ADVERSE EFFECTS ON SECOND-LINE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) AMONG HIV INFECTED ADULTS AND CHILDREN TREATED AT MILDMAY UGANDA

BY

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RESEARCH DISSERTATION

Submitted in fulfilment of the requirements for the degree of

Master of Public Health

In the

Faculty of Health Sciences

At the

University of Limpopo, South Africa

2011

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DECLARATION

I, **Namukanja Phoebe Monalisa- Mayambala,** declare that the research dissertation hereby submitted to the University of Limpopo, for the degree of Master of Public Health has not previously been submitted by me for a degree at this or any other University; that it is my work in design and in execution, and that all material contained herein has been duly acknowledged.

PM Namukanja (Dr) **22nd April 2011**

200726076

DEDICATION

To the glory of God the Father, God the Son and God the Holy Spirit.

ACKNOWLEDGEMENTS

Sincere gratitude and utmost appreciation goes to my supervisor Prof. Ntambwe (Gustav) Malangu for his invaluable support, guidance and mentorship during my period of study and write up of this dissertation.

Special thanks go to my husband-Mr. Mayambala and children- Elisha and Eunice Mayambala, my parents, siblings and their families for the continuous encouragement throughout my entire study period.

Many thanks go to the staff and students of the National school of Public Health (NSPH), University of Limpopo-Medunsa campus for their support and various contributions during the research protocol development stage.

The Management and staff of Mildmay Uganda are also hereby appreciated for their support during the period of this study.

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LIST OF ACRONYMS AND ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
MUg	Mildmay Uganda
NVP	Nevirapine
PI	Protease Inhibitor
PLWHA	Person(s) Living With HIV/AIDS
PMTCT	Prevention of Mother-To-Child Transmission of HIV
RLS	Resource Limited Setting
UNAIDS	United Nations
WHO	World Health Organization

SUMMARY

Background

Available and affordable second-line antiretroviral treatment regimens are a key component of universal access to treatment and its continuation. However, providing second-line ART is affected by a number of factors including infrastructure, skills and cod competency of available personnel, cost and availability of second-line drugs.

Like first-line antiretroviral agents, second-line drugs have also inherent toxicities. While these have been described in adults, few studies reported this in children. Hence, the need to conduct this study. The aim of the study was to characterize the adverse effects on second-line antiretroviral therapy among HIV infected adults and adolescents and children treated at Mildmay Uganda (MUg).

Method

This was a cross-sectional study based on the review of patients' records. Data was extracted from client medical charts of patients on second-line antiretroviral treatment regimens treated at Mildmay Uganda Centre from January 2000 to December 2008.

Results

In total, 247 cases, the majority (90.7%) of the study participants were aged 13 years and above, female (53.0%), and single (68.0%). With regard to reasons that led to the second-line regimen, the main reason for switching was treatment failure (83%), followed by toxicity (5.7%), and other reasons such as the onset of Kaposi Sarcoma disease, maintaining regimen after transfer, and nevirapine pre-exposure.

Overall, 55 out of 247 patients suffered from one or more adverse effects, a prevalence of 22.3%. The mean number of adverse drug reactions (ADR) was 1.3 per patient. Of the 55 who experienced adverse effects, 76.4% experienced one type of adverse effect. The three most common adverse effects were gastro-intestinal, followed by hematological and peripheral neuropathy. Based on age, while adults experienced a broad range of adverse

drug reactions including metabolic and hepatic ADRs besides the three cited above; children experienced two types only, gastrointestinal, and hematological ADRs. Hematological ADRs were significantly more prevalent in children than adults (66.7% versus 21.4%); they were also more prevalent in females than males (30.8% versus 15.2%). In contrast, while metabolic ADRs were equally distributed, peripheral neuropathy was more prevalent in males than females (30.3% versus 20.5%). Based on the number of ADRs experienced, more males than females (19.8% versus 14.5%) experienced one type of adverse effect whereas more females than males (6.1% versus 4.3%) experienced two to three adverse drug reactions to second-line regimens.

Clinically, the didanosine-based regimens were the most associated with ADRs in both children and adults. In Children, the regimen, ABC/DDI/LPV/R, was responsible of 66.7% of ADRs documented; while in adults it was involved in 60.3% of ADRs. Similarly, TDF-, zidovudine-, and stavudine-based regimens were also involved respectively in 52.9%, 17.8%, and 14.7% of ADRs. Based on gender, didanosine-containing regimen, with either TDF or stavudine with lopinavir/r were responsible of 66.7% of ADRs reported in males; while TDF-based regimen with lamivudine or FTC were involved in 21.1% of ADRs also in males. In females, didanosine-, TDF-, zidovudine-, and stavudine-based regimens were also involved respectively in 57.9%, 36.9%, 23.7%, and 7.9% of ADRs. The regimen, TDF/DDI/LPV/R, was also the most associated with the occurrence of ADRs in females as it was in males. Moreover, although no difference was found among patients whose bodyweights increased significantly and those whose did not, patients whose CD4 counts increased significantly experienced more ADRs than those whose had not (8.8% versus 1.3%, $p= 0.03$).

Conclusion

Overall, second-line regimens seem to be well tolerated as the overall prevalence of adverse effects was 22.37%. The didanosine-containing regimens were most associated with the occurrence of ADRs. Hematological ADRs were more prevalent in children than

adults; and more in females than males. In contrast, while metabolic ADRs were equally distributed, peripheral neuropathy was more prevalent in males than females. These findings emphasize the need to individualize treatment based on the characteristics of the patient.

CHAPTER 1- INTRODUCTION

1. 0 Introduction

Standard antiretroviral therapy (ART) consists of the use of at least three antiretroviral (ARV) drugs to maximally suppress the HIV virus and stop the progression of HIV disease.[1]

WHO and UNAIDS estimate that at least 14.6 million people globally were in need of antiretroviral therapy in 2009. As of the end of 2009, 5.25 million people had access to antiretroviral therapy in low- and middle-income countries.[1] In Uganda, 350,000 PLWHAs are in dire need of ART with only less than half approximately 115,000 PLWHAs receiving it based on UNAIDS/WHO methodology. [2]

Antiretroviral agents are responsible for a broad range of toxicities, ranging from low-grade intolerances that may be self-limiting to life- threatening side- effects. Drug-related adverse events can occur early (the first few weeks or months of treatment) and late (after six months or more of treatment). Adverse events can vary in severity from mild to severe and life-threatening. ARV toxicity may be specific to the drug or to the class of drugs in use.[3]

Second-line ART is the next regimen used in sequence immediately after first-line therapy has failed either clinically, and or immunologically, and or virologically. Current WHO treatment guidelines recommend that the Protease Inhibitor (PI) class should be reserved for second-line ART and that ritonavir-boosted protease inhibitors (bPIs) are preferred supported by two agents from Nucleoside Reverse Transcriptase Inhibitors (NRTI) class.[4]

Available and affordable second-line ARV regimens are a key component of universal

access to high quality HIV treatment [4] however providing second-line ART for PLWHAs in RLS is complicated by a number of factors including cost and availability of second-line drugs.[5]

Boyd and Cooper confirm that access to second-line ART regimens in developing countries is problematic, mainly because of the high prices of HIV protease inhibitors (PIs) [6]

1.1 Overview of the Uganda Health care system and National ART Programme

1.1.1 The Country of Uganda

Uganda is a landlocked country bordered by Kenya in the East, Sudan in the North, Congo in the West, Rwanda and Burundi in the South West and Tanzania in the South.[7]Uganda has an estimated population of 33 million people, 50% of whom are below 15 years of age distributed over 241,038 square kilometers of land. [7] Uganda is regarded a low income country with a per capita GDP US $1,200 (2010 est.) and with 35% (2001 est.) of her population below poverty line. [7] English is the official national language though various ethnic groups exist including Baganda 16.9%, Banyakole 9.5%, Basoga 8.4%, Bakiga 6.9%, Iteso 6.4%, Langi 6.1%, Acholi 4.7%, Bagisu 4.6%, Lugbara 4.2%, Bunyoro 2.7%, other 29.6% (2002 census). [7]The religions present in Uganda comprise of Roman Catholic 41.9%, Protestant 42% (Anglican 35.9%, Pentecostal 4.6%, Seventh Day Adventist 1.5%), Muslim 12.1%, other 3.1% and none 0.9% (2002 census). [7]

1.1.2 The Uganda Health care system

Uganda's government health system consists of the district health system (village health teams (VHTs), HCs II, III and IV and district general hospitals), regional referral hospitals (RRH) and national referral hospitals (NRH), which are self accounting and

autonomous institutions, respectively. [8]District health services are managed by the Ministry of Local Government. [8]

The district health system is further divided into health sub districts (HSDs).[8] In general, district management capacity is still very limited in many districts: leadership, management and specialist skills are in short supply at all levels of health care and high levels of attrition tend to curtail capacity building initiatives. [8]Although 72% of the households in Uganda live within 5km from a health facility (public or PNFP), utilization is limited due to poor infrastructure, lack of drugs and other health supplies and the shortage and low motivation of human resource in the public sector. [8]The functionality of the health system in Uganda is a challenge and systems strengthening especially at district level will be required to effectively deliver services. [8]

The Human Resources for Health (HRH) situation is critical: in November 2008 only 51% of the approved positions at national level were filled. [8] The situation is worse in conflict and post conflict and in rural and hard to reach areas. [8] Reports show that national doctor-to-population ratio stands at 1:36,000, the nurse to population ratio is 1:5,000; and the midwife-to-population ratio is 1:10,000.[9]

1.1.3 The Uganda National ART programme

The history of AIDS in Uganda can be divided into three distinct phases.[10]

The first stage saw the rapid spread of HIV through urban sexual networks and along major highways from its origin in the Lake Victoria region. [10] Doctors in this area had become aware of a surge in cases of severe wasting known locally as ‘slim disease’, as well as a large number of fatal opportunistic infections. In 1982, the first AIDS case in Uganda was diagnosed, and the link between ‘slim disease’ and AIDS was clinically recognized. [10] It was not until 1986 when the Ugandan civil war ended and President Museveni was firmly in power that the country had a major HIV prevention programme.

By this time the country was in the midst of a major epidemic, with prevalence rates of up to 29% in urban areas. [10]

Uganda's first AIDS control programme (ACP) was set up in 1987 to educate the public about how to avoid becoming infected with HIV. [10] The programme promoted the ABC approach (abstain, be faithful, use condoms), ensured the safety of the blood supply and started HIV surveillance. Strong political leadership and commitment to tackling the rampaging AIDS epidemic was a key feature of the early response to AIDS in Uganda. [10]

The second phase of the Ugandan HIV epidemic ran from 1992 to 2000. During this period the HIV prevalence fell dramatically, from a peak in 1991 of around 15% among all adults, and over 30% among pregnant women in the cities, to around 5% in 2001. [10] The current HIV prevalence in Uganda is estimated at 6.5% among adults and 0.7% among children. HIV prevalence is higher in urban areas (10% prevalence) than rural areas (6%).[10]

The third phase of HIV/AIDS in Uganda has seen the stabilization of prevalence during 2000-2005, and reports of a slight increase in prevalence from 2006. [10] Uganda was the setting for one of the first test programmes in Africa distributing life-saving antiretroviral medication (ARVs). [10] The programme began in 1998 with the aim of assessing the feasibility of setting up and running an antiretroviral drug clinic in a resource-poor country. [10] It was not until June 2004 that Uganda began to offer free ARV medication to people living with HIV as part of a five-year pilot programme. [10] Since the government of Uganda launched the universal access to free antiretroviral drugs in 2004, 409 public and private facilities have been accredited to provide antiretroviral therapy (ART) by the end of December 2008.[11]

There are an estimated 1.2 million people living with HIV in Uganda, which includes 150,000 children. [10] An estimated 64,000 people died from AIDS in 2009 and 1.2 million children have been orphaned by Uganda's devastating epidemic. Currently just over

200,000 people in Uganda are receiving antiretroviral treatment, an estimated 39% of those in need, according to the latest WHO guidelines (2010). [10]

1.2 Definition of terms

1.2.1 Adverse effect(s)

A harmful or abnormal result. An adverse effect may be caused by administration of a medication or by exposure to a chemical and be indicated by an untoward result such as by illness or death.[12]

1.2.2 Second-line HAART

Second-line ART is the next regimen used in sequence immediately after first-line therapy has failed either clinically, and or immunologically, and or virologically.[4] For purposes of this study a second-line ART regimen consisted of a ritonavir-boosted protease inhibitors (bPIs) based ART regimen.

1.3 Problem Statement/ Rationale of the study

Regardless of their severity, adverse events may affect adherence to therapy thus compromising patient health and safety as well as lead to treatment interruption. Adverse metabolic effects of potent antiretroviral therapy are a major concern because they may stigmatize the patient and because hyperlipidaemia (high fat accumulation in the body) and insulin resistance may increase the long-term risk of cardiovascular disease. Rates of metabolic complications have been relatively poorly recorded in ART programs in resource-limited settings.[3]

Furthermore, no study has been undertaken on adverse events on second-line HAART among HIV infected adults and adolescents and children at MUg.

