to ART failure include comorbidities substitution of cART regimen and duration of follow up of more than 60 month and poor adherence, WHO clinical stage 3 or 4, age group 6 to 9 years, baseline CD4, male gender, motherless children and stavudine containing regimen[13]

Tanzania MoHCDGEC, in collaboration with WHO and other stakeholders, is implementing strategies designed to meet the 95, - 95, - 95 globalgoals by 2030. This global means by 2030; 95% of people living with HIV know their HIV status; 95% of people who know their HIV status are on treatment; and 95% of people on treatment have sustained suppressed viral loads. The last strategy,'95', requires sustained adherence, and none or minimal treatment failure, even in children. The government responses are guided by the Third National Multi-Sectoral Framework on HIV and AIDS (NMSF III) and the Health Sector HIV Strategic Plan [7], which among others, locally translates the UNAIDS Fast Track Strategy. The guidelines intend to enable the achievement of the 95,-95,-95 strategy by 2030; which strives for having95 percent of all people living with HIV(PLHIV) in Tanzania tested by 2030, placing 95 percent of those testing positive on continuous ART, and having 95 percent of those on ART virally suppressed in all affected including paediatrics.

1.2 Problem Statement

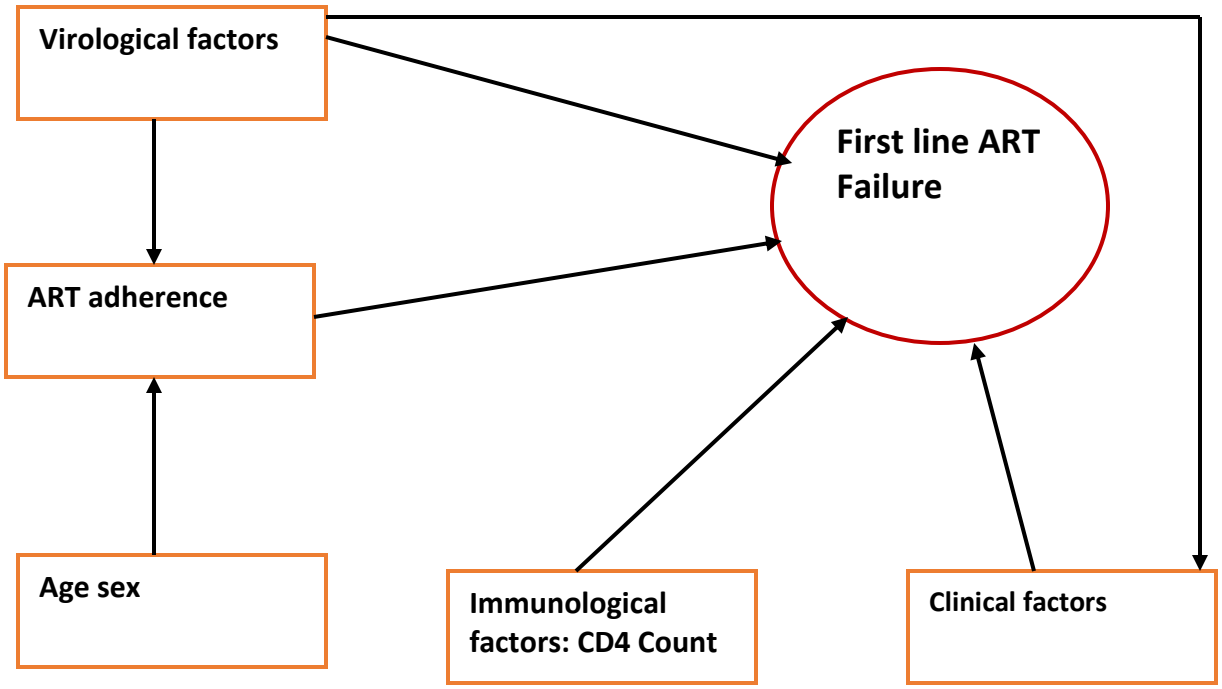
Treatment failure, especially in children on ART, is a continuous challenge which requires sustained effort to monitor and take real-time remedial action to avert its impact.Several studies conducted in Tanzania have shown ART treatment failure in children ranging from 25.4% to 40%.[15], [16]. The studies associate ART treatment failure with factors such as infant ARV prophylaxis unavailability[17], T.B. infection at the time of diagnosis, the substitution of initial cART regimen, duration of follow up of more than 60 months, and poor adherence [13], the WHO clinical stage 3 or 4 at the start of ART, age group 6 to 9 years, baseline CD4 count less than 50 cells/mm3, male gender, motherless children and stavudine-containing regimen[13], [18].

However, there is a dearth of Information on predictors of first line ART treatment failure among HIV-infected children currently on second line ART treatment. Indeed the predictors could be grouped in socio-demographic characteristics, clinical, immunological and health system.

