PREVALENCE AND SEVERITY OF ADVERSE DRUG REACTIONS AMONG ADULT PATIENTS USING DEFAULT FIRST LINE AND MODIFIED ANTIRETROVIRAL COMBINATIONS IN MBEYA REGION, TANZANIA

By

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CERTIFICATION

The undersigned certifies that he has read and hereby recommends for examination of dissertation entitled **Prevalence and Severity of Adverse Drug Reactions Among Adult Patients Using Default First line And Modified Antiretroviral Combinations in Mbeya Region, Tanzania** in fulfillment of the requirements for the degree of Master of Science (Pharmaceutical Management) of Muhimbili University of Health and Allied Sciences.

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Date ……

CERTIFICATION

The undersigned certifies that he has read and hereby recommends for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled **Prevalence and Severity of Adverse Drug Reactions Among Adult Patients Using Default First line And Modified Antiretroviral Combinations in Mbeya Region, Tanzania** in (partial) fulfillment of the requirements for the degree of Master of Science (Pharmaceutical Management) of Muhimbili University of Health and Allied Sciences.

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Supervisor

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I, **William Ndimbumi Mwamakimbula Reuben** declare that this **dissertation** is my own original work and that it has not been presented and it will not be presented to any other University for a similar or any other degree award.

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DEDICATION

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ABSTRACT

Background information:

For more than three decades now in the world, HIV /AIDS has emerged as a serious medical problem. The Government of Tanzania responded by provision of free antiretroviral (ARV) medicines to patients. The goals of ART are to provide maximal and durable suppression of viral load in patients in expectation of halting the disease progression; preventing/delaying medicine resistance, among others.
Mbeya region is among the ART beneficiaries and ARVs provision started in late 2004. The antiretroviral used in the program by then included: zidovudine, didanosine, lamivudine, Abacavir, nevirapine, efavirenz, lopinavir, ritonavir , saquinavir and stavudine.

Stavudine has been withdrawn from new default first line due to high adverse drug reactions. Although ADRs from these medicines are known worldwide, as a matter of fact, adverse reactions vary among various populations and geographical locations. Therefore, data that are derived from within the country are more plausible for patients monitoring, treatment guidelines review, planning and decision-making than those borrowed from another country. In response to that, a study to document the commonly reported ADRs in Tanzania was done in Dar es Salaam and Mbeya regions. However, the study reported ADRs from stavudine-based combination which was a default first line at that time but due to its higher adverse effects, currently is no longer initiated. Therefore, a new default combination is practiced which include zidovudine, lamivudine and efavirenz. Similarly, this combination has its substitutes which include nevirapine, tenofovir and emtricitabine. The last two substitutes were not evaluated in the previous studies because they were yet to be introduced in the programme. This change in default combination of ARVs first line and introduction of two substitutes in combination based regimen, demands for a follow up study to determine their adverse effects.

Objective:

To assess prevalence and severity of adverse drug reactions among adult patients using new default first line and modified antiretroviral combinations in Mbeya region, Tanzania

Methodology

The data (prevalence and severity of ADRs) for this study was collected retrospectively from Care and Treatment Clinic form number two (CTC 2) found in each patient's files receiving antiretroviral therapy in Mbeya referral, regional and three district hospitals in the region. In these forms, ADRs that were reported by patients were documented by clinicians attending them. ADRs were considered as minor if the patient induced with ADR continued with the same medicines or serious when patient was switched to other medications. A study sample of 639 patients files were studied of which comprised of; 280(AZT/3TC/EFV), 280(AZT/3TC/NVP) and 79(TDF/FTC/EFV). Statistical Package for Social Science, Chi-square and Fisher's exact tests were used to analyze the data.

Results

It was found that the overall prevalence of ADRs from use of new default first line combination was: skin rashes (1.07%), peripheral neuropathy (2.14%) and liver toxicity (0.36%). On the other hand, the severity was; 1 case of serious liver toxicity, 6 cases of mild peripheral neuropathy, 3cases of dry skin rash and 1 case of mild anaemia.