With this background therefore, it is imperative to carry out a study among the above population groups on adverse effects on second-line HAART so as to create awareness about the magnitude of the problem, enhance knowledge and suggest/promote interventions for the preservation of second-line HAART regimens. This will contribute

to minimize the public health challenge of second-line ART drug access and enhance HIV/AIDS patient survival in Uganda, Sub-Saharan Africa and other resource limited settings.

This study set out to answer the following research questions:

1. What is the prevalence of adverse effects among adult and adolescent clients and children on second-line HAART at Mildmay Uganda?

2. What are the types of adverse effects experienced among adult and adolescent clients and children on second-line HAART at Mildmay Uganda?

3. What are the risk factors associated with the adverse effects experienced among adult and adolescent clients and children on second-line HAART at Mildmay Uganda?

4. What are the reasons for switching from first-line to second-line regimens of ART among HIV-infected adults and children at Mildmay Uganda?

1.3.1 Purpose of the study

The aim of the study was to characterize the adverse effects on second-line antiretroviral therapy among HIV infected adults and adolescents and children treated at Mildmay Uganda (MUg).

1.3.2 Study objectives

The specific study objectives were:

1. To determine the prevalence of adverse effects among adult and adolescent clients and children on second-line HAART at Mildmay Uganda?

2. To describe the adverse effects among adult and adolescent clients and children on second-line HAART at Mildmay Uganda?

3. To identify the risk factors associated with the adverse effects experienced among adult and adolescent clients and children on second-line HAART at Mildmay Uganda?

4. To determine the reasons for switching from first-line to second-line antiretroviral regimens.

1.3.3. Justification of the study

An inventory of adverse effects due to second-line regimens of ART can serve as a tool for planning the treatment and also training health care workers as family care givers. This understanding is expected to assist in the formulation of recommendations for ART programs implementers. Based on the findings, it seems that it is important to motivate ART program implementers to pay more attention to known adverse effects early enough so as to increase the benefits from the antiretroviral therapy.

CHAPTER 2 - LITERATURE REVIEW

2.0 Introduction

The section below highlights and discusses literature on the adverse effects of second-line HAART among HIV infected adults and adolescent and children from reviewed resources.

2.1 Adverse effects and Second-line HAART in Adults and adolescents

According to a WHO survey on Use of antiretroviral therapy in resource-limited settings, only 4% of adults were reported to be on second-line regimens, 61% of whose ART regimens concur with WHO guidelines. Approximately 25% of patients were reported to be having a WHO preferred second-line regimen (almost all of them using ABC/ddI/LPV/r), 36% an alternative second-line regimen and 12% were on a regimen not recommended as a second-line option by WHO.[4] According to WHO projections (based on an estimated average switch rate from first to second-line ART of 3% per year approximately 120,000 and 180,000 patients will need second-line regimens in 2007 and 2008 respectively [4]. WHO recommends a second line regimen should be chosen to substitute first line regimens when needed (for toxicity or treatment failure).[3]

In a study by Dieleman et al [16], they stated that the burden of toxicity resulting from highly active antiretroviral therapy (HAART) is of concern as it constitutes a threat to sustained success of HIV treatment. In addition, a meta-analysis by Humphreys et al [17] concluded that there is insufficient evidence to evaluate second-line therapies in patients with HIV who fail first-line treatment using standard first-line ART regimens. While acknowledging the above author's contribution however, currently there are second-line ART treatment options available for patients with HIV who fail a standard first-line ART treatment regimen and therefore there exists some evidence to evaluate second-line ART therapy.

Furthermore, a study by Castelnuovo et al [5], to evaluate the safety and virological response to lopinavir/ritonavir containing second-line therapy after failing a first line nonnucleoside reverse transcriptase inhibitor (NNRTI) based regimen confirms lopinavir/ritonavir-based second-line regimen but with a high rate of toxicities (62%).

Adverse events that have been documented with the use of second-line ART in adults include abnormal lipid profiles as a result of LPV/r use, hyperbilirubinaemia and nephrolithiasis with ATV/r use; diarrhea and skin rash following FPV/r use, and renal insufficiency following the use of TDF [4]. Nguyen [18] further mentions that some common adverse effects associated with PIs are nausea, vomiting, diarrhoea, hyperglycaemia, elevated liver enzymes, increased risk of bleeding in haemophiliacs, lipid abnormalities, and alterations in body fat distribution.

Additionally, McNicholl [19] noted that all PIs are associated with metabolic abnormalities including dyslipidemia, hyperglycemia, insulin resistance, and lipodystrophy although Atazanavir is less likely to cause dyslipidemia. McNicholl [19]also noted that PIs may increase the risk of bleeding in hemophiliacs.

In another article [20], it is reported that PIs have been shown to have a 3-5% frequency in causing insulin resistance and diabetes and they have also been documented to raise levels of cholesterol and triglycerides.

A study by McKeage K, Perry CM and Kean SJ [21] highlighted the most common adverse events associated with once- or twice-daily boosted darunavir in treatment-experienced or -naive patients were diarrhea, nausea, headache, upper respiratory tract infection and nasopharyngitis. The most common boosted darunavir-related grade 2-4 laboratory abnormalities in treatment-experienced patients included increased triglycerides and increased total cholesterol. However, experience with darunavir in the treatment of HIV-1 infection in RLS including Uganda and other developing countries is very limited

owing to its high cost, unavailability and inaccessibility. Uganda's healthcare performance is still ranked as one of the least-performing by the World Health Organization.[42]

In addition, Nguyen [18] states that the most common symptomatic adverse effects associated with darunavir include diarrhoea, nausea, headache, and rash. Liver toxicity, including severe hepatitis, has been reported with darunavir, especially in patients with chronic hepatitis B or C or other chronic liver disease. Severe skin rash, including erythema multiforme, and Steven Johnson syndrome were reported during the development program of darunavir. Furthermore, McNicholl [19] reports rash and elevated liver function tests as adverse events associated with darunavir.

In a Nigerian study by Adamu et al [22], dysmetabolic syndrome was described in a patient who developed abnormal lipid profile notably hypertriglyceridaemia in addition to diabetes following use of a PI ARV drug Indinavir. Furthermore, the patient also had a lipoma of recent onset, which could be attributed to fat redistribution that could occur in this syndrome. Additionally a study by McNicholl[19] has reported nephrolithiasis, flank pain, hyperbilirubinemia, elevated liver function tests, alopecia, dry skin, ingrown nails, insomnia and taste perversion associated with Indinavir.

Lopinavir/ritonavir has been documented to cause hypertriglyceridaemia and is associated with a higher incidence of hypercholesterolemia than atazanavir (alone or boosted) in a study by Oldfield V and Plosker GL.[23]

According to Nguyen [18], the most frequent adverse effect associated with atazanavir is indirect hyperbilirubinemia that sometimes can lead to jaundice or sclera icterus. Additionally, severe cases of nephrolithiasis and asymptomatic first-degree atrioventricular block have been reported. Furthermore, McNicholl[19] has reported

elevated liver function tests, PR interval prolongation in addition to hyperbilirubinaemia and jaundice with atazanavir.

Metabolic toxicity, including dyslipidemia and insulin resistance, has been reported with fosamprenavir Nguyen [18]. According to McNicholl [19], diarrhoea, nausea, vomiting, rash, elevated liver function tests and hyperlipidemia has been reported with fosamprenavir ART use.

According to a study by McNicholl [19], diarrhoea, nausea, vomiting, elevated liver function tests and fatigue have been reported with Nelfinavir use. In addition, nausea, vomiting, diarrhoea, elevated liver function tests, headache and oral ulcerations have been reported due to Saquinavir use. Furthermore, nausea, vomiting, diarrhoea, abdominal pain, elevated liver function tests, fatigue, circumorol/peripheral numbness, taste perversion and hyperuricemia have been associated with Ritonavir. Additionally, the same author reports that tipranavir has been associated with nausea, vomiting, diarrhoea, elevated liver function tests, elevated total cholesterol and triglycerides, rash and intracranial haemorrhage whereas Lopinavir has been associated with diarrhoea, nausea, vomiting, dyslipidemia, elevated liver function tests and taste perversion.

Adverse effects of Kaletra according to Nguyen [18] include gastrointestinal intolerance e.g. diarrhoea, hyperglycaemia, and hyperlipidemia (e.g. hypertriglyceridemia). A study by Ashish Chandwani and Jonathan Shuter [24]states that, Lopinavir/ritonavir-containing antiretroviral regimens are generally well tolerated. The most frequent side effects reported are diarrhoea, nausea, and vomiting. Serious side effects of lopinavir/ritonavir therapy are unusual. Pancreatitis has been seen rarely in patients on lopinavir/ritonavir therapy, and may have been related to marked elevations in triglyceride levels. Lopinavir/ritonavir can cause transient elevations in transaminase levels, but these are not clinically significant. Additionally, like other members of the protease inhibitor class, lopinavir/ritonavir may cause significant lipid elevations and fat redistribution.

Hypertriglyceridemia (triglycerides >750 mg/dL) and hypercholesterolemia (total cholesterol >300 mg/dL) were the most frequently observed laboratory abnormalities in lopinavir/ritonavir recipients in clinical trials and may be the reason for discontinuation of therapy in some patients. [24]

PIs including lopinavir/ritonavir have been associated with insulin resistance, new onset diabetes, and worsening of pre-existing diabetes requiring hypoglycaemic agents. Fat redistribution including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy including lopinavir/ritonavir.[24] Less common adverse effects of lopinavir/ritonavir therapy include allergic reaction, asthenia, malaise, headache, myalgias, arthralgias, myocardial infarction, seizures, and lactic acidosis.[24]

A Ugandan study by Shihab et al [25] reported bilateral pedal edema in a patient as a potential adverse event of a Lopinavir/ritonavir containing antiretroviral regimen as well as a mild bout of self-resolving diarrhea. Patients in Low, Middle Income Countries (LMIC) currently face significant barriers in accessing most of the above preferred PI options, primarily due to high prices and the absence of registered generic and/or branded versions of each product [4]. This therefore contributes to the limited experience of second-line HAART use in LMIC hence the need to enhance knowledge on second-line ART use in resource-limited settings by carrying out the above study.

2.2 Adverse effects and Second-line HAART in children

A study by Bowen et al [26] highlights that major challenges in delivering paediatric ARV treatment include the lack of paediatric ARV formulations that can be dosed in small children and limited studies examining safety and efficacy for those that we do have. The authors further mention that recommendations for second-line regimens are to include three new drugs, with one or more from a new ARV class [26]. However, there are few available, generic second-line paediatric ARV formulations, making choices for second-line agents after failed first-line therapy even more difficult in paediatric HIV/AIDS care and treatment.

It is sometimes difficult to differentiate between complications of HIV disease and toxicity (also known as adverse events) secondary to ARV drugs used for the management of HIV infection or drug-drug interactions. Alternative explanations for toxicity must be excluded before concluding that it is secondary to the ARV drugs. There are fewer data on ARV drug toxicity in children than in adults, although the full spectrum of ARV toxicities observed in adults has also been reported in children. Some toxicities are more common in children than adults or occur only in children (e.g. TDF- related loss of mineral bone density).[27]

Drug related adverse events may be acute, occurring soon after a drug has been administered; they may be sub-acute, occurring within 1 to 2 days of administration; or they may be late, occurring after prolonged drug administration. Such adverse events may vary in severity from mild to severe and life-threatening. [27] Experience with ARV drugs has led to the recognition of several types of distinct adverse drug effects that may be most common with certain ARV drugs or drug classes, including:

- hematological adverse events associated with drug-induced bone-marrow suppression, most commonly seen with AZT therapy (anemia, neutropenia and, more rarely, thrombocytopenia); [27]

- mitochondrial dysfunction, primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy (the NRTIs differ in their ability to affect mitochondrial function, d4T having greater toxicity than AZT and 3TC, and ABC even less so); [27]

- lipodystrophy and metabolic abnormalities, primarily seen with d4T and the PI class, and to a lesser degree with certain other NRTI drugs (abnormalities include fat maldistribution and body habitus changes, hyperlipidaemia; hyperglycemia, insulin resistance, diabetes mellitus, osteopaenia, osteoporosis and osteonecrosis); [27]

- allergic reactions such as skin rashes and hypersensitivity reactions, more common with the NNRTI drugs but also seen with certain NRTI drugs, such as ABC. [27]

Toxicity can be monitored clinically on the basis of child/guardian reporting and physical examination, and can also be assessed by means of a limited number of laboratory tests, depending on the specific ARV combination regimen that is utilized and the health care setting. Routine laboratory monitoring, although desirable, is not required and cannot be carried out in many decentralized facilities.[27]