1.3 Conceptual Framework

The conceptual framework in Fig 1 shows the factors that have been found to determine TLE treatment failure in children below 15 years in various studies. As shown in the figure, a high viral load occurs when ART fails to suppress and sustain a person's viral load to less than 200 copies/mL [3].The virological predictor may increase comorbidities such as Pneumonia and Tuberculosis, and immunological predictors such as low CD4 may be the indirect predictors of poor treatment outcome[15]. Immunological predictors interfere withthe clinical stage of the disease. Lack of adherence ultimately leads to the emergence of resistance to ART drugs and, thus, treatment failure [19]. Poor adherence to ARTs may lead to worse clinical predictors due to lower individual immunity, and thus cause the disease to progress into the advanced WHO stage. Other predictors are such as poor adherence demographic, immunological and virological predictors [20], [21] andpoor nutrition; which increases the risk of infection and chronic diarrhoea which decreases drug absorption and impairs metabolism [22].

Figure 1: Conceptual Framework



1.4 Rationale

In line with the conceptual framework, the present study aimed to determine the predictors of TLE regimen failurein childrenin Tanzania. The findings of the study inform the government and policymakers to plan and set initiatives for controlling the failure of the newly initiated TLD as the current first-line ART regime. Similarly, the study further informs the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC) in developing and implementing targeted, cost-effective interventions to improve treatment outcomes in HIV children on TLD.

1.5 Research Questions

What were the predictors of the first-line ART treatment failure in HIV-infected children attending the second-line ART in Tanzania from 2016 to 2018?

1.6 Study Objectives

1.6.1 Main Objective

To determine predictors of first line ART treatment failure in HIV infected children receiving the second-line antiretroviral therapy in Tanzania from 2016 to 2018?

1.6.2 Specific Objectives

1. To determine social-demographic predictors of the first-line ART treatment failure in HIV infected children who are currently on second-line antiretroviral therapy in Tanzania, from 2016 to 2018?
2. To determine disease profile predictors of the first-line ART treatment failure in HIV infected children who are currently on second-line antiretroviral therapy in Tanzania, from 2016 to 2018

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Prevalence of the First-Line ART Regimen Failure in HIV-infected Children

According to the WHO report of 2016, about 41% of the children's treatment failure was in Sub-Saharan Africa[23].Several studies conducted revealed that ART treatment failure in children ranged from 7.7% to 23.5%. It is also reported that about 69.8% of the children were switched to second-line treatment due to treatment failure [24]. Similarly, studies conducted in Tanzania show that the prevalence of treatment failure in children ranges from 25.4% to 40%. [15], [16]. ART treatment failure is attributed to poor adherence, the status of the caregiver, and poor nutrition. However, these studies had a small sample size (213) and were not representative of the whole country. Similarly, there are inconsistent findings on the magnitude of the ART first-line treatment failure between studies[13]; therefore, there is a need to emphasize more studies to be done at the country level.

2.2 Predictors of the First-line ART Treatment Failure in HIV-infected Children

2.2.1 Age

In Ethiopia, a study revealed that younger age at cART initiation was a predicting factor for treatment failure. Children who were initiated on ART at 11 months or younger had an increased chance of ART failure [13]. This may be due to the inability to take medication on time and poor drug absorption due to other comorbidities and malnutrition. On the contrary, a study done in Thailand reported that younger age at the time of cART initiation was a protecting factor of treatment failure[22]. Another survey by Kuhn et al. in 2018 showed that children initiated on cART between 2 and 4 months had a decreased chance of failure [25]. On the other hand, initiation at $\geq$ five months increased the chances of failure[26]

2.2.2 Sex

A study conducted in Western Kenya revealed that male gender was among the potential risk factors for ART virologic failure. The study revealed that male children, compared to females, were twice as likely to have a high viral load at routine viral load testing[27].

However, in the study conducted in Tanzania, females were more associated with treatment failure than males; the author explained that girls were more vulnerable to virologic failure and the development of HIV-Drug Resistance Mutation(DRM) for reasons that could not be explained in the framework of the study [28]

2.2.3 Nutritional Status

The study done in Ethiopia found that chronic malnutrition was an independent predictor. It found that the higher the prevalence of underlying malnutrition, the higher the risk of infection and chronic diarrhoea, which in turn decreases drug absorption and impair metabolism [22]. Another study showed that malnutrition could impair the immune response and contribute to HIV disease progression even in children on ART [27]. Malnutrition is associated with the immune system, as was recently observed that low BMI correlated significantly with the decrease in CD4 count and the increase in viral load, which advances the stage of the disease, leading to treatment failure [19].

2.2.4 Comorbidity

TB-HIV comorbidities have been associated with treatment failure due to the infectiousness properties of the T.B. bacilli that cause an opportunistic infection at any level CD4 count in HIV infected patients [29]. Another mechanism on which TB-HIV comorbidities induce treatment failure is through T.B. drug metabolism demands, especially rifampicin, which induces cytochrome P450 enzymes that facilitate the metabolic activity of the liver. This leads to a low therapeutic level of ART drugs, especially nevirapine[30]. Nevertheless, the study conducted in Kenya found that Children with a history of tuberculosis had better virologic outcomes. The result is attributed to the close monitoring, frequent clinic visits, and adherence support, including directly observed therapy provided as part of tuberculosis treatment [27].