Conclusion and Recommendation:

The finding suggests that the new default first line combination is safer to the old one and therefore, recommended to continue to serve as default first line until when a better option is found.

TABLE OF CONTENTS

LIST OF ACCRONYMS

1. ADR - Adverse Drug Reactions
2. AIDS - Acquired immune deficiency syndrome
3. ART - Antiretroviral therapy
4. ARV - Antiretroviral
5. AZT/3TC/EFV- Zidovudine / Lamivudine / Efavirenz
6. AZT/3TC/NVP- Zidovudine / Lamivudine / Nevirapine
7. CD4 - Cluster Differentiation 4
8. CTC 2 - Care and Treatment clinic form number 2
9. HAART - Highly Active Antiretroviral Therapy
10. HIV - Human immunodeficiency virus
11. MUHAS - Muhimbili University of Health and Allied Sciences
12. N - Total sample size
13. n - Specific sample size by regimen
14. n’ - Frequencies of events
15. NACP - National AIDS Control Program
16. PEPFAR - President’s Emergency Plan for AIDS Relief
17. PIs - Protease inhibitors
18. SPSS - Statistical Package for Social Sciences
19. TDF/FTC/EFV- Tenofovir/Emtricitabine/Efavirenz
20. TDF/FTC NVP- Tenofovir/Emtricitabine/Niverapine

21. TDF/3TC/EFV- Tenofovir/Lamivudine/Efavirenz

22. TDF/3TC NVP- Tenofovir/Lamivudine/Niverapine

23. UNAIDS - United Nations AIDS

24. WHO - World Health Organization

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXES

CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is an advanced human immune virus (HIV) disease of the human immune system caused by the HIV[1, 2, 3]. In the world, it was first reported by United State Center of Disease Control (Los Angeles) in June 5, 1981[4]. Since then it has been a growing killer, affecting a large population in the world. United Nations AIDS (UNAIDS) reported that Acquired immunodeficiency syndrome is considered a pandemic[5]. In 2007, the United Nations AIDS (UNAIDS) estimated 33.2 million people worldwide had AIDS and the disease killed 2.1 million people in the course of that year including; 330,000 children, and 76% of those deaths occurred in sub-Saharan Africa. In 2009, World Health Organization (WHO) estimated that 33.4 million people worldwide were living with HIV/AIDS, there were 2.7 million new HIV infections per year and 2.0 million annual deaths due to AIDS

Furthermore, according to UNAIDS reports (2010), the Sub-Saharan Africa remains the region most heavily affected by HIV worldwide, accounting to over two thirds (67%) of all the people living with HIV and for nearly three quarters (72%) of AIDS related deaths in 2008. In addition, the same report estimated that in the Sub-Saharan Africa 1.3million people who died of HIV related illness comprised of 72% of the total 1.8 million deaths attributable to the epidemic, among those, 86,000 deaths occurred in Tanzania.

Antiretroviral (ARV) medicines are medications for the treatment of infection by retroviruses, primarily HIV. When several such medicines, typically three or four, are taken in combination, the approach is known as Highly Active Antiretroviral Therapy (HAART). Considerable progress has been made in providing global access to Antiretroviral Therapy (ART), with five million people currently on antiretroviral medicines around the world. This is a major public health achievement, however still represents only 35% of the people who need HIV therapy now.[6]

In general, the use of HAART has had an important impact on the course and treatment of the disease and disease-related morbidity of HIV-infected patients, increasing their life span and quality of life[7]. However, it has been reported that these advantages have been accompanied with marked increase in the number of adverse drug reactions (ADRs), including minor and serious cutaneous adverse drug reactions[8].

1.2 Literature review

An adverse drug reaction is an expression that describes harm associated with the use of given medications at a normal dosage[9]. United States Food and Drug Administration defined serious adverse event as one when the patient outcome has one of the following eventualities: death, life-threatening, hospitalization, resulted in switching/discontinued and disability (i.e., significant impairment, damage or disruption) in the patient's body function/structure [10]. On the other hand, minor effects are those which get better as the treatment continues or can be easily treated. ADRs may occur following a single dose or prolonged administration of medicine or result from the combination of two or more medicines.