In the first ever paediatric switch study by McComsy et al [28], the authors state that; recently, many serious metabolic complications have emerged and are believed to be attributable to antiretroviral therapy. The most common metabolic abnormalities encountered are hypercholesterolemia, hypertriglyceridemia, and insulin resistance. Other abnormalities include peripheral fat wasting, visceral fat accumulation, and hypertension.[28] After much debate in the past few years on the causes of these complications, the spotlight remains on the protease inhibitors (PIs) as being the main culprit in most of these abnormalities, mainly the dyslipidemias and insulin resistance.[28]

McComsy et al [28] reported that in general, children have a more difficult time maintaining viral suppression because of many factors, including frequent nonadherence and less availability of antiretrovirals in palatable forms. Recent reports underline that children experience long-term metabolic abnormalities in the same manner that adults do and perhaps these consequences are even more worrisome in children secondary to long-term expected survival.[28] The researchers mentioned that as in the adult HIV population, PI therapy has the greatest association with dyslipidemia in children.[19] Additionally, high frequency of dyslipidemia in children on PI containing therapy was found in a study by Lainka et al [29]

Indinavir has been reported to cause haematuria and nephrolithiasis in children according to a study by Mueller et al [30]. In another paediatric study by Fraaij et al [31], reported Indinavir associated adverse events were often mild and of gastrointestinal origin. However, serious adverse were reported in seven children including nephrolithiasis (n = 2), silent nephrolithiasis found upon ultrasound research (n = 2), jaundice (n = 1), impaired liver functions, vomiting and malaise (n = 1) and dehydration due to vomiting (n = 1). [31]

Gonzalez-Tome et al [32] reported that metabolic complications are prevalent in HIV-infected children treated with highly active antiretroviral therapy (HAART). Nowadays, lipodystrophy and osteopenia had also been reported in HIV-infected children. [32] Lipodystrophy syndrome is characterized by physical and metabolic abnormalities including fat redistribution, dyslipidemia and insulin resistance. Protease inhibitors (PIs) have been associated with the development of these events. This is one of the most important limiting factors for long term therapy with HAART. [32]

In their study, Hyperlipidemia was considered if cholesterol was ≥ 6.5 mmol/L and/or LDL-cholesterol was ≥ 4 mmol/L and/or triglycerides were ≥ 5.5 mmol/L. Lipodystrophy was diagnosed if patients presented at least one of the following features: peripheral loss

of adipose tissue: sunken cheeks, thinning extremities, hips or buttocks (lipoatrophy), central gain in adiposity: dorsocervical and/or abdomen fat accumulation (lipohypertrophy) or both features (mixed syndrome). [32] Gonzalez-Tome et al [32] found out that the use of PIs among their study subjects prior to switching to Nevirapine was associated with the development of hyperlipidemia in 3 cases and lipodystrophy in 1 case. [32]

Michael Neely and Andrea Kovacs [33] in their study reported that Darunavir associated adverse events in children included diarrhoea and rash. Laboratory abnormalities included a decreased absolute neutrophil count**,** increased pancreatic amylase, increased alanine aminotransferase and aspartate aminotransferase and lipase. Several other studies cited by Michael Neely and Andrea Kovacs [33] i.e. POWER 1 and 2 studies, ARTEMIS and TITAN studies showed darunavir to be associated with increased total cholesterol and increased pancreatic amylase. [33] Increased pancreatic lipase was reported in the POWER 1 and 2, and TITAN studies whereas increased triglycerides were reported in the POWER 1 and 2, and ARTEMIS studies. [33]

Other reported adverse effects of darunavir according to the study by Michael Neely and Andrea Kovacs [33] were nausea , nasopharyngitis, upper respiratory infection, herpes simplex, abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhoea, fatigue, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycaemia, hypertriglyceridemia, immune reconstitution syndrome, low density lipoprotein increased, nausea, pancreatic enzyme increased, rash, Stevens-Johnson Syndrome and vomiting. [33]

In the P1051 study cited by Michael Neely and Andrea Kovacs [33], a high percentage of children in the tipranavir high dose cohort experienced adverse effects the most common being vomiting (42%), cough (30%), diarrhoea (26%), pyrexia (21%), nausea (18%),

nasopharyngitis (12%) and headache (11%). Grade 3 elevations in ALT occurred in 6% and bleeding occurred in 14% of those receiving capsules. [33]

The adverse events diabetes and high cholesterol were found to be associated with Nelfinavir use in children as well as a high prevalence of lipodystrophy following long-term follow-up according to a study by Scherpbier et al .[34]

Croxtall et al [35] state that although generally well tolerated, lopinavir/ritonavir is associated with generally manageable adverse gastrointestinal side effects and hypertriglyceridaemia and hypercholesterolemia, which may require co administration of lipid-lowering agents to reduce the risk of coronary heart disease.

Furthermore, a study by Christoph Rudin, Marcel Wolbers, David Nadal, et al [36] found that among the 12 children with suspected toxicity, adverse events were: gastrointestinal in five (including liver and pancreas in one each), and related to fat redistribution, the nervous system, the endocrine system, cardiovascular disease, hypersensitivity, blood count abnormality and unspecified in one each. Grade 3 or 4 laboratory abnormalities were documented in 27 children, but only three children stopped LPV/r (thrombocytopenia (11×109/l without recovery after treatment cessation), a liver enzyme elevation (aspartate aminotransferase 185 IU/l) and an amylase elevation (870 IU/ml without elevation of serum lipase) in one each).[36]

Designing potent and effective second-line regimens for infants and children is particularly difficult because of the current lack of experience with use of second-line regimens in children and the limited formulary maintained in most resource-limited settings.[27]

2.3 Concluding remarks

In conclusion, though some studies have been conducted in various developed countries, very few studies have been published from Africa and Uganda particularly evaluating second-line antiretroviral therapy use among adults and children. No study has been published in Uganda on adverse effects on second-line HAART among HIV infected children. Hence the need for this study in order to answer the proposed research questions.

CHAPTER 3-METHODOLOGY

3.0 Introduction

The section below highlights the methodology that was used in carrying out the above study.

3.1 Study design

This was an observational study which used a cross-sectional study design approach. The researcher retrospectively reviewed HIV infected adult, adolescent and pediatric client charts on second-line HAART at Mildmay Uganda. A cross-sectional study design approach was used because it was quick and inexpensive [37] given the time frame to conduct the study, and the inadequate resources available at the study site. The above study design is also useful for investigating exposures that are fixed characteristics of individuals such as gender and ethnicity [37]

3.2 Study setting

Mildmay Uganda, where the study was done is specialist HIV/AIDS prevention, care and treatment centre in Uganda which was founded in 1998. It provides comprehensive HIV/AIDS clinical care to HIV/AIDS clients as well as training to health and other allied professionals in HIV/AIDS care and management. Mildmay Uganda was among the first beneficiaries countrywide to provide free ART to HIV/AIDS clients needing HAART through programs like the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM).[38] It receives both adults and pediatric clients from all over the country with the majority of the patients being of low socio- economic status.

3.3 Study population

To date, there are about 4,459 clients accessing HAART through Mildmay Uganda main out-patient clinic of whom about 266 are on second-line HAART.[39]

3.4 Sample Size and Sampling

A census of all HIV-infected adult and pediatric client charts on second-line ART regimens treated at Mildmay Uganda between January 2000 to December 2008, was performed.

3.5 Data collection

Data was collected using a data extraction sheet. The designed data extraction sheet was pre-tested and refined as needed. The pre-testing was conducted at the outpatient department of Mildmay Uganda using 10 current patients' files that were not part of the study population.

Data that was collected included social demographic characteristics such as age, gender, ethnicity and marital status (where applicable). Clinical characteristics such as WHO stage, weight, height (where applicable), CD4 count, date of starting first-line ART regimen, date of starting initial second-line ART regimen, ART drug combination/regimen of first-line, initial and current second-line Antiretroviral therapy, documented/recorded clinical adverse events experienced on a second-line regimen, documented laboratory tests done, number of clinical adverse event(s) experienced on second-line regimen, number of laboratory confirmed adverse event(s) experienced on second-line regimen, most likely offending drug(s) of adverse event(s), WHO toxicity grading of adverse events, total duration on a second-line ART regimen and the reason(s) for switching from first-line to second-line HAART among HIV infected adults and children at Mildmay Uganda.

Two assistants with background training in healthcare were recruited and trained on adequate completion of the data collection forms as well as all relevant aspects of the study such as study aim and objectives, confidentiality, etc.

Initial listing of relevant records was done through the computerized Mildmay Uganda patients' database. Records of those who met the criteria were physically collected from the filing office in batch of 20 to 25 on Wednesdays and Saturdays. After data was collected, the files were sent back on Thursday mornings and Saturday evenings. This arrangement ensured that patients' files were used when they were likely not to be needed by clinicians.

3.6 Data Analysis

Data was abstracted from the client files using a data abstraction sheet, coded and entered using Excel 2007. The data was validated by double entry and comparison of the two entries. Further cleaning was done by putting checks and controls in the data entry programme. Data was then exported to STATA Release 11 for data analysis.

Descriptive statistics were used to analyze the occurrence of adverse effects among the study participants, the age and gender distribution. The descriptive statistics were also used to determine the prevalence of adverse effects and the associated risk factors among the study participants.

Chi-square test was used to assess the association between the risk factors and adverse effects experienced by the study participants. Logistics regression was used to determine the type of association if any.

3.7 Validity, Reliability, Bias

Validity is the degree to which the data collected accurately gauges what is being measured and reliability is the consistency with which data measures what is being attempted to be measured over time.[40]

Validity was ensured by pre-testing the data extraction tool and necessary adjustments were made to the tool to improve its quality. The research assistants were thoroughly

trained on every aspect of the data extraction tool so as to ensure reliability. Information bias and missing data was minimized by ensuring that missing client charts were found by all means and illegible handwriting traced back to the respective clinician to provide the appropriate data.

3.8 Ethical considerations

Permission to access client data was sought from Mildmay Uganda Research committee (appendix 3); while approval to conduct the research was obtained from the Medunsa Research and Ethics Committee (MREC) of the University of Limpopo. To further enhance patients' confidentiality, no personal identifiers such as clients' names were recorded and access to client data was limited to the study team. Completed data collection forms as well as patients' files were kept under lock and key to ensure that nothing was lost and their confidentiality maintained.

3.9 Data Collection Tool

Data was abstracted from patient client charts using a Data Extraction sheet which was pretested and modified accordingly to abstract all the necessary data to appropriately answer the proposed research questions.

The data extraction sheet comprised of three main sections. Section one consisted of socio-demographic data that was abstracted from patient client charts, Section two consisted of abstracted clinical adverse events data as well as laboratory and other test investigations done to confirm or support clinical diagnosis of reported adverse events and section three consisted of abstracted data describing first and second-line HAART drug regimen characteristics including WHO stage, CD4 count, Viral load data (where applicable) and the reason for switching therapy from first-line to second-line ART.

CHAPTER 4- RESULTS

4.0 Introduction

This chapter summarizes the results of the study. In the subsequent pages, data are presented in tables and figures beginning with the sociodemographic characteristics of the study participants to the reasons for switching from first-line to second-line highly active antiretroviral therapy.

Of the 266 expected numbers of patients files, 10 were used in the pre-testing of the tools and later not included in the final sample; 9 files were not retrieved, so the final sample was 247 cases.

4.1: Sociodemographic characteristics of the sample

4.1.1. Age characteristics

The mean age of patients was 33.1±15.5 years old, with a wide range as shown in the following figure.

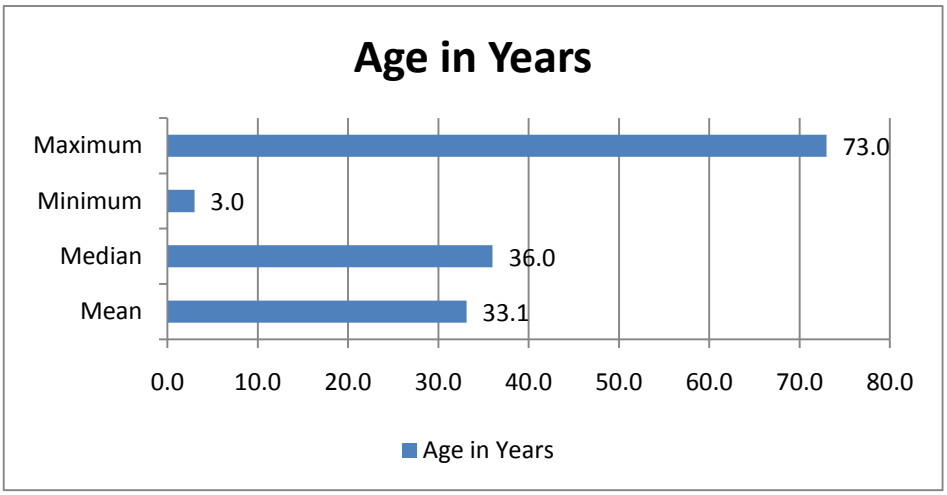

Fig.1: Age parameters (n=247)

This figure shows that the age of patients in the sample ranged from 3 to 73 years. The median age was 33 years.