2.2.5 Virological Failure

Virological failure occurs when viral load rebounds to detectable levels or never becomes undetectable when taking treatment [32].Studies have revealed that virological failure

occurs when antiretroviral therapy (ART) fails to suppress and sustain a person's viral load to less than 200 copies/ml after six months [3]. WHO recommends viral load estimation as the preferred monitoring approach to diagnose and confirm treatment failure [33].Virologic failure can be caused by, among other things, drug resistance, drug toxicity, and poor adherence to ART [31]. Poor adherence to combined antiretroviral therapy (cART) is a major determinant of virologic failure, the emergence of drug-resistant virus, disease progression, hospitalizations, mortality, and health care costs.

Varied response to different first-line regimens has been reported from pediatric observational cohorts from different regions of the world. Despite the reduction in morbidity and mortality, a considerable proportion of patients fail to achieve a sustained Virologic response to therapy [34]. However, in low and middle-income countries, such monitoring has proved difficult given the inadequate laboratory facilities, shortage of trained staff, and expensive reagents [35]. The success of ART depends on the maintenance of long-term virological suppression, which is mainly, a challenging in children living with HIV [36].

2.2.6 Immunological Failure

The primary goals of HIV treatment include suppression of viral replication, restoration of the immune response, a halt in the progression of the disease, increased survival rates, reduced morbidity, and a better quality of life [38]. Several studies have found out that low CD4 count is associated with treatment failure[Emmett *et al.*, 2010; Bacha *et al.*, 2012].Experts haveestablished that children with low CD4 count at initiation of ART could have an increased risk ofopportunistic infections which further impairs the positive effects of the AR T[22]. It is well known that CD4 T-cell count has an inverse relationship with viral replication and load. As patients' immune status becomes declined, the rate of viral replication increases compared to their immune-competent counterparts. Besides, clients with compromised immunity are more vulnerable to different opportunistic infections that sustain the vicious cycle of immunity and viral replication [19].Further, viral load can lead to the evolution of drug resistance, with subsequent immunological failure [36]

Monitoring of the early warning signs of failure should therefore be intensified to prevent resistance to ARVs, one of which is through the identification of clinical and/or immunological failure, which are surrogate markers to the presence of virological failure.

2.2.7 Type of Regimen

The study done in Tanzania showed that children on nevirapine-based regimens were more likely to have virological failure than those on efavirenz and protease inhibitor-based regimens [39]. Another study conducted at KCMC Referral Hospital in Northern Tanzania found that the use of nevirapine-based regimens in children aged less than three years in conjunction with antituberculosis therapy resulted in a higher likelihood of treatment failure [15]. Additionally, a study conducted in Woldia Hospital, Northeast Ethiopia found out that the use of zidovudine (AZT) as part of the NRTI backbone is associated with treatment failure. The author pointed out that the use of zidovudine is associated with more adverse effects such as nausea and vomiting, that may potentially reduce treatment adherence[40].

On the other hand, some studies reported that tenofovirdisoproxilfumarate (TDF) performed better than either AZT, most notably with less drug substitution and mortality, less serious renal toxicity, like acute renal failure requiring dialysis, progressive decline in renal function, proximal renal tubular dysfunction, and Fanconi-syndrome were also reported by some kinds of literature [41].

2.2.8 WHO Clinical Stage

Different studies revealed that children who at baseline had WHO HIV stage 3 and 4 had more chance of failing on the first-line regimen compared to children at stage 1and 2[Workneh *et al.*, 2009; Costenaro *et al.*, 2014;] Patients with advanced disease stage were more likely to change the initial regimen which can result in drug toxicity that adversely affects the quality of life and potentiality for optimum adherence. Lack of adherence ultimately leads to the emergence of resistance to ART drugs and treatment failure [19]. Nevertheless, a study conducted in Kenya indicated that baseline WHO clinical stage was

not a predictor of treatment failure. The author postulated that patients in WHO stage IV are likely to have experienced disproportionately higher and early mortality before first-line treatment failure could be ascertained, and this is likely to have masked the true effect of advanced WHO stage on the risk of treatment failure[40].

2.2.9 ART Adherence

The study conducted in Zambia associated ART failure with poor adherence by the patient and/or poor compliance to guidelines by prescribers. Treatment success needs strict lifelong drug adherence and strong guideline compliance to achieve potentially lifelong suppression of HIV replication[46]. However, despite being one of the main determinants of viral suppression after ART initiation, adherence has not consistently been found to correlate with viral suppression in children. A study conducted in Ethiopia showed that adherence to ART regimens was not a statistically significant predictor of treatment failure in the study. This could be due to the high self-reported adherence rate in the study, which made a comparison between the groups difficult[22]. Monitoring children receiving ART is essential to ensure successful treatment, identify adherence problems, and determine whether and which ART regimens should be switched in case of treatment failure.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

This study was a retrospective unmatched nested case-control design, using secondary data of HIV positive Children below 15 years old that were on second line ART or TLE from 2016 to 2018. The data were obtained from the CTC3 Macro Database at the Tanzania National AIDS Control Program.