HIV-infected patients at the beginning of the antiretroviral treatment can frequently show a wide variety of adverse drug effects such as rashes, hyperpigmentation, hair loss, hypersensitivity reactions, injection site reaction, urticarial reaction, erythema multiforme, toxic epidermal necrolysis (TEN) or Stevens–Johnson syndrome (SJS)[11].Further,it has been reported that up to 80% of HIV-infected patients experience adverse drug reactions at some point during their therapy, presumably as a result of immune dysregulation, altered medicine metabolism and/or polypharmacy[12].However, HIV-infected patients are more prone to developing cutaneous reactions than the non-infected population[13]. It has been reported that severity of cutaneous adverse reactions varies greatly, and some may be difficult to manage[12]. Cutaneous adverse drug reactions have been reported with all antiretroviral medications.[11] So far, clinical trials have not given conclusive safety results. It is critical to be very cautious when including these agents into HIV treatment regimens.

The reactions related to use of antiretroviral medicines may severely jeopardize confidence in the safety of these medicines and alter patient's adherence to antiretroviral therapy. Within the first year of treatment, adverse reactions, and not treatment failure, are the most common reasons for the discontinuation of ARVs among HIV-infected patients[12]. Although many factors may interfere with proper adherence to ART, adverse drug reactions are among the most important ones. In one trial, it was found that patients experiencing adverse events were 13 times less likely than those not experiencing adverse events to have the highest levels (95-100%) of adherence[8]. Therefore, monitoring and managing ADRs are important for establishing a successful HIV regimen[8]. If patients fail to adhere with ARV schedules, conceivably, such event will not only reduce the treatment efficacy , but also reduce the effectiveness of the treatment program which eventually may lead to the emergence of secondary medicine resistance. Therefore the study intended to determine ADRs prevalence and its severity from adult HIV/AIDS patients.

Recent increases in access to HAART have made the management of adverse drug reactions an increasingly crucial component of HIV/AIDS care in developing countries. However, the spectrum of adverse effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of conditions such as anaemia, malnutrition, tuberculosis and frequent initial presentation with advanced HIV disease[14].The severity of adverse effects may vary as a result of host genetics and diagnostic delays attributable to inadequate laboratory monitoring. From the protocol, the study will determine prevalence and severity of ADRs among HIV/AIDS patients using new default first line and modified based combinations.

1.2.1Adverse drug reactions (ADR)

It is an expression that describes harm associated with the use of given medications at a normal dosage. ADRs may occur following a single dose or prolonged administration of medicine or result from the combination of two or more medicines[15]. A numbers of antiretroviral medicines related adverse effects are as explained below:

1.2.2 Morbilliform exanthematous eruptions

The morbilliform eruption is the most common type of reaction after HIV treatment. HIV-infected patients are more prone to medicine-related rashes than the general population[11].

This type of cutaneous drug reaction is usually observed secondary to HAART or treatment with antibiotics such as amoxicillin, cephalosporins and sulphonamides. These are characterized by widespread pink-to-red blanchable macules and papules. These eruptions usually affect the trunk and proximal extremities and are accompanied by pruritus, which may be intense and uncomfortable[11]. Morbilliform medicine eruptions usually appear between 2 to 10 weeks after starting antiretroviral therapy. However, re-exposure to a previous offender medicine can trigger the reaction in 1–2 days. A maculopapular medicine eruption may take up to 2 weeks to resolve after discontinuation of the offending agent[16]. Also was reported that a maculopapular medicine eruption will occasionally evolve into exfoliative erythroderma[17]. It is not definitively known whether maculopapular drug reactions may evolve into Stevens–Johnson syndrome/toxic epidermal necrolysis[18].But the presence of necrosis, ulcers, mucosal involvement, fever and signs of systemic involvement should alert the clinician to the presence of a severe bullous reaction.