4.1.2. Other Sociodemographic characteristics

Table 1: Sociodemographic characteristics of the sample

Variables	Frequencies	Percentage
Age category		
Younger than 13 years old	23	9.3
13 years and older	224	90.7
Sex		
Male	116	47.0
Female	131	53.0
Marital status		
Single	168	68.0
Married and cohabiting	79	32.0

The majority of the participants in the study were adults and adolescents 13 years and above, representing 90.7% of the whole sample. There were more females and more single participants comprising 53.0% and 68.0% respectively of the whole sample. All study participants were Black Africans.

4.2. Clinical data of the sample

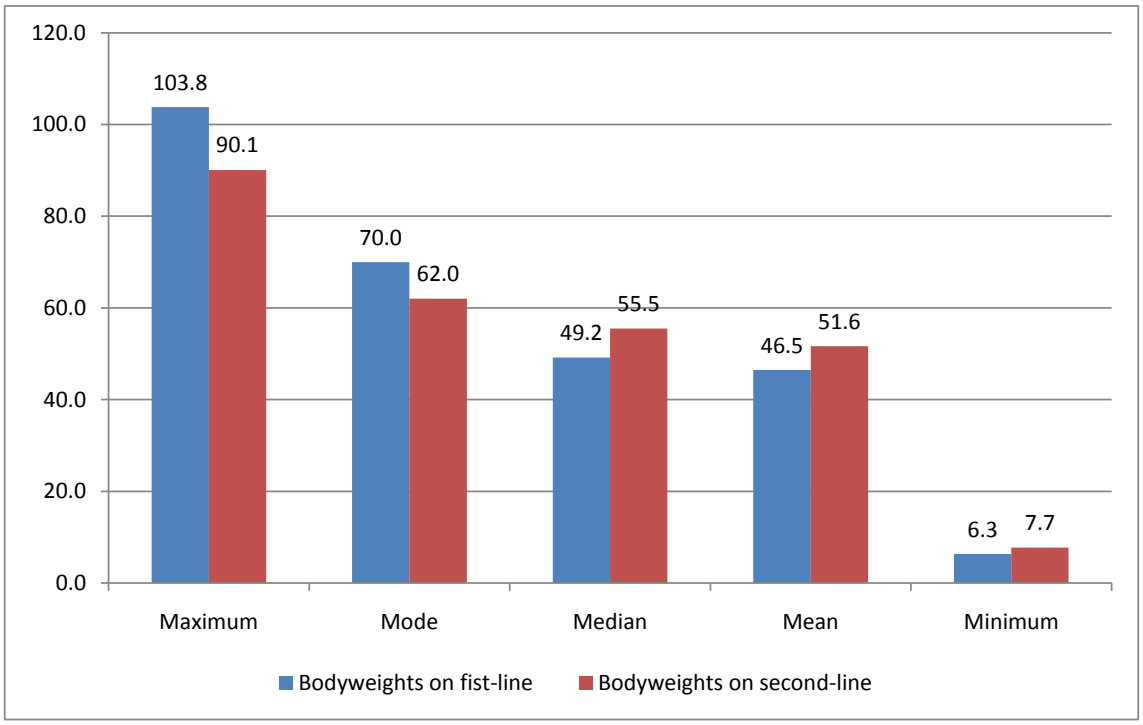

Fig.2: Bodyweights parameters (n=173)

The mean weight on first-line HAART among the study participants was 46.5±21.8 kilograms (kgs) whilst the mean weight on second-line HAART was 51.6±19.5 kilograms (kgs) as shown in figure 2 above.

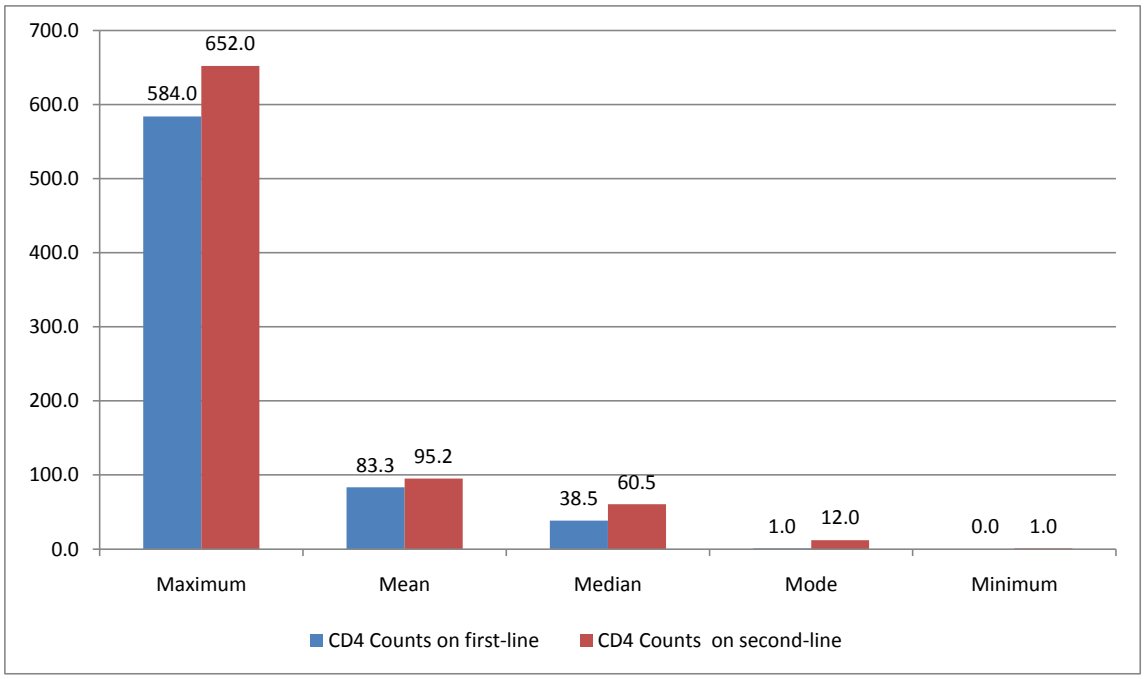

Fig.3: CD4 Counts parameters (n=192)

From figure 3 above, the mean CD4 count on first-line HAART was 83.3 cells per cubic millimeter of blood and the mean CD4 count on second-line HAART was 95.2 cells per cubic millimeter of blood among the study subjects.

Table 2: Clinical improvements in bodyweights and CD4 Counts

Bodyweights increased by 30% or more	68	39.3%
CD4 Counts increased by 30% or more	113	59.5%

In reference to Table 2, more than half 59.5% of the study participants had CD4 counts increased by 30% or more whereas 39.3% of the study subjects had 30% increase or more in their bodyweights.

From figure 4 below the mean total duration on a second-line ART regimen was 32±26 months and the mean duration on a first line before switching to a second-line ART regimen was 30±18 months.

According to this study the median follow up time or duration on a second-line ART regimen was 24 months whereas the median follow up duration on first line ART before switching to a second-line ART regimen was 29 months as illustrated in the figure below.

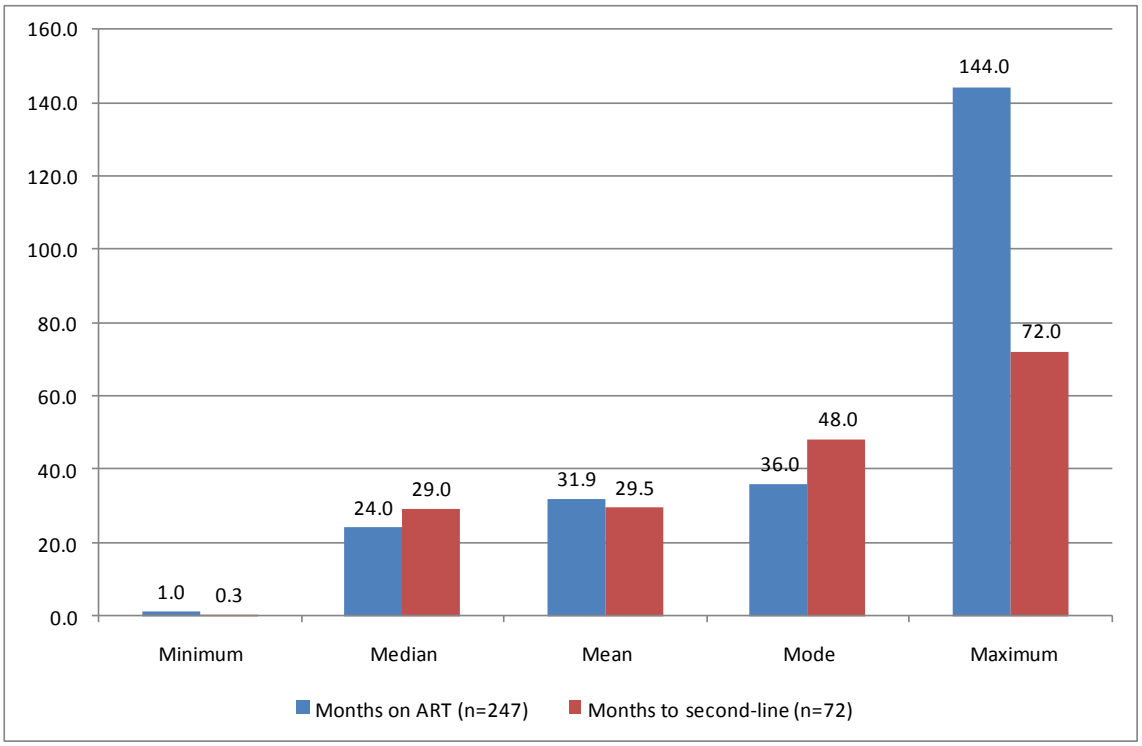

Fig. 4: Duration on antiretroviral treatment

Table 3: Combinations of first-line regimen prescribed

Regimen	Frequencies	Percentage
AZT-3TC-NVP	65	26.4
AZT-3TC-EFV	59	24.0
D4T-3TC-NVP	55	22.4
AZT-NVP-LPV/R	40	16.3
D4T-3TC-EFV	17	6.9
TDF-FTC-EFV	7	2.8
TDF-FTC-NVP	3	1.2
Total	246	100.0

From the above Table, 83.7% of patients were on a recommended first-line regimen according to the Uganda National Antiretroviral Treatment and Care guidelines [42]. Slightly over half, 50.4% were on a recommended AZT based first-line regimen, 29.3% were on a recommended d4T based first-line ART regimen and 4% were on a recommended TDF based first-line ART regimen.

Table 4: Combinations of second-line regimens prescribed

Regime	Frequencies	Percentage
3TC-TDF-LPV/R	61	24.7
ABC-DDI-LPV/R	40	16.2
TDF-DDI-LPV/R	38	15.4
AZT-3TC-LPV/R	36	14.6
FTC-TDF-LPV/R	31	12.6
D4T-DDI-LPV/R	10	4.0
AZT-DDI-LPV/R	9	3.6
AZT-3TC-IDV/R	7	2.8
ABC-3TC-LPV/R	6	2.4
AZT-3TC-IDV/R	2	0.8
D4T-3TC-LPV/R	2	0.8
ABC-TDF-LPV/R	1	0.4
AZT-3TC-SQV/R	1	0.4
D4T-DDI-IDV/R	1	0.4
3TC-NVP-IDV/R	1	0.4
FTC-TDF-IDV/R	1	0.4
Total	247	100.0

The majority of patients 94.7% on second-line HAART were on a Lopinavir/ritonavir (LPV/r) based protease inhibitor regimen. A small percentage (2.0%) was on an Indinavir/ritonavir (IDV/r) based protease inhibitor regimen and 0.4% was on a Saquinavir/ritonavir (SQV/r) based protease inhibitor regimen.

4.3. Adverse effects on second-line regimen

4.3.1. Prevalence of ADRs on second-line regimen

Overall, 55 out of 247 patients suffered from one or more adverse effects, a prevalence of 22.3%. The mean number of ADR episode was 1.3 per patient as shown in the following figure.