3.2 Study Area

This study was conducted in Tanzania, a country in East Africa within the African Great Lakes region. It borders Uganda to the north, Kenya to the northeast, the Comoro Islands and the Indian Ocean to the east, Mozambique and Malawi to the south, Zambia to the southwest and Rwanda, Burundi and the Democratic Republic of the Congo to the west. The study was conducted at the National AIDS Control Program(NACP). This is a public organization which operates under the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC). The program originated from the National Task Force (NTF) constituted in 1985 by the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC) as an institutional effort to combat HIV/AIDS. This was so because the HIV/AIDS epidemic was first perceived as a health problem and the initial control efforts were formulated and based within the health sector (MOHCDGEC, 2018). In 1988, the task force was transformed into a fully-fledged National AIDS Control Programme (NACP).NACP has five units: Care, Treatment and Support Unit (CTSU), Prevention (P.U.), Finance and Administrative (FAU), Pharmacy, Laboratory and Support Unit (PLSU) and Strategic Information Unit (SIU). SIU works closely with the University of Dar es Salaam to develop the CTC database which this study used. The CTC database is drawn from all health facilities providing the CTC services across Tanzania.

3.3 Study Population

3.3.1 Cases

All HIV-Infected Children below 15 years old who had been switched from the first line ART treatment because of failure to the second line ART treatment from January 2016 to December 2018. They were on the CTC3 database on TLE from 2016 to December 2018.

3.3.2 Exclusion Criteria

HIV infected children on ART with the incomplete outcome (case/control) were excluded from the analysis.

3.3.3 Controls

All HIV infected children below 15 years of age who were on first-line ART treatment from January 2016 to December 2018.

3.4 Sample Size

A total of 43337 children living with HIV aged less than 15 years and who were enrolled in HIV and AIDs care and treatment services electronic registers across Tanzania from 2016 to2018. Among those eligible children, those on second line ART treatment (having failed from first line ART treatment) included 3669 who also had no missing information thus became eligible cases for this study. Eligible controls were those who were still on first line ART treatment who were 39668 among whom 3669 were randomly selected and included in to the study as controls. This is to say, the study sampled 7338 participants (3669 cases and 3669 un-matched controls) from the Tanzania NACP ART treatment electronic data base.

3.5 Study Variables

Data was constructed from the electronic CTC 3 register to compose an Excel file containing the cases (being on second-line ART treatment subsequent to first to line ART antiretroviral treatment failure). Thus, the first line ART treatment failure was being on second-line observed in the Tanzania CTC3 register from 2016 to 2019. This was

determined by reviewing the CTC3 register to ascertain as to whether a person had been switched from the first line ART treatment to the second line ART treatment between 2016 and 2018. The Excel also contained demographic, clinical, immunological and virologic characteristics as selected predictor variables. The demographic characteristics included sex and age. Clinical characteristics included WHO stage, nutritional status and type of regimen. Others were attributes were CD4 count and viral load.

3.6 Data Management and Analysis

The CTC server's constructed data sets were checked for completeness and dummy variables created and variable dictionary assembled. The analysis was performed using STATA version 15. All tests of significance were two-sided with a p-value of less than 0.05 considered significant. Where all variables were binary or qualitative, chi-square/Fischer's exact test was used to compare the differences among the variables between the cases and controls. Bivariate and multivariable unconditional logistic regression models were used to assess the predictors of the first-line ART failure in the study subjects using crude Odds Ratio (COR) and Adjusted Odds Ratio (AOR), respectively, and p values. Independent variables with $p < 0.2$ in the bivariate analysis were included in the multivariable analysis. Thus, both bivariate and multivariable analyses were performed using unconditional logistic regression for unpaired data to assess the significance of the selected predictor variables and the first line ART treatment failure in the study population.

3.7 Ethical Consideration

Ethical approval was sought from Muhimbili University of Health and Allied Science (MUHAS). Data were extracted using a unique I.D. number before analysis, and access was limited to approved personnel only. Approval to use the data was obtained from the Ministry of Health, Community Development, Gender, Elderly, and Children through the National AIDS Control Program.

CHAPTER FOUR

4.0 RESULTS

4.1 Introduction

A total sample of the study was 7338, of which, 3669 constituted cases and 3669 controls. Table 1 presents the characteristics of cases and controls; controls had a lower (46.4%) proportion of males, whereas cases had more males (50.4%). There was a significant difference between males and males at ($p<0.01$). A similarity between cases and control was in age groups, ART adherence, and WHO staging. Others were health facility ownership and health facility type($p<0.01$).

Table 1: Comparison of the Social-Demographic Predictors between Cases and Controls

	Controls	Cases	
Variable	n (%)	N (%)	P-value
Sex			
Male	18,501 (46.6)	1,850 (50.4)	<0.01
Female	21,167 (53.4)	1,819 (49.6)	
Age(Years)			
0-4	17,963 (47.5)	2,145 (61.4)	
5-9	10,814 (28.6)	754| (21.5)	<0.01
10-14	9,019 (23.9)	597 (17.1)	
ART Adherence			
Good	21,543 (96.6)	2,355 (2.6)	
Poor	754 (3.4)	187 (7.4)	<0.01
WHO Stage			
Stage 1	14,347 (36.7)	1,182 (32.7)	
Stage 2	11,375 (29.2)	945 (26.2)	
Stage 3	11,206 (28.7)	1,190 (32.9)	<0.01
Stage 4	2,100 (5.4)	296 (8.1)	
CD4 Count(Cell/ul)			
<200	883 (22.5)	93 (21.7)	
200-349	463 (11.8)	52 (12.2)	0.9
350+	2,575 (65.7)	283 (66.1)	
Nutritional Status			
Moderate	2,393 (6.4)	187 (5.3)	
Ok	34,433 (91.6)	3,052 (91.9)	0.046
Severe	757 (2.0)	83 (2.5)	
Health facility ownerships			
FBO	6,982 (18.0)	676 (19.0)	
Private	607 (1.6)	91 (2.5)	<0.01
Public	31,146 (80.4)	2,798 (78.5)	
Health Facility Type			
Dispensary	13,081 (33.8)	800 (22.4)	
Health Centre	14,408 (37.2)	1,228 (34.4)	<0.01
Hospital	11,246 (29.0)	1,537 (43.1)	