1.2.3 Hyperpigmentation

Nail and skin hyperpigmentation have been reported in long-standing patients infected with HIV. Hyperpigmentation can also be shown as a manifestation of photosensitivity in HIV-infected patients. It has been observed either related to or independent of the HAART therapy. Therefore, in patients with HIV infection, it is difficult to distinguish the reason for the aetiology of hyperpigmentation. These adverse effects resemble the dermatological effects of retinoid. Homologies between the amino acid sequences of retinoic acid-binding protein 1 and the catalytic site of HIV type-1 (HIV-1) proteases have been noted to be differential diagnosis of each other[19]. Moreover, medicine-induced nail pigmentation typically involves several nails and is usually reversible. However, it may take several years to recover melanin production by melanocytes of the nail matrix after medicine withdrawal.

1.2.4 Urticaria

Urticaria is characterized by transient swellings of the skin, which fluctuate over several hours. Deeper swellings of the subcutaneous and sub mucosal tissue are known as angio-edema. Urticarial eruptions occur in a generalized fashion, but tend to occur more frequently in areas covered by clothing. The plaques, also known as wheals, hives or welts, result in a localized oedema of the dermis. They appear as white, oedematous zones that

vary in size from a few millimeters up to centimeters. They are surrounded by erythema and are often accompanied by pruritus[20]. Urticaria may be classified as acute, chronic or physical. It is termed acute when the condition lasts from a few hours to a few weeks, as opposed to chronic urticaria, which may occur several times a week and last for at least 6 weeks. Medicines may cause urticaria by different mechanisms, the most well-known mechanism is the allergic reaction mediated by immunoglobulin E antibodies, which induce acute generalized urticarial.[21]

1.2.5 Stevens–Johnson syndrome /Toxic Epidermal Necrolysis

Stevens–Johnson syndrome (SJS**)** is a rare, severe cutaneous reaction caused by antiretroviral agents. The diagnosis of SJS can be made only when the skin eruption is at its final stage. SJS manifests at mucosal sites with involvement in conjunction with widespread skin lesions, which may either be target-shaped or consist of erythematous macules. The prodromal phase of the eruption is more intense than the one observed with erythema multiforme and includes fever, arthralgia, malaise, headache, vomiting, diarrhoea and myalgia. Lesions usually involve the eyes and mouth, and occasionally the upper airway, gastrointestinal tract, myocardium and/or kidneys. SJS is relatively rare; with approximately 1–7 cases per million persons reported each year[22]. Medicines are the most common cause of SJS; more than 100 different agents have been reported to cause SJS[23]. Nevirapine is the classic example of an HIV medicine associated with SJS[24].

Toxic epidermal necrolysis (TEN) is also a rare, severe cutaneous reaction caused by antiretroviral agents. The diagnosis of TEN can be made only when the skin eruption is at its final stage. TEN rapidly progresses to involve complete detachment of the epidermis involving >30% and up to 100% of the body surface, with a mortality rate of 25% to 75% [25].It is a morbilliform eruption that occurs soon after medicine administration, and it is accompanied by large erythematous and tenderness over areas of the skin. Medicines play 80% to 90% of the role in the aetiology of TEN [26]. The correlation between the illness and the medicine intake is based on the recognition that TEN usually develops 1–3 weeks after the administration of the offending medicine. The clinical diagnosis is based on the presence of characteristic eruptions of erythematous confluent maculae and bullae, together with a positive Nikolsky's sign (detachment of epidermis from a finger with lateral pressure). Typical targetoid lesions develop on the face, neck and trunk and involve >30%

of the body surface. Its Squealer includes pathological scarring, disturbances in skin pigmentation, ocular diseases, heterotopic ossification and abnormal nail growth. Morbidity and mortality are high (25% to 50%), usually from fluid and electrolyte imbalances and secondary bacterial infections[27]. Nevirapine is the classic example of an HIV medicine associated with TEN.[24]

To date, there is no established treatment for SJS/TEN. Early withdrawal of the offending medicine is essential. A study in Europe and United states examined the result of discontinuing all potentially causative medicines at the first sign of a blister or eruption (typical of SJS or TEN), the difference in mortality was 11% for early recognition and medicine withdrawal versus 27% for late withdrawal [28].