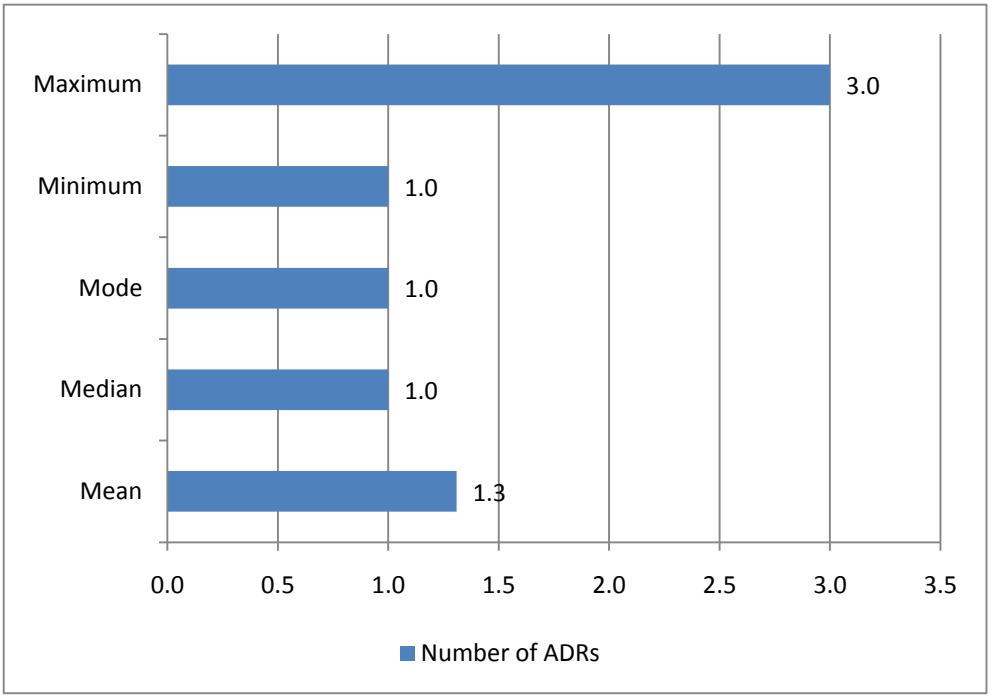

Fig.5: Number of ADRs

The majority (76.4%) of those affected by ADRs, suffered from one type of ADR, but over 20% of them suffered from 2 to 3 types of ADRs as shown in the following table.

Table 5: Co-morbidity of episodes per type of ADR

Co-morbidity of types of ADR	**Frequencies**	**Percentage**
Had experienced one type of ADR	42	76.4
Had experienced two types of ADR	9	16.4
Had experienced three types of ADR	4	7.3
Total	55	100.0

4.3.2. Types of ADRs on second-line regimen

The most common type of ADRs were gastro-intestinal including nausea, vomiting, diarrhea, abdominal pain and pancreatitis evidenced by raised serum amylase levels.

Table 6: Number of episodes per type of ADR

Types of ADR	**Frequencies**	**Percentage**
Gastro-intestinal ADR	22	30.6
Hematologic ADR	17	23.6
Peripheral neuropathy	17	23.6
Metabolic ADR	11	15.3
Hepatic ADR	5	6.9
Total	72	100.0

Based on the frequencies, the above Table shows that peripheral neuropathy and hematologic ADRs occurred in similar frequencies. The hematological adverse effects reported were anemia, neutropenia and thrombocytopenia.

The metabolic effects reported were fat maldistribution and body changes, hyperlipidaemia, hypertriglyceridaemia, hyperglycemia, hypercholesterolemia and less commonly allergic hypersensitivity reactions, lactic acidosis, osteopaenia, osteonecrosis, osteoporosis, electrolyte imbalances such low serum calcium and low serum phosphate

blood levels. The hepatic ADRs were hepatomegaly with associated pain, nausea and vomiting.

Among those who suffered from multiple ADRs, the most common were those who had peripheral neuropathy ADRs together with metabolic ADRs 4 patients (44.4%); as well as gastro-intestinal ADRs together with hepatic ADRs 2 patients (22.2%) as illustrated in the table 7 below.

Table 7: Types of ADRs in patients that experienced co-morbidity

Had experienced two types of ADR	**Frequencies**	**Percentage**
Peripheral neuropathy and metabolic ADR	4	44.4
Gastro-intestinal and hepatic ADR	2	22.2
Gastro-intestinal and peripheral neuropathy	1	11.1
Hematologic and peripheral neuro ADR	1	11.1
Hematologic and gastro-intestinal ADR	1	11.1
Total	9	100.0
Had experienced three types of ADR		
Hematologic, gastro-intestinal and hepatic ADR	1	25.0
Hematologic, gastro-intestinal and peripheral neuropathy	1	25.0
Hematologic, peripheral neuropathy and metabolic ADR	1	25.0
Gastro-intestinal, peripheral neuropathy and hepatic ADR	1	25.0
Total	4	100.0

4.3.3. Sociodemographic and clinical factors associated ADRs

4.3.3.1. ADRs and Sociodemographic characteristics

The table below shows the types of ADRs on second-line HAART among the study participants in relation to gender distribution.

Table 8: ADRs on second-line regimen per sex of patients

Type ADR	Males		Females		
	Frequencies (n=116)	Percent	Frequencies (n=131)	Percent	P-Value
Gastro-intestinal ADR (n=15)	8	**6.9**	7	5.3	0.62
Hematologic ADR (n=11)	5	4.3	6	4.6	0.93
Peripheral neuropathy (n=8)	5	**4.3**	3	2.3	0.40
Metabolic ADR (n=6)	3	2.6	3	2.3	0.89
Hepatic ADR (n=2)	2	1.7	0	0.0	N/A
Had experienced one type of ADR (n=42)	23	**19.8**	19	14.5	0.27
Had experienced two types of ADR (n=9)	4	3.4	5	3.8	N/A
Had experienced three types of ADR(n=4)	1	0.9	3	**2.3**	N/A

Gastrointestinal (GIT) ADRs and Peripheral neuropathy ADRs were reported more in males than females. GIT ADRs occurred among 8 cases (6.9%) in males compared to 7 cases (5.3%) in females whereas Peripheral neuropathy ADRs were reported among 5 cases (4.3%) in males compared to 3 cases (2.3%) in females. Hematological ADRs occurred more in females 6 cases (4.6%) compared to 5 cases (4.3%) in males. Metabolic ADRs almost occurred in equal proportions among the study subjects, that is, 3 cases (2.6%) in males and 3 cases (2.3%) in females. Hepatic ADRs only occurred in the male population with 2 cases (1.7%).

More males 23 cases (19.8%) experienced one type of ADR to second-line HAART compared to females 19 cases (14.5%). More females 8 cases (6.1%) than males 5 cases (4.3%) recorded two and three types of ADRs as shown in table 8 above.

The table below shows the types of ADRs on second-line HAART among the study participants in relation to age distribution.

Table 9: ADRs on second-line regimen per age category of patients

Type ADR	Under 13 years		13 years and over		
	Frequencies (n=23)	Percentage	Frequencies (n=224)	Percentage	P-value
Gastro-intestinal ADR (n=15)	1	4.3	14	**6.3**	0.80
Hematologic ADR (n=11)	2	**8.7**	9	4.0	0.34
Peripheral neuropathy (n=8)	0	0.0	8	3.6	N/A
Metabolic ADR (n=6)	0	0.0	6	2.7	N/A
Hepatic ADR (n=2)	0	0.0	2	0.9	N/A
Had experienced one type of ADR (n=42)	3	13.0	39	**17.4**	0.64
Had experienced two types of ADR (n=9)	0	0.0	9	4.0	N/A
Had experienced three types of ADR(n=4)	0	0.0	4	1.8	N/A

All the types of ADRs including gastrointestinal (6.3%), hematological (4.0%), peripheral neuropathy (3.6%), metabolic ADRs (2.7%) and hepatic ADRs (0.9%) were recorded in the older population 13 years of age and above as compared to those less than 13 years of age who recorded only two types of adverse events on second-line HAART comprising gastrointestinal ADRs (4.3%) and hematological ADRs (8.7%) as shown in the table 9 above.

Hematological ADRs occurred more commonly in the pediatric population (8.7%) than in the adult and adolescent population (4.0%).

There were 39 cases (17.4%) in the age category 13 years and above who experienced one type of ADR compared to 3 cases (13.0%) aged less than 13 years. Only patients aged13 years and above 13 cases (5.8%) experienced more than one ADR to second-line HAART as shown in table 9 above.

4.3.3.2. ADRs and Clinical variables

The table below shows the ADRs on second-line regimen per most common regimen prescribed.

Table 10: ADRs on second-line regimen per most common regimen prescribed

	Hema (n=17)		GIT (n=22)		Liver(n=5)		PN (n=17)		Metabo(n=11)	
Regimen	Frequencies	Percent	Frequencies	Percent	Frequencies	Percent	Frequencies	Percent	Frequencies	Percent
3TC-TDF-LPV/R (n=61)	2	11.8	6	**27.3**	0	0.0	2	**11.8**	0	0.0
ABC-DDI-LPV/R (n=40)	3	**17.6**	0	0.0	0	0.0	0	0.0	0	0.0
TDF-DDI-LPV/R (n=38)	3	**17.6**	2	9.1	0	0.0	2	**11.8**	1	**9.1**
AZT-3TC-LPV/R (n=36)	1	5.9	1	4.5	0	0.0	1	5.9	1	**9.1**
FTC-TDF-LPV/R (n=31)	0	0.0	3	**13.6**	0	0.0	0	0.0	0	0.0
Total	9	52.9	12	54.5	0	0.0	5	29.4	2	18.2

From the above table, hematological ADRs occurred most and in equal proportions 17.6 % among patients on ABC/DDI/LPV/r and TDF/DDI/LPV/r second-line HAART regimens. Patients on 3TC/TDF/LPV/r regimen accounted for 11.8% of the hematological ADRs whereas patients on AZT/3TC/LPV/r accounted for only 5.9%. There were no hematological ADRs recorded on FTC/TDF/LPV/r second-line ART regimen.

Gastrointestinal (GIT) ADRs occurred most 27.3% on 3TC/TDF/LPV/r regimen, followed by 13.6% on FTC/TDF/LPV/r, 9.1% on TDF/DDI/LPV/r and lastly 4.5% on AZT/3TC/LPV/r ART regimen. No gastrointestinal ADRs occurred among patients on ABC/DDI/LPV/r.

Peripheral neuropathy ADRs occurred most and in equal proportions 11.8% among patients on 3TC/TDF/LPV/r and TDF/DDI/LPV/r ART regimens. AZT/3TC/LPV/r accounted for only 5.9% of the peripheral neuropathy ADRs whilst on second-line ART. There were no peripheral neuropathy ADRs recorded among patients receiving ABC/DDI/LPV/r and FTC/TDF/LPV/r ART regimens.

Metabolic ADRs occurred only and in equal proportions 9.1% among patients receiving TDF/DDI/LPV/r and AZT/3TC/LPV/r regimens. There were no hepatic or liver ADRs recorded with regard to all the above common prescribed regimens.

Table 11: ADRs on second-line regimen based on bodyweights improvement

Type ADR	Bodyweight Improved by >30%		Bodyweight Not Improved		
	Frequencies (n=68)	Percent	Frequencies (n=105)	Percent	P-value
Gastro-intestinal ADR (n=8)	4	5.9	4	3.8	0.55
Hematologic ADR (n=8)	4	5.9	4	3.8	0.55
Peripheral neuropathy (n=5)	2	2.9	3	2.9	0.96
Metabolic ADR (n=3)	0	0.0	3	2.9	N/A
Hepatic ADR (n=1)	1	1.5	0	0.0	N/A
Had experienced one type of ADR (n=25)	11	16.2	14	13.3	0.61
Had experienced two types of ADR (n=3)	1	1.5	2	1.9	N/A
Had experienced three types of ADR (n=3)	2	2.9	1	1.0	N/A

Among the study population whose body weight increased by more than 30%, equal proportions 5.9% each recorded both GIT and hematological ADRs on second-line ART. In addition, 2.9% recorded peripheral neuropathy ADRs and 1.5% recorded hepatic or liver ADRs.

Of the study population whose body weight increased by more than 30%, 16.2% experienced one type of ADR whereas 1.5% and 2.9% experienced two and three types of ADRs to second-line HAART respectively as shown in table 11 above.

Table 12: ADRs on second-line regimen based on CD4 Counts improvement

Type ADR	CD4 Improvement		CD4 Not Improvement		
	Frequencies (n=113)	Percent	Frequencies (n=77)	Percent	P-value
Gastro-intestinal ADR (n=11)	10	**8.8**	1	1.3	**0.03**
Hematologic ADR (n=9)	4	3.5	5	**6.5**	0.37
Peripheral neuropathy (n=5)	3	2.7	2	2.6	0.99
Metabolic ADR (n=4)	2	1.8	2	2.6	0.72
Hepatic ADR (n=1)	1	0.9	0	0.0	N/A
Had experienced one type of ADR (n=30)	20	17.7	10	13.0	0.41
Had experienced two types of ADR (n=5)	3	2.7	2	2.6	N/A
Had experienced three types of ADR (n=3)	3	**2.7**	0	0.0	N/A

From table 12 above, the majority 10 cases (8.8%) of patients whose CD4 counts increased by 30% or more experienced gastrointestinal ADRs compared to 1 case (1.3%) whose CD4 count did not increase (p value 0.03).

Hematological ADRs among those whose CD4 counts increased by 30% or more occurred in 3.5% of patients whereas peripheral neuropathy ADRs occurred in 2.7% of patients, metabolic ADRs occurred in 1.8% of patients and hepatic ADRs occurred in 0.9% of patients.