4.2 Factors Associated with the First-line ART Failure in Children Living with HIV

Table 4 presents bivariate analysis crude Odds Ratio (COR)and multivariate analysis adjusted Odds Ratio (AOR), the crude Odds Ratio (CRO) results of the bivariate analysis reveals that sex, age, ART adherence, WHO stage, health facility types and health facility ownership were statistically significantly associated with the first line ART treatment failure. Furthermore, sex, age, ART adherence, health facility types and health facility ownership were statistically significantly predictors of first line ART treatment failure. Thus being a female compared to a male the odds of failure was 0.12 lower the difference was significant (AOR: 0.88; 95%CI 0.81, 0.96 also participants aged 0-4 years had almost two times higher odds of the first-line ART failure compared to those aged 10-14 years (AOR: 1.59; 95%CI: 1.42, 1.78). Furthermore, participants who had poor ART adherence had 2.2 times higher odds of the first-line ART failure compared to participants who had good ART adherence (AOR: 2.15; 95%CI: 1.79, 2.57) and private health compared to others had 2 times more likely the odds of the first-line ART failure compared to facility-based organization counterparts (AOR: 1.52; 95%CI: 1.08, 2.15)

Table 2: Factors associated with the first line ART failure in children living with HIV in Tanzania

Variable	Bivariate			Multivariate (adj)		
	COR	95%CI	P-value	AOR	95%CI	P-value
Sex						
Male	1.00					
Female	0.89	(0.83,0.96)	0.001	0.88	(0.81,0.96)	0.01
Age(Years)						
0-4	1.80	(1.64,1.98)	0.001	1.59	(1.42,1.78)	0.001
5-9	1.05	(0.94,1.18)	0.34	1.04	(0.91,1.18)	0.53
10-14	1.00					
ART Adherence						
Good	1.00			1.00		
Poor	2.14	(1.80,2.55)	0.001	2.15	(1.79,2.57)	0.001
WHO Stage						
Stage 1	0.62	(0.54,0.72)	0.001	0.89	(0.73,1.07)	0.23
Stage 2	0.61	(0.53,0.70)	0.001	0.85	(0.70,1.00)	0.11
Stage 3	0.77	(0.67,0.88)	0.001	0.94	(077,1.14)	0.54
Stage 4	1.00					
Nutritional Status						
Normal	1.00					
Moderate poor	0.90	(0.78,1.05)	0.20			
Severely poor	1.12	(0.95,1.51)	0.13			
Health facility ownerships						
Private	1.57	(1.23,1.99)	0.001	1.52	(1.08,2.15)	0.02
Public	0.96	(0.86,1.03)	0.23	1.10	(0.98,1.22)	0.12
Facility Types						
Dispensary	0.44	(0.40,0.49)	0.001	0.44	(0.39,0.50)	0.001
Health Centre	0.61	(0.56,0.66)	0.001	0.60	(0.54,0.66)	0.001
Hospital	1.00					

CHAPTER FIVE

5.0 DISCUSSION AND CONCLUSION

5.1 Discussion

This case-control study involved 3669 cases (with first-line ART regime failure) and a similar number of controls. The study used secondary data that were extracted from the CTC3 macro database at the Tanzania National AIDS Control Program (NACP). Predictors that were significantly associated with the first line ART treatment failure were being in the age group 0-4years, poor ART adherence, attending private health facility, attending health centre and dispensary.

The study revealed that participants aged 0-4 years compared to other ages had higher odds of the first-line ART treatment failure, where other factors are controlled. Similarly, a study done in Ethiopia revealed that children who were initiated on ART at 11 months or younger had an increased chance of failure [13]. This may be due to the inability to take medication on time and poor drug absorption due to other comorbidities and malnutrition. On the contrary, a study done in Thailand reported that younger age at the time of cART initiation was a protecting factor of treatment failure [22]. Another study by Kuhn et al. in 2018, support that younger children are less likely to experience the first-line treatment failure [25].

This study also revealed that being a male gender was a predicting factor for ART's first line regimen failure. Male children had higher odds of developing first-line treatment failure in comparison to female children. Similar results have been reported in a study conducted in Western Kenya which revealed that male gender was among the potential risk factors for ART virologic failure: Male children compared to female were twice as likely to have a high viral load at routine viral load testing[27]. However, a study conducted in Tanzania found that females were more likely associated with treatment failure. The researcherreported that girls were more vulnerable to virologic failure and the development of HIV-Drug Resistance Mutation(DRM) for reasons that could not be explained in the

framework of the study [28]. Thus to clarify this opposing observation, more prospective cohort research is needed.