1.2.6 Drug hypersensitivity syndrome (DHS)

Drug hypersensitivity syndrome is an acronym of the DRESS syndrome (drug rash with eosinophilia and systemic symptoms). It occurs between 1 to 6 weeks after the initiation of medicine therapy. This syndrome is characterized by exfoliative dermatitis, fever and potentially life-threatening damage (hepatitis, nephritis and pneumonitis). Eosinophilia is also common and corresponds to the most characteristic analytical feature of this syndrome. Visceral involvement in DHS can include the kidneys, liver, heart, lung, thyroid and brain[29].

The cutaneous eruption in DHS often progresses from macular erythema, which starts on the face, upper trunk and upper extremities, to a dusky reddish and confluent papular rash that is pruritic and can often desquamate. The face, upper trunk and extremities are initially involved[30]. Oedema is a hallmark of DRESS, particularly in a facial distribution[31]. In contrast to SJS and TEN, involvement of the mucous membranes is rare. This condition must be recognized early in order to immediately stop the suspected medicines, but this is not always sufficient to achieve a full recovery. Abacavir is the classic example of HIV medicine associated with DHS.

1.3 The associated adverse drug reactions of individual groups of antiretroviral medicines

1.3.1. Protease inhibitors (PIs) associated adverse reactions

Protease inhibitors have potent activity against HIV, and treatment with these agents has been shown to reduce the incidence of mortality in HIV-infected patients. However, side effects associated with these medicines often limit their long-term tolerability. The most common adverse reaction of PIs is lipodystrophy syndrome, abnormal fat distribution, central adiposity, insulin resistance, hyperglycemia and hyperlipidaemia[32]. Moreover; cutaneous side effects are well described for many PIs. The rate of rash in patients treated with a PI has been recently estimated as around 5 %[32]. PIs include indinavir, ritonavir, nelfinavir, lopinavir, amprenavir, fosamprenavir, atazanavir, tipranavir and darunavir.

1.3.2 Lopinavir / ritonavir associated adverse reactions

Excellent therapeutic efficacy has been documented by multiple clinical trials for the treatment of antiretroviral-naive and -experienced patients with lopinavir/ritonavir. The main side effects associated with lopinavir/ritonavir are gastrointestinal disturbances and elevations of serum lipids. Lopinavir/ritonavir therapy was also associated once with a multi-organ hypersensitivity reaction in an HIV patient[33]. The manufacturer of lopinavir/ritonavir suggests that hair loss occurred in only 0.01% of the patients treated [34].

1.3.3 Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) associated adverse reactions

Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) are potent antiretroviral that were introduced in 1996 for the treatment of HIV infection. They work by disrupting one of the early steps in the HIV life cycle, called reverse transcription. During normal reverse transcription, HIV's reverse transcriptase enzyme converts HIV's Ribonucleic Acid (RNA)-a single strand of genetic information-into Deoxyribonucleic acid (DNA)-a double strand of genetic information. It does this by recoding the RNA building blocks into complementary DNA building blocks. As the HIV life cycle proceeds, the newly formed DNA is used to make more copies of HIV virus. These classes of medicines have two advantages: they increase the adherence to the HAART and delay the use of PIs. Cutaneous problems (rash) and hepatotoxicity are the main side effects induced by NNRTI. An important factor in NNRTI rash is previous history of adverse cutaneous

reactions. A retrospective study conducted at Sihanouk hospital, Cambodia reported that patients with a history of sulfonamide rash were more likely to develop NNRTI rash than those who had taken sulfonamide group but had not experienced a rash[35]. NNRTIs include nevirapine, efavirenz and etravirine.

1.3.4 Nevirapine associated adverse reactions

Nevirapine may cause a number of effects: Severe Liver Problems (Hepatotoxicity and Hepatic impairment)-Cases of severe liver problems leading to liver failure and even death have been reported in people taking nevirapine.[23]Liver problems can occur at any time during treatment, but the risk is highest during the first 18 weeks of treatment [36]. A study done in United states reported that individuals with a higher CD4+ cell count have nevirapine higher risk of liver problems, especially women with CD4+ counts higher than 250 cells/mm3 and men with CD4+ counts higher than 400 cells/mm^3 [37,38]. Also, those who have abnormal liver tests before starting nevirapine and those with hepatitis B or C have a greater chance of experiencing liver problems.