4.3.4. Regimens and ADRs

4.3.4.1. Second-line HAART regimens and associated ADRs based on age category

Table 13: Regimens associated with ADRs in children less than 13 years old

Regimen	Gastro-intestinal ADR	Hemato-logic ADR	Peripheral neuropathy	Metabolic ADR	Hepatic ADR	Total	Percent
ABC-DDI-LPV/R	**2**	0	0	0	0	2	66.7
ABC-3TC-LPV/R	0	**1**	0	0	0	1	33.3
TOTAL	2	1	0	0	0	3	100.0

According to the information in Table 13 above the regimen ABC/DDI/LPV/R was associated with 66.7% occurrence of gastrointestinal ADRs including nausea, vomiting, abdominal pain, diarrhea and pancreatitis evidenced by raised serum amylase levels among children treated at Mildmay Uganda on second-line HAART. The drug regimen ABC/3TC/LPV/R was associated with only hematological ADRs including anemia and neutropaenia occurring among 33.3% of the pediatric subjects

Gastrointestinal tract (GIT) ADRs occurred more commonly (2 cases) among the pediatric study population than hematological ADRs (1 case) from the table above. Peripheral neuropathy, metabolic and hepatic ADRs on second-line ART were not recorded in this study's pediatric population.

Table 14: Regimens associated with ADRs in patients aged 13 years and above

Regimen	Gastro-intestinal ADR	Hematologic ADR	Peripheral neuropathy	Metabolic ADR	Hepatic ADR	Total	Percent
TDF-DDI-LPV/R	**5**	**6**	2	**7**	3	23	**33.8**
ABC-DDI-LPV/R	**4**	**3**	2	1	0	10	**14.7**
3TC-TDF-LPV/R	2	**6**	0	2	0	10	**14.7**
D4T-DDI-LPV/R	1	0	1	**3**	**3**	8	**11.8**
AZT-3TC-IDV/R	0	1	0	2	2	5	7.4
AZT-3TC-LPV/R	1	1	0	1	1	4	5.9
FTC-TDF-LPV/R	0	3	0	0	0	3	4.4
D4T-3TC-LPV/R	0	0	0	1	1	2	2.9
AZT-3TC-IDV/R	0	1	0	0	0	1	1.5
AZT-3TC-SQV/R	0	0	0	0	1	1	1.5
AZT-DDI-LPV/R	1	0	0	0	0	1	1.5
TOTAL	14	21	5	17	11	68	100.0

Table 14 above shows that the second-line ART drug regimen with the highest proportion 33.8% of ADRs was TDF-DDI-LPV/R comprising metabolic, hematological, gastrointestinal, hepatic and peripheral neuropathy ADRs among the study population 13 years and above treated at Mildmay Uganda.

The second-line HAART drug regimens ABC-DDI-LPV/R and 3TC-TDF-LPV/R had equal proportions 14.7% each of the associated ADRs among the study subjects 13 years and above however ABC-DDI-LPV/R was associated with only gastrointestinal, hematological, peripheral neuropathy and metabolic ADRs whereas 3TC-TDF-LPV/R was associated with only hematological, gastrointestinal and metabolic ADRs.

D4T-DDI-LPV/R accounted for 11.8% of the ADRs among the age group 13 years and above exhibiting hepatic, metabolic, hematological and gastrointestinal ADRs.

Indinavir-based regimens were responsible for 9.1% of ADRs including hematological, hepatic and metabolic effects.

Five and less than five ADRs were seen with the following second-line ART regimens: AZT-3TC-LPV/R 4 (5.9%), FTC-TDF-LPV/R 3 (4.4%), D4T-3TC-LPV/R 2 (2.9%) AZT-3TC-IDV/R 1 (1.5%), AZT-3TC-SQV/R 1 (1.5%) and AZT-DDI-LPV/R 1 (1.5%).

In addition, hematological ADRs (21 cases) were the most common ADRs among adults and adolescents aged 13 years and above on second-line ART treated at Mildmay Uganda. These were followed by metabolic ADRs (17 cases), gastrointestinal ADRs (14 cases), hepatic ADRs (11 cases) and the least peripheral neuropathy ADRs (5 cases).

4.3.4.2. Second-line HAART regimens and associated ADRs based on gender

Table 15: Regimens associated with ADRs in males

Regimen	Gastro-intestinal ADR	Hemato-logic ADR	Peripheral neuropathy	Metabolic ADR	Hepatic ADR	Total	Percent
TDF-DDI-LPV/R	**3**	**4**	**2**	**4**	2	15	**45.5**
D4T-DDI-LPV/R	1	0	1	**3**	**2**	7	**21.2**
3TC-TDF-LPV/R	1	**2**	0	**2**	0	5	**15.2**
FTC-TDF-LPV/R	0	2	0	0	0	2	6.1
ABC-3TC-LPV/R	0	1	0	0	0	1	3.0
AZT-3TC-IDV/R	0	1	0	0	0	1	3.0
AZT-3TC-LPV/R	0	1	0	0	0	1	3.0
AZT-3TC-SQV/R	0	0	0	0	1	1	3.0
TOTAL	5	11	3	9	5	33	100.0

The following second-line ART drug regimens were found to be associated with ADRs in males as shown in table 15 above. TDF/DDI/LPV/R had the highest number of ADRs 15 (45.5%) including metabolic 4, hematological 4, gastrointestinal 3, hepatic 2 and peripheral neuropathy 2.

D4T/DDI/LPV/R had 7 (21.2%) ADRs including metabolic 3, hepatic 2, peripheral neuropathy 1 and gastrointestinal 1 whereas 3TC/TDF/LPV/R had a total of 5 (15.2%) ADRs including metabolic 2, hematological 2 and gastrointestinal 1.

The following second-line ART regimens had less than three (3) ADRs for example FTC/TDF/LPV/R had 2 (6.1%), ABC/3TC/LPV/R had 1 (3.0%), AZT/3TC/IDV/R had 1(3.0%), AZT/3TC/LPV/R had 1 (3.0%) and AZT/3TC/SQV/R had 1(3.0%).

Furthermore, among the male study subjects the most commonly occurring ADRs were found to be hematological ADRs with 11 cases, followed by metabolic ADRs 9 cases, hepatic and gastrointestinal ADRs had the same frequency, that is, 5 cases each and the least occurring type of ADRs among males was peripheral neuropathy with 3 cases as illustrated in the table above.

Table 16: Regimens associated with ADRs in females

Regimen	Gastro-intestinal ADR	Hemato-logic ADR	Peripheral neuropathy	Metabolic ADR	Hepatic ADR	Total	Percent
ABC-DDI-LPV/R	**6**	**3**	2	1	0	12	**31.6**
TDF-DDI-LPV/R	**2**	**2**	0	**3**	1	8	**21.1**
3TC-TDF-LPV/R	1	**4**	0	0	0	5	**13.2**
AZT-3TC-IDV/R	0	1	0	**2**	**2**	5	**13.2**
AZT-3TC-LPV/R	1	0	0	1	1	3	**7.9**
D4T-3TC-LPV/R	0	0	0	1	1	2	5.3
AZT-DDI-LPV/R	1	0	0	0	0	1	2.6
D4T-DDI-LPV/R	0	0	0	0	1	1	2.6
FTC-TDF-LPV/R	0	1	0	0	0	1	**2.6**
TOTAL	11	11	2	8	6	38	100.0

Table 16 above shows the second-line HAART regimens that were found to be associated with ADRs in females. ABC/DDI/LPV/R had the highest number of ADRs 12 (31.6%) among the female study subjects including gastrointestinal 6, hematological 3, peripheral neuropathy 2 and metabolic 1.

TDF/DDI/LPV/R was associated with 8 (21.1%) ADRs including metabolic 3, gastrointestinal 2, hematological 2 and hepatic 1. Equal proportions of ADRs 13.2% each were associated with 3TC/TDF/LPV/R and AZT/3TC/IDV/R second-line ART drug regimens as shown in the table above.

A number of second-line ART drug regimens were associated with less than five (5) ADRs for example AZT/3TC/LPV/R had 3 (7.9%), D4T-3TC-LPV/R had 2 (5.3%), AZT/DDI/LPV/R had 1 (2.6%), D4T/DDI/LPV/R had 1 (2.6%) and FTC/TDF/LPV/R had 1 (2.6%).

In addition, the most commonly occurring ADRs among the female study subjects were gastrointestinal and hematological ADRs with 11 cases each followed by metabolic ADRs with 8 cases, hepatic ADRs with 6 cases and the least occurring ADR was peripheral neuropathy with 2 cases.

4.4. Rationale for switching from first-line to second-line regimens

Table 17: Reported reasons for switching from first-line to second-line regimens

Reasons for switching to second line regimen	Frequency	Percent
Treatment failure	205	83.0
Onset of toxicity	14	5.7
Onset of Kaposi sarcoma	8	3.2
Maintain regimen after transfer	6	2.4
Got pregnant	5	2.0
Started on PI due to clinical events	4	1.6
Previously exposed to NVP now pregnant	3	1.2
Wanted to get pregnant	1	0.4
Request from immigrating patients	1	0.4
Total	247	100.0

Most of the study participants 205 (83%) were switched to second-line ART due to treatment failure as shown in table 17 above and most of those 101 (50%) had both immunological and virological failure as shown in table 18 below. Those who switched ARV therapy from first-line to second-line ART due to toxicity were 14 (5.7%) and additionally, onset of Kaposi sarcoma cancer among 8 (3.2%) of the study subjects was the commonest reason for switching from first-line to second-line antiretroviral therapy in the "other reasons for switching" category.

Table 18: Treatment failure categories

Treatment failure category	Frequency	Percent
Immunological plus Virological failure	101	50.00
Immunological failure	41	20.30
All (Clinical +Immunological + Virological) failure	26	12.87
Clinical plus Immunological failure	18	8.90
Virological failure	10	4.95
Clinical failure	3	1.49
Clinical plus Virological failure	3	1.49
Total	202	100.00

From Table 18 above, most patients 101 (50%) had both immunological and virological failure according to the 2006 WHO ART treatment guidelines criteria. Immunological failure alone was recorded in 41 (20.3) patients. Twenty six patients about 13% had all categories of treatment failure including clinical, immunological and virological failure. The least proportions each with 3 cases (1.49%) were clinical failure and clinical plus virological failure.

CHAPTER 5- DISCUSSION OF RESULTS, CONCLUSIONS AND RECOMMENDATIONS

5.0. Introduction

This chapter discusses the findings from the study, and ends with the presentation of the conclusions drawn based on these findings and relevant recommendations. The limitations of the study are also stated.

5.1 Clinical data of the sample.

5.1.1 Body weights and CD4 counts parameters

From this study the median body weight of the study subjects on first-line HAART was found to be 49.2 kilograms (kgs) whilst that on second-line ART was 55.5 kilograms.
The mean weight on first-line HAART among the study participants was 46.5±21.8 kilograms (kgs) whilst the mean weight on second-line HAART was 51.6±19.5 kilograms (kgs).

In a study by Mar Pudjades-Rodriguez et al [41] on second-line ART among adults in RLS a median BMI of 19.7 was found among their patients on first-line ART and a median BMI of 20.1 was found among their patients on second-line ARV therapy.

The median CD4 count on first-line ART among the study participants in this study was 38.5 cells/mm^3 as compared to 110 cells/μl among the study participants in the study by Mar Pudjades-Rodriguez et al [41]. The median CD4 count on second-line ART among the study participants in this study was 60.5 cells/mm^3 as compared to 99 cells/μl among the study participants in the study by Mar Pudjades-Rodriguez et al [41].

The very low CD counts at the start of first-line antiretroviral therapy in this study's subjects could be attributed to the fact that patients in Uganda usually present late to health facilities for treatment.

5.1.2 Clinical improvements in bodyweights and CD4 counts and duration on ART

Regarding clinical improvements in body weights and CD4 counts after starting second-line HAART, about 60% of the patients on second-line ART registered increases in their CD4 counts by 30% or more and about 39% of the patients registered increases in their bodyweights by 30% and more on second-line ARV therapy during the period of study.
This finding is consistent with reports from other settings as reported by Pudjades-Rodriguez et al [41] who reported increases in the median CD4 counts among a cohort of adults on second-line ART; they reported an increase of 90 and 135 cells/μl at 6 and 12 months respectively.

According to this study the median duration on a first-line ART regimen before switching to a second-line ART regimen among the study subjects was 29 months and the median follow up duration on second-line ART among the study subjects was 24 months. In comparison to this study, another study [41] among adults on second-line ART followed up participants on ART before switching to second-line ART for 18 months and whilst on second-line for 8 months. The duration of follow up of participants in this study on both first and second-line ART regimens was longer than in the study by Mar Pudjades-Rodriguez et al [41].