Prior poor adherence to ART was also found to be among the predictors of the first-line treatment failure in this study. Those who were categorized as poor ART adherents, compared to, good adherents had very high odds of the first-line treatment failure; thus they had a higher chance of developing the first-line regimen failure because they were more exposed toadvanced disease stages and other complication that warranted switching to the second line. Poor adherence ultimately also leads to the emergence of resistance to ART drugs and treatment failure [19]. Therefore efforts to promote adherence should be heightened to include adherence counselling, health education and other support to caregivers as well as the clients.

Patients attending private health facilities compared to other facility ownership had a higher likelihood of first-line treatment failure. This implies that public health facilities provided quality care which results in good adherence.

5.2 Conclusion

The study confirmed that predictors of the first line ART treatment failure and consequent switch to the second line ART included patients' sex, age group, and poor ART adherence. Also health system predictors included health facility type and health facility ownership, thus suggesting that these predictors have to be taken in consideration to achieve the global goal of 95-95-95 by 2030.

5.3 Recommendations

In the Tanzanian contexts both patients and health system characteristics were identified as significant predictors of first line ART treatment failure. Consequently, health managers and providers need to adopt policies and actions that mitigate against the identified significant predictors. Moreover, more research on how the predictors mediate the first line ART treatment failure is recommended to inform providers and decision maker’s effective methods and strategies to institute real time-based interventions.

REFERENCES

[1] W. Manosuthi *et al.*, "Guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2014, Thailand," *AIDS Res. Ther.*, vol. 12, no. 1, p. 12, 2015.

[2] NACP, *National Guidelines for the Management of HIV and AIDS*. Ministry of Health and Social Welfare Dar es Salaam, Tanzania, 2012.

[3] R. . Gupta *et al.*, "HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis," *Lancet Infect. Dis.*, vol. 18, no. 3, 2018.

[4] M. Sidibé, "UNAIDS Data 2018," *UNAIDS. Đường link http//www. unaids. org/sites/default/files/media_asset/unaids-data-2018_en. pdf*, 2018.

[5] I. Singini *et al.*, "Predictors of late virologic failure after initial successful suppression of HIV replication on efavirenz-based antiretroviral therapy," *HIV Clin. Trials*, vol. 17, no. 5, pp. 173–180, 2016.

[6] MoHCDGEC, *Tanzania Country Operational Plan COP 2019 Strategic Direction Summary*. 2019.

[7] NACP, "Health Sector HIV and AIDS Strategic Plan IV (2017-2022)." National AIDS Control Programme, 2017.

[8] TACAIDS, "Tanzania Commission for AIDS, annual report, 2018," Dar es Salaam, 2018.

[9] H. Wang *et al.*, "Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015," *Lancet HIV*, 2016, doi: 10.1016/S2352-3018(16)30087-X.

[10] NACP, *Tanzania National guidelines for the management of HIV and AIDS*. Dar es Salaam, 2015.

[11] UNAIDS, "Start Free, Stay Free, AIDS-Free: A Super Fast Track Framework for Ending AIDS in Children, Adolescents and Young Women by 2020." 2018.

[12] YT Yimer, "Magnitude and predictors of antiretroviral treatment (ART) failure in

private health facilities in Addis Ababa, Ethiopia," *PLoS One*, vol. 10, no. 5, 2015.

[13] G. S. Haile, "Predictors of treatment failure, time to switch and reasons for switching to the second-line antiretroviral therapy in HIV infected children receiving the first-line antiretroviral therapy at a Tertiary Care Hospital in," pp. 1–9, 2019.

[14] M. . Campaign, "Untangling the web of antiretroviral price reductions 18th Edition," 2016.

[15] S. D. Emmett *et al.*, "Predicting virologic failure among HIV-1-infected children receiving antiretroviral therapy in Tanzania: a cross-sectional study," *J. Acquir. Immune Defic. Syndr.*, vol. 54, no. 4, p. 368, 2010.

[16] Z. J. Tabb *et al.*, "Antiretroviral drug concentrations in hair are associated with virologic outcomes among young people living with HIV in Tanzania.," *AIDS*, vol. 32, no. 9, pp. 1115–1123, 2018.

[17] J. Estill *et al.*, "The need for second-line antiretroviral therapy in adults in sub-Saharan Africa up to 2030: A mathematical modelling study," *Lancet HIV*, vol. 3, no. 3, 2016.

[18] D. P. O'Brien *et al.*, "Treatment outcomes stratified by baseline immunological status among young children receiving nonnucleoside reverse-transcriptase inhibitor-based antiretroviral therapy in resource-limited settings," *Clin. Infect. Dis.*, vol. 44, no. 1245–1248, 2007.

[19] M. Ahmed, H. Merga, H. Jarso, and H. Jarso, "Predictors of virological treatment failure among adult HIV patients on first-line antiretroviral therapy in Woldia and Dessie hospitals, Northeast Ethiopia: a case-control study," *BMC Infect. Dis.*, vol. 19, no. 1, p. 305, 2019.