A study done in Netherlands reported that severe rash and skin reactions can happen at any time during treatment but the risk is highest during the first 6 weeks of starting nevirapine [39], similar to other studies reported[40,41,42]. Although skin rash is the most common side effect of nevirapine, some rashes and skin reactions might have been severe or life-threatening, leading to death. Nevirapine may cause other side effects, in clinical practice; general cutaneous reactions appear to be less common with efavirenz than with nevirapine[43.] Furthermore, due to somewhat dissimilar structures, skin rashes occurring during therapy with nevirapine may not recur with subsequent administration of efavirenz.

1.3.5 Efavirenz associated adverse reactions

Efavirenz skin rashes are generally a mild-to-moderate diffuse maculopapular skin eruption or pruritic erythema. New onset rash was reported in 26% of the efavirenz-treated patients compared with 17% of the patients in control groups[44]. The onset of rash was generally 11 days after starting treatment in adults with a median duration of 16 days[44]. Occasionally, it could develop as vesicles, moist desquamations and/or mouth ulcerations.[45]

It has also been shown that efavirenz could induce photosensitive medicine eruptions. In all cases, the photosensitivity developed about two months after starting administration of efavirenz and the rash appeared only in the sun-exposed areas[46]. Moreover, there are some papers reporting cases of cutaneous leucocytoclastic vasculitis associated with efavirenz treatment[47]. However, efavirenz has been implicated in SJS[48]. Although reported with an incidence of 0.14% in all studies and expanded access[49]. Efervirenz treatment related to immune hypersensitivity reaction is rare. A study done in Madrid, Spain had reported severe pulmonary hypersensitivity, maculopapular pruritic rash, myalgia and fever for 10 days after the initiation of efavirenz treatment[50]. That event immediately resolved upon discontinuation of efavirenz and treatment with corticosteroids. Rechallenge with efavirenz led to a generalized erythema with fever and mucosal involvement toxicity associated to efavirenz in HIV-infected persons enrolled in an expanded access program[51].

DRESS syndrome was reported in association with efavirenz 20 days after starting efavirenz, lamivudine and stavudine. All medicines were discontinued and an intravenous steroid therapy was started. The patient was also rechallenged with lamivudine, stavudine and nelfinavir, but not with efavirenz, without recurrence. Not-DRESS syndrome, which consists of acute hypersensitivity syndrome with severe hepatitis, pneumonitis and interstitial nephritis, has been related to efavirenz administration. This case report stated that the absence of skin changes and eosinophilia did not exclude the development of hypersensitivity syndrome related to efavirenz therapy[52]. The patient hypersensitivity reaction manifested with rash and fever preceding severe medicine-induced hepatitis. It was resolved after discontinuation of the HAART. The same patient was rechallenged with tenofovir and emtricitabine one year later; no reactions reappeared[53].This was similar to the study that described a patient with efavirenz-induced hypersensitivity syndrome reaction, who was successfully desensitized to efavirenz .[54]

1.3.6 Nucleoside reverse transcriptase inhibitors (NRTIs) associated adverse reactions

Nucleoside reverse transcriptase inhibitors were the first medication approved for the treatment of HIV infection. Class-wide side effects include lactic acidosis, hepatic steatosis and lipoatrophy[55].In Tanzania, the nucleoside analogues used comprised of zidovudine, didanosine, lamivudine, stavudine, abacavir and emtricitabine.

1.3.7 Tenofovir associated adverse reactions

Tenofovir disoproxil fumarate is a nucleotide analogue similar to adefovir and cidofovir which have well documented renal toxicities including proximal renal tubule cell dysfunction and acute renal failure (ARF) [56, 57]. Studies in HIV treatment-naive patients indicated that, rash occurred in 18% of the patients who received treatment