5.1.3 ART drug combinations of prescribed first-line regimen

The four first-line ART regimens that were prescribed in this study included a regimen made of zidovudine, lamivudine and nevirapine, making up 26.4%; followed by a regimen consisting of zidovudine, lamivudine and efavirenz, used in 24.0% of patients; and the combination of stavudine, lamivudine and nevirapine that was used by 22.4% of

patients; while zidovudine, nevirapine and lopinavir/ritonavir (AZT/NVP/LPV/r) was prescribed to 16.3% of patients.. Other regimens less used were made of stavudine, lamivudine and efavirenz (D4T/3TC/EFV); tenofovir, emtricitabine and nevirapine (TDF/FTC/NVP); as well as tenofovir, emtricitabine and efavirenz (TDF/FTC/EFV). In comparison, the most frequently prescribed first-line ART regimen in the study by Mar Pudjades-Rodriguez et al [41] was the combination of stavudine, lamivudine, and nevirapine that was prescribed to 86% of patients. The findings from this study suggest that clinicians have been trying to choose the most appropriate regimens given the existence of co-morbidities and other clinical and social circumstances.

Hence, the regimen made of AZT/NVP/LPV/r is not one of the recommended as first-line regimen in Uganda according to the 2006 Uganda ART Guidelines for both adults and children. It seems that the above combination could have been found in patients who come back to Uganda having started ART from other countries or had been initiated from private health facilities within Uganda and then referred to Mildmay Uganda for further or continued HIV/AIDS care and management.

5.1.4 ART drug combinations of prescribed second-line regimen

In comparison to a large study by Mar Pudjades-Rodriguez et al [41] on second-line ART in resource-limited settings, where a lopinavir/ritonavir (LPV/r) based second-line antiretroviral regimen was given to 51% of patients, nelfinavir-based regimen to 43% and 6% of patients on a type of protease inhibitor which was neither lopinavir/ritonavir nor nelfinavir. In this study, a Lopinavir/ritonavir (LPV/r) based second-line regimen was given to 94.7% of patients starting a second-line regimen; an Indinavir/ritonavir (IDV/r) based second-line regimen was given to 2.0% of patients, a Saquinavir/ritonavir (SQV/r) based second-line regimen was given to 0.4% of patients and 2.8% of patients were started on a second-line ART regimen other than the ones documented above.

According to the Uganda ART Guidelines for adults and children [44] it is documented that the choice for second-line regimen depends on the existing first-line regimen. The PI class is reserved for second-line treatments preferably supported by two new NRTIs. For economic reasons and for the simplicity of administration only Lopinavir/ritonavir (LPV/r) is being recommended as the PI for second-line regimen for treatment failure in adults and adolescents. [44]

With regard to recommended second-line regimens for infants and children, the Guidelines mention that second-line therapy for children in the event of first-line failure would include a change in nucleoside backbone (e.g. from ZDV/3TC to ABC/DDI) plus a PI (LPV/r). [44] Use of PIs other than LPV/r is more problematic in children due to lack of suitable pediatric drug formulations of IDV and SQV. Pediatric formulations are now available for ATV but must be used when boosted with ritonavir. [44] This explains in part the diversity of regimens used as reported above.

5.2 Adverse effects on second-line Highly Active Antiretroviral therapy

5.2.1 Prevalence of adverse drug reactions (ADRs) on second-line ART

In this study, a prevalence rate of 22.3% of adverse effects on second-line HAART was shown among the study participants. Very few studies [5, 41] quote differing toxicity prevalence rates 62% and 1% respectively on second-line antiretroviral therapy. Additionally the above studies [5, 41] report on second-line toxicity prevalence rates in adults aged 15 years and above. The prevalence rate of adverse effects on second-line HAART among children in resource limited settings are poorly documented.

The mean number of ADR episode was 1.3 per patient in this study with a maximum number of 3 ADRs and a minimum number of 1.0 ADR among the study subjects. The majority of study participants suffered from one type of ADR. The figure of 76.4% is higher than what was reported in another study among adults on second-line ART

reported from Uganda [5] where the figure was 62%. In the same study, over 20% of the study participants suffered from 2 to 3 types of ADRs.

5.2.2 The types of adverse effects on second-line ART

Gastrointestinal ADRs such as nausea, vomiting, diarrhea, abdominal pain and pancreatitis evidenced by raised serum amylase levels were the most commonly occurring ADRs among the study population. Similarly, a study by Castelnuovo et al [5] reported that gastrointestinal side effects were common but generally mild and self-limited comprising 17% of nausea or vomiting and 22% of diarrhea.

Hematological ADRs including anemia, neutropaenia and thrombocytopenia accounted for 23.6% of the total ADRs experienced in this study. Similarly peripheral neuropathy and lipodystrophy associated ADRs such as muscle wasting, prominent blood vessels, pain and numbness of hands and feet, fatigue and loss of energy also occurred among 23.6% of the study participants.

In comparison to a study by Castelnuovo et al[5] lipodystrophy particularly lipoatrophy was found among 5 adult patients on a second-line Lopinavir/ritonavir based HAART regimen and additionally 17% developed peripheral neuropathy.

Metabolic ADRs including fat maldistribution and body changes, hyperlipidaemia, hypertriglyceridemia, hyperglycemia, hypercholesterolemia and less commonly allergic hypersensitivity reactions, lactic acidosis, osteopaenia, osteonecrosis, osteoporosis, electrolyte imbalances such low serum calcium and serum phosphate blood levels occurred among 15.3% of study participants. Fat accumulation, high cholesterol and high triglyceride blood levels were reported adverse effects in one adult patient in a certain study 5 secondary to second-line HAART. In addition hepatic ADRs occurred among 6.9% of the study subjects and these included hepatomegally with associated abdominal pain, nausea and vomiting.

5.2.2.1 Types of ADRs in patients that experienced co-morbidities

Among patients that experienced co-morbidities, 44.4% had both peripheral neuropathy and metabolic ADRs; whereas, 22.2% experienced both gastrointestinal and hepatic ADRs. Additionally among patients who experienced two types of ADRs equal proportions of 11.6% of patients experienced hematological and gastrointestinal ADRs on one hand; hematological and peripheral neuropathy ADRs; and gastrointestinal ADRs and peripheral neuropathy on the other hand.

Furthermore, equal proportions of patients (25%) experienced the three types of ADRs to second-line. These co-morbidities of ADRs involved hematological, gastrointestinal and hepatic ADRs; peripheral neuropathy, hematological, and gastrointestinal ADRs; hematological, peripheral neuropathy and metabolic ADRs; as well as gastrointestinal, peripheral neuropathy and hepatic ADRs. This is an important finding from this study, as it suggests that multiple ADRs are possibly becoming common.

5.3 Sociodemographic and clinical factors associated with ADRs

5.3.1 Adverse drug reactions on second-line HAART by gender distribution

According to this study gastrointestinal, peripheral neuropathy and metabolic adverse drug reactions were reported more among males 6.9%, 4.3% and 2.6% than females 5.3%, 2.3% and 2.3% respectively. Hematological ADRs were reported slightly more in females 4.6% than males 4.3% whereas hepatic ADRs were reported only among males 1.7%. It is not documented in other studies [5, 41] the type (s) of ADR reported with respect to gender therefore this may be the first study to report on the type of ADR experienced by patients on a second-line ART drug regimen with respect to gender distribution of the study subjects. Furthermore, more males 19.8% compared to females 14.5% experienced one type of ADR to second-line ART whereas more female participants experienced two 3.8% and three 2.3% ADRs compared to male subjects 3.4% and 0.9% respectively.

5.3.2 Adverse drug reactions on second-line HAART by age category

All the types of adverse drug reactions recorded in this study were reported in the older population 13 years and above whereas the pediatric population in this study registered only gastrointestinal and hematological ADRs.

Owing to the extremely limited formulary maintained in most resource limited settings [27]and problematic access to second-line ART regimens due to the cost of HIV protease inhibitors (PIs) in developing countries [6], a lopinavir/ritonavir based protease inhibitor second-line regimen was what all the children were receiving whilst starting on second-line HAART at Mildmay Uganda (MUg) during the time of this study. Therefore, the adverse effects highlighted in the discussion below with respect to children (less than 13 years of age) pertain to a lopinavir/ritonavir based PI second-line regimen but in combination with different non-nucleoside reverse transcriptase inhibitors (NRTI) backbone components.

Gastrointestinal adverse effects had 6.3% occurrence in adults and adolescents compared to 4.3% occurrence in children. Gastrointestinal adverse effects included nausea, vomiting, abdominal pain, diarrhea and pancreatitis evidenced by raised serum amylase levels. Gastrointestinal adverse effects such as nausea, vomiting, diarrhea following use of protease inhibitors have been reported in one study [18]. Several other studies [19, 24, 25] have also reported nausea, vomiting, diarrhea, abdominal pain and less commonly pancreatitis following lopinavir/ritonavir (LPV/r) use as second-line antiretroviral therapy.

Additionally, from reviewed literature [35, 36] gastrointestinal side (adverse) effects have been documented occurring secondary to lopinavir/ritonavir usage in children. Pancreatitis and an amylase elevation have been documented as an adverse effect following lopinavir/ritonavir based second-line regimen in children [36] which was a similar finding in this study.

Hematological ADRs occurred more commonly 8.7% in the pediatric population compared to 4.0% in the adult and adolescent population aged 13 years and above. Among children in this study the hematological side effects included anemia and neutropaenia. A decreased absolute neutrophil count (neutropaenia) has been observed in a particular study [33] however this adverse effect was reported among children who were on a protease inhibitor Darunavir which is not readily available in resource constrained settings like Mildmay Uganda hence with limited usage in developing countries.

In addition from literature [33], bleeding is documented to have occurred in 14% of children receiving tipranavir capsules probably as a result of thrombocytopenia or low platelet blood counts which could have resulted in bleeding tendencies among the children in the above study. Tipranavir is neither readily available nor accessible in resource constrained settings and therefore its usage if at all is very limited. Tipranavir is not available in Mildmay Uganda and therefore information regarding its adverse effects in children at Mildmay Uganda is not available.

Thrombocytopenia without recovery after treatment cessation has been documented in children in a study by Christoph Rudin et al [36] following lopinavir/ritonavir second-line protease inhibitor use. In this particular study thrombocytopenia was not found to be an adverse effect on a lopinavir/ritonavir based second-line regimen among children aged 13 years and below.

Hematological adverse drug reactions among adults in this study included anemia, neutropaenia and thrombocytopenia. Two studies [18, 19] have reported occurrence of increased risk of bleeding in hemophiliacs secondary to protease inhibitor (PI) use. This could probably be related to the finding in this study that thrombocytopenia (low platelet counts in blood) which clinically predisposes a patient to increased risk of bleeding was found to be a potential adverse effect on second-line (protease inhibitor based) antiretroviral therapy.

Anemia and neutropenia which were hematological adverse effects observed among adults in this study have not been mentioned in reviewed literature as potential adverse effects following protease inhibitor based second-line antiretroviral therapy.

Peripheral neuropathy, metabolic and hepatic ADRs were documented only in the adult population 13 years and above in this study. Peripheral neuropathy and lipodystrophy associated adverse effects included muscle wasting, prominent blood vessels, pain and numbness of hands and feet, fatigue and loss of energy. A number of studies [5, 19, 24] have highlighted the occurrence of lipodystrophy with Protease inhibitor (PI) use including lipoatrophy, peripheral wasting and facial wasting shown to be associated with lopinavir/ritonavir use. Metabolic adverse effects observed among adults aged 13 years and above on second-line antiretroviral therapy in this study included fat maldistribution and body changes, hyperlipidaemia, hypertriglyceridaemia, hyperglycaemia, hypercholesterolaemia and less commonly allergic hypersensitivity reactions, lactic acidosis, osteopaenia, osteonecrosis, osteoporosis, electrolyte imbalances such low serum calcium and serum phosphate blood levels.

Most of the metabolic adverse effects on second-line ART in adults mentioned above have also been documented in some studies [4, 5, 18, 19, 20, 23, and 24] however almost all of the above studies [4, 18, 19, 20, 23, and 24] provide literature from resource rich countries. Only a few published studies [5, 41] so far in RLS have reported drug-related toxicity or adverse drug reactions associated with second-line highly active antiretroviral therapy.

Of importance to mention, adverse effects affecting bone mineral density secondary to tenofovir (a common NRTI used in second-line antiretroviral therapy in adults causing either and/or any of the following conditions osteopaenia, osteonecrosis, and osteoporosis was observed in this study which was not a common finding from literature. A common adverse effect occurring with tenofovir use in adults that has been mentioned in a certain study [4] was renal insufficiency.

Other adverse effects secondary to lopinavir/ritonavir based second-line regimen in children documented in some studies [35, 36] include hypertriglyceridemia, hypercholesterolemia, adverse events related to fat redistribution, the nervous system, the endocrine system, cardiovascular system, hypersensitivity, blood count abnormality (thrombocytopenia) and laboratory abnormalities (elevated liver enzymes and an amylase elevation). Most of the above mentioned adverse effects except raised serum amylase levels were not observed among children in this study probably because of the relatively short duration on second-line ART among the study participants reflecting the limited experience of both patients and clinicians on second-line Protease inhibitor based regimens in resource limited settings compared to those in resource rich settings.