[20] D. Negese *et al.*, "HIV-Positive Status Disclosure and Associated Factors among Children in North Gondar, Northwest Ethiopia," *Int. Sch. Res. Netw. ISRN AIDS*, vol. 2012, 2012, doi: 10.5402/2012/485720.

[21] N. Tsuchiya *et al.*, "Incidence and predictors of regimen-modification from first-line

antiretroviral therapy in Thailand: A cohort study," *BMC Infect. Dis.*, vol. 14, no. 565, pp. 2–8, 2014.

[22] T. Bacha, B. Tilahun, A. Worku, and A. Worku, "Predictors of treatment failure and time to detection and switching in HIV-infected Ethiopian children receiving first-line antiretroviral therapy," *BMC Infect. Dis.*, vol. 12, no. 197, pp. 2–8, 2012.

[23] WHO, "Global strategy for women's, children's and adolescents' health (2016-2030)," *Organization*, 2016.

[24] B. A. Yihun, G. D. Kibret, C. Tesema, and L. Id, "Incidence and predictors of treatment failure among children on first-line antiretroviral therapy in Amhara Region Referral Hospitals, northwest E," 2019, doi: 10.1371/journal.pone.0215300.

[25] T. Puthanakit, S. J. Kerr, J. Ananworanich, T. Bunupuradah, P. Boonrak, and V. Sirisanthana, "Pattern and predictors of immunologic recovery in human immunodeficiency virus-infected children receiving nonnucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy," *Pediatr. Infect. Dis. J.*, vol. 28, no. 6, pp. 488–492, 2009.

[26] L. Kuhn *et al.*, "Age at antiretroviral therapy initiation and cell-associated HIV-1 DNA levels in HIV-1-infected children," *PLoS One*, vol. 13, no. 4, p. e0195514, 2018.

[27] J. Kadima *et al.*, "Adoption of routine virologic testing and predictors of virologic failure among HIV-infected children on antiretroviral treatment in western Kenya," *PLoS One*, vol. 13, no. 11, p. e0200242, 2018.

[28] L. Muri *et al.*, "Development of HIV drug resistance and therapeutic failure in children and adolescents in rural Tanzania: an emerging public health concern," *AIDS*, vol. 31, no. 1, p. 61, 2017.

[29] J. Landier *et al.*, "Switch to second-line ART in West African routine care: incidence and reasons for switching," *AIDS Care*, vol. 23, no. 1, pp. 75–78, 2011.

[30] C. J. Hoffmann *et al.*, "Hepatotoxicity in an African antiretroviral therapy cohort:

the effect of tuberculosis and hepatitis B," *Aids*, vol. 21, no. 10, pp. 1301–1308, 2007.

[31] National Library of Medicine, "AIDSinfo GLOSSARY of HIV/AIDS-Related Terms," 2018.

[32] D. Germanaud, A. Derache, … M. T.-J. of, and U. 2009, "Level of viral load and antiretroviral resistance after 6 months of nonnucleoside reverse transcriptase inhibitor first-line treatment in HIV-1-infected children in Mali," *academic.oup.com*, 2010.

[33] A. Mukherjee, N. Shah, R. Singh, M. Vajpayee, S. K. Kabra, and R. Lodha, "Outcome of highly active antiretroviral therapy in HIV- infected Indian children," *BMC Infect. Dis.*, 2014, doi: 10.1186/s12879-014-0701-2.

[34] C. . Solem *et al.*, "Cost of treatment in a U.S. commercially insured, HIV-1-infected population," *PLoS One*, vol. 9, no. 5, p. e98152, 2014.

[35] J. Fellay *et al.*, "Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study," *Lancet*, vol. 358, no. 9290, pp. 1322–1327, 2001.

[36] N. . Johnson, L. . Hayes, K. Brown, E. . Hoo, and E. K.A., "Division of HIV/AIDS prevention strategic plan 2017-2020," *MMWR Morb Mortal Wkly Rep*, vol. 63, no. 4, pp. 3–27, 2014.

[37] Insight Start Study Group, "Initiation of antiretroviral therapy in early asymptomatic HIV infection," *N. Engl. J. Med.*, vol. 373, no. 3, pp. 795–807, 2015.

[38] M. . Kamya *et al.*, "Predictors of long-term viral failure among Ugandan children and adults treated with antiretroviral therapy," *JAIDS J. Acquir. Immune Defic. Syndr.*, vol. 46, no. 2, pp. 187–193, 2007.

[39] Mgelea, Edward, Machage, and Kisenge, "Detecting virological failure in HIV-infected Tanzanian children," *South African Med. J.*, vol. 104, no. 10, pp. 696–699, 2014.

[40] C. M. Kwobah, A. W. Mwangi, J. K. Koech, G. N. Simiyu, and A. M. Siika, "Factors associated with first-line antiretroviral therapy failure amongst HIV-infected African patients: a case-control study," 2012.

[41] S. Wilhelmson, A. Reepalu, T. T. Balcha, G. Jarso, and P. Björkman, "Retention in care among HIV-positive patients initiating second-line antiretroviral therapy: A retrospective study from an Ethiopian public hospital clinic," *Glob. Health Action*, vol. 9, no. 1, p. 29943, 2016.