Hepatic or liver related adverse drug effects which were also only observed in the adult and adolescent population included hepatomegaly with associated pain, nausea and vomiting. Furthermore, more adults aged 13 years and above suffered one type of ADR than the younger ones (17.4% versus 13.0%); additionally, only adult patients experienced more two and three types of ADRs (4.0% and 1.8% respectively).

5.3.3 ADRs on second-line regimen per most common regimen prescribed

Gastrointestinal ADRs occurred most commonly with the drug regimens containing TDF such as 3TC/TDF/LPV/R and FTC/TDF/LPV/R; whilst hematological ADRs occurred more commonly with the DDI-containing regimens such as ABC/DDI/LPV/R, TDF/DDI/LPV/R. Peripheral neuropathy ADRs occurred most frequently among patients who were treated with both TDF and DDI-containing regimens (3TC/TDF/LPV/R and TDF/DDI/LPV/R). Similarly, metabolic ADRs were only registered in patients on TDF/DDI/LPV/R and AZT/3TC/LPV/R.

5.3.4 ADRs on a second-line ART regimen based on body weights and CD4 counts improvement.

Gastrointestinal ADRs occurred most commonly among the study subjects who registered improvement in both body weight 5.9 % and CD4 counts 8.8 %. Hematological ADRs occurred in 5.9 % of patients who registered more than 30% body weight increase and 3.5% among patients who registered more than 30% CD4 count increase. Peripheral neuropathy occurred almost equally in the two groups (2.9% versus 2.7%); whereas hepatic ADRs were more prevalent in patients whose bodyweights increased than in those whose CD4 counts improved (1.5% versus 0.9%). In contrasts metabolic ADRs were only found among patients who registered more than 30% CD4 count improvement. The above findings suggest that there might be a relationship between the immune and clinical status and the occurrence of ADRs, but this could not be established in this study given the limited number of cased involved.

5.4 Regimens and Adverse Drug Reactions (ADRs)

5.4.1 Second-line HAART regimens and associated ADRs based on age category

The regimen ABC/DDI/LPV/R was found to be associated with 66.7% occurrence of gastrointestinal ADRs among children in this study whereas ABC/3TC/LPV/R was found to be associated with 33.3% occurrence of hematologic ADRs in children.

Significantly, among the adult population TDF/DDI/LPV/R was associated with the most occurrence of ADRs in 33.8% of cases including metabolic, hematologic, gastrointestinal and hepatic ADRs as well as peripheral neuropathy.

The regimens made of ABC/DDI/LPV/R and 3TC/TDF/LPV/R, both second-line regimens, were associated with 14.7% occurrence of ADRs among adults and adolescents whereas D4T/DDI/LPV/R was associated with 11.8% occurrence of ADRs among participants aged 13 years and above.

Overall, regardless of particular second-line ART drug regimens among adults and adolescents aged 13 years and above, hematological ADRs were the most commonly occurring ADRs (21 cases) and these were followed by metabolic ADRs (17 cases), gastrointestinal ADRs (14 cases), hepatic ADRs (11 cases) and the least occurring ADRs were peripheral neuropathy ADRs (5 cases).

5.4.2 Second-line HAART regimens and associated ADRs based on gender

Among male study participants TDF/DDI/LPV/R drug regimen was significantly associated with 45.5% occurrence of ADRs namely metabolic ADRs 4, hematologic ADRs 4, gastrointestinal ADRs 3 peripheral ADRs 2 and hepatic ADRs 2. D4T/DDI/LPV/R had 21.2% occurrence of ADRs whereas 3TC/TDF/LPV/R had 15.2% occurrence of ADRs among males.

Generally, regarding ADRs among males in this study group, hematological ADRs were the most commonly occurring ADRs (11 cases) followed by metabolic ADRs (9 cases), hepatic ADRs (5 cases), gastrointestinal ADRs (5 cases) and peripheral neuropathy (3 cases).

With respect to the female study participants the second-line ART drug regimen associated with the highest number of ADRs was ABC/DDI/LPV/R 12 cases (31.6%) followed by TDF/DDI/LPV/R 8 cases (21.1%), 3TC/TDF/LPV/R and AZT/3TC/IDV/R both had 5 cases each (13.2% each).

Among females, generally regardless of particular second-line drug regimen, hematological and gastrointestinal ADRs occurred most with 11 cases each followed by metabolic ADRs 8 cases, hepatic 6 cases and peripheral neuropathy 2 cases. Peripheral neuropathy ADRs occurred least among both gender populations whereas females

generally experienced more ADRs to second-line HAART 38 cases compared to the total number of ADRs among males of 33 cases.

5.5 Switching from first-line to second-line

According to the first published study [41]of second-line ART in RLS, reasons for switch to second line ART were not prospectively collected.
From the results of this study, various reasons for switching from first-line to second-line Highly Active Antiretroviral therapy (HAART) were found, have been documented and are discussed here below.

Most of the switches 205 (83%) were due to treatment failure on a first-line ART regimen. Switching due to toxicity accounted for 14 (5.7%), onset of Kaposi Sarcoma malignant cancer disease accounted for 8 (3.2%), maintaining regimen after transfer 6 (2.4%), request from immigrating patients 1 (0.4%), got pregnant 5 (2.0%), started on a protease inhibitor due to clinical events 4 (1.6%), previously exposed to nevirapine, now pregnant 3 (1.2%) and wanted to get pregnant 1 (0.4%).

WHO recommends a second-line regimen should be chosen to substitute first-line regimens when needed (for toxicity or treatment failure).[3] However, in this study various reasons existed for switching from first-line ART to second-line ART regimens in a resource limited setting. This is the first study so far in a RLS to highlight various reasons (other than toxicity or treatment failure to first-line ART) for switching from first-line ART to second-line ART regimens.

In this study, 205 subjects (83%) switched ART due to treatment failure on a first-line ART regimen. In a study by Mar Pujades-Rodriguez et al [41], 230 (62%) had at least one of the criteria of immunological treatment failure according to the 2006 WHO criteria.

According to this study, most patients/clients 101 (50%) registered both immunological and virological failure to first-line HAART.

5.6 Limitations

- Poorly written or no referral notes/letters from other health facilities both from Europe and within Uganda for clients coming to Mildmay Uganda for continued HIV/AIDS care, support and treatment. This contributed to missing data especially regarding previous ART treatment history including information on ART adverse effects;

- Time constraints. The study participants need be followed up for a longer duration so that the long term adverse effects on second-line HAART can be studied as access to and experience on second-line ART increases in RLS;

- The severity and impacts of adverse effects were not assessed in this study.

5.7. Conclusions

The purpose of this study was to characterize the adverse effects on second-line antiretroviral therapy among HIV infected adults and adolescents and children treated at Mildmay Uganda (MUg). To achieve this, the prevalence of adverse effects had to be determined and their distribution based on socio-demographic and clinical factors as well as the reasons that led to for switching from first-line to second-line antiretroviral regimens.

In total, 247 cases, the majority (90.7%) of the study participants were aged 13 years and female (53.0%), and single (68.0%). With regard to reasons that led to the second-line regimen, the main reason for switching was treatment failure (83%), followed by toxicity (5.7%), and other reasons were the onset of Kaposi Sarcoma disease, maintaining regimen after transfer, and nevirapine pre-exposure.

Overall, 55 out of 247 patients suffered from one or more adverse effects, a prevalence of 22.3%. The mean number of ADR was 1.3 per patient.

Of the 55 who experienced adverse effects, 76.4% experienced one type of adverse effect. The three most common adverse effects were gastro-intestinal, followed by hematological and peripheral neuropathy. Based on age, while adults experienced a broad range of adverse drug reactions including metabolic and hepatic ADRs besides the three cited above; children experienced two types only, gastrointestinal, and hematological ADRs.

Hematological ADRs were significantly more prevalent in children than adults (66.7% versus 21.4%); they were also more prevalent in females than males (30.8% versus 15.2%). In contrast, while metabolic ADRs were equally distributed, peripheral neuropathy was more prevalent in males than females (30.3% versus 20.5%). Based on the number of ADRs experienced, more males than females (19.8% versus 14.5%)

experienced one type of adverse effect whereas more females than males (6.1% versus 4.3%) experienced two to three adverse drug reactions to second-line regimens.

Clinically, the didanosine-based regimens were the most associated with ADRs in both children and adults. In Children, the regimen, ABC/DDI/LPV/R, was responsible of 66.7% of ADRs documented; while in adults in was involved in 60.3% of ADRs. Similarly, TDF-, zidovudine-, and stavudine-based regimens were also involved respectively in 52.9%, 17.8%, and 14.7% of ADRs. Based on gender, didanosine-containing regimen, with either TDF or stavudine with lopinavir/r were responsible of 66.7% of ADRs reported in males; while TDF-based regimen with lamivudine or FTC were involved in 21.1% of ADRs also in males.

In females, didanosine-, TDF-, zidovudine-, and stavudine-based regimens were also involved respectively in 57.9%, 36.9%, 23.7%, and 7.9% of ADRs. The regimen, TDF/DDI/LPV/R, was also the most associated the occurrence of ADRs in females as it was in males. Moreover, although no difference was found among patients whose bodyweights increased significantly and those who did not, patients whose CD4 counts increased significantly experienced more ADRs than those who had not (8.8% versus 1.3%, $p= 0.03$).

Concluding remarks

Overall, second-line regimens seem to be well tolerated as the overall prevalence of adverse effects was 22.37%. The didanosine-containing regimens were most associated with the occurrence of ADRs. Hematological ADRs were more prevalent in children than adults; and more in females than males. In contrast, while metabolic ADRs were equally distributed, peripheral neuropathy was more prevalent in males than females. These findings emphasize the need to individualize treatment based on the characteristics of the patient.

5.8 Recommendations

In regard to the findings of this study, the researcher makes the following recommendations:

- Because the main reason for switching regimen is treatment failure, there is an urgent need to have the necessary laboratory tests and equipment as well as the appropriate organizational structure so that tests can be conducted when required;
- Given the prevalence of adverse effects, it is important that clinicians should be educated in the principles and practices of pharmacovigilance so that they can report these effects and contribute to the establishment of a database that can be used for regulatory, clinical, and educational purposes
- Because, adverse effects affect population groups differently, there is a need to provide in-service training to health care workers involved in ART so that they can understand the need to individualize treatment based on the characteristics of the patient.
- Since the severity and impact of adverse effects on second-line regimens were not assessed in this study, further research is needed to evaluate these aspects in Uganda and other resource-limited settings.

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APPENDICES

Appendix I- Mildmay Approval Letter

Appendix III

Mildmay Uganda Approval Letter

MILDMAY
Transforming AIDS Care

May 26, 2009

The Medunsa Research and Ethics Committee
University of Limpopo
MEDUNSA Campus
South Africa

Dear Sir/Madam,

Recommendation for Dr. Namukanja Phoebe M - Mayambala

This is to introduce to you Dr. Namukanja Phoebe M-Mayambala who has been working with Mildmay Uganda for five years now. She is currently a student pursuing her MPH degree at the National School of Public Health, University of Limpopo, Student Number 200726076.

She has presented her research proposal titled, 'Adverse Effects on Second-line Antiretroviral Therapy among HIV infected Adults and Children Treated at Mildmay Uganda' to the Mildmay Uganda Research and Ethics Committee. One of the policies of the Centre is to support staff members doing research at the Centre after careful review by the Research and Ethics Committee and all efforts will be made to support her in this endeavor. This letter is therefore to confirm that as management we will support Phoebe to do her research here under the above mentioned topic.

Thanks for all your assistance during her time of study.

Yours Faithfully,

Dr. Barbara N. Mukasa
Deputy Director of Clinical Services
Mildmay Uganda

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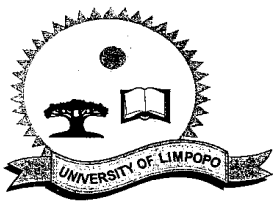
Appendix II: MREC Clearance Certificate

UNIVERSITY OF LIMPOPO
Medunsa Campus



MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

P O Medunsa
Medunsa
0204
SOUTH AFRICA

Tel: 012 - 521 4000
Fax: 012 - 560 0086

MEETING: **06/2009**

PROJECT NUMBER: **MREC/PH/112/2009: PG**

PROJECT :

Title: Adverse effects on second-line highly active Antiretroviral Therapy (HAART) among HIV infected adults and children treated at Midway Uganda

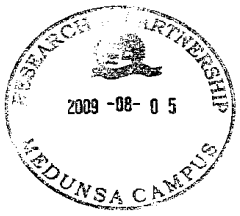
Researcher: Ms P Namukanja
Supervisor: Dr N Malangu
Department: Epidemiology
School: Public Health
Degree MPH

DECISION OF THE COMMITTEE:

MREC approved the project.

DATE: 05 August 2009

PROF GA OGUNBANJO
CHAIRPERSON MREC



Note:
i) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.**
ii) **The budget for the research will be considered separately from the protocol.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

African Excellence - Global Leadership