[42] S. Yassin and G. B. Gebretekle, "Magnitude and predictors of antiretroviral treatment failure among HIV- infected children in Fiche and Kuyu hospitals, Oromia region, Ethiopia: a retrospective cohort study," *Pharmacol. Res. Perspect.*, vol. 5, no. 1, p. e00296, 2017.

[43] P. Costenaro *et al.*, "Predictors of treatment failure in HIV-positive children receiving combination antiretroviral therapy: cohort data from Mozambique and Uganda," *J. Pediatric Infect. Dis. Soc.*, vol. 4, no. 1, pp. 39–48, 2014.

[44] Workneh, Girma, Woldie, and Mirkuzie, "Immunologic and clinical outcomes of children on HAART: a Retrospective cohort analysis at Jimma University specialized hospital," *Ethiop. J. Health Sci.*, vol. 19, no. 2, 2009.

[45] J. H. Van Dijk *et al.*, "HIV-infected children in rural Zambia achieve good immunologic and virologic outcomes two years after initiating antiretroviral therapy," *PLoS One*, vol. 6, no. 4, p. e19006, 2011.

[46] Z. Ataro *et al.*, "Magnitude and causes of first-line antiretroviral therapy regimen changes among HIV patients in Ethiopia: a systematic review and meta-analysis," *BMC Pharmacol. Toxicol.*, vol. 20, no. 1, p. 63, 2019.

[47] C. M. Kwobah, A. W. Mwangi, J. K. Koech, G. N. Simiyu, and A. M. Siika, "Factors Associated with First-Line Antiretroviral Therapy Failure amongst HIV-Infected African Patients : A Case-Control Study *," no. November 2012, doi: 10.4236/wja.2012.24036.

[48] Y. S. Low, F. Islahudin, K. A. M. Razali, and S. Adnan, “Modification of Initial Highly Active Antiretroviral Therapy (HAART) Regimen in Paediatric HIV Patients,” *Open AIDS J.*, vol. 12, p. 11, 2018.

APPENDICES

Appendix I: Ethical clearance letter

APPENDIX 1: ETHICAL CLEARANCE LETTER

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
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Ref. No. DA.287/298/01A/ 21st February, 2020

Daudi Sabas Jorojick
MSc. Applied Epidemiology,
School of Public Health and Social Sciences,
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: " PREDICTORS OF TREATMENT FAILURE AMONG HIV INFECTED CHILDREN RECEIVING THE FIRST LINE (TLE) ANTI-RETROVIRAL THERAPY IN TANZANIA."

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from **21st February, 2020 to 20th February, 2021.** In case you do not complete data analysis and dissertation report writing by **20th February 2021,** you will have to apply for renewal of ethical clearance prior to the expiry date.

Dr. Emmanuel Balandya
ACTING: DIRECTOR OF POSTGRADUATE STUDIES

cc. Director of Research and Publications
cc: Dean, School of Public Health and Social Sciences, MUHAS

Appendix II: Request for NACP for data analysis and Publication

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
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21June, 2019

Permanent Secretary- Health
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RE: REQUEST FOR NACP DATA FOR DATA ANALYSIS AND PUBLICATION

Dr.Daudi Sabasa Jorojick is a postgraduate student at Muhimbili University of Health and Allied Sciences (MUHAS) undertaking Master of Science in Applied Epidemiology. His mentors include Dr.Innocent Semali and Dr Candida Moshiro of MUHAS. He plans to undertake a study titled **"Predictors of treatment failure among HIV infected children receiving the first-line antiretroviral therapy in Tanzania 2018"**.

The objectives of his study are:1)To determine predictors associated with treatment failure among HIV infected children receiving first-line antiretroviral therapy in Tanzania, 2018, 2)To asses the magnitude of treatment failure among HIV infected children who are receiving first-line antiretroviral therapy in 2018 and 3)To map the geographical difference of first-line ART failure in Tanzania in 2018. The findings from this study will identify predictors of ART treatment failure, and the magnitude of the ART failure which will help to inform government and policymakers to plan and set initiative on how to control the first-line ART failures. Similarly Identifying such factors has programmatic importance to develop and implement targeted cost-effective interventions at National Aids Control Program (NACP) to improve treatment outcome among HIV children on ART.

We are requesting for access to CTC3 database from the National Aids Control Program (NACP) starting from January to December 2018. The data extracted will be used to address the objectives of the study. We are requesting the involvement of a Data Manager, whose skills are essential to ensure that the required data is well extracted and processed. Furthermore, the team would benefit from having an Epidemiologist from the Ministry involved in this activity. He/she will be helpful in providing advice on which variables to extract, the type of analysis to be performed and interpretation of the findings.

This study will lead to publication of at least one manuscript. All persons involved including the Epidemiologist and Data Manager will contribute towards the development of the manuscript and become co-authors.

The research fellow will develop a full proposal in collaboration with the Epidemiologist and Data Manager, and submit for ethical approval to the MUHAS ethical review committee once the Ministry commits to provide the data.

The department would be grateful if an opportunity could be given to Dr Daudi Sabas to work on the CTC-3 data. The concept note for this study is attached.

Looking forward to your positive response.

Sincerely,

Dr. Candida Moshiro
Head, Epidemiology and Biostatistics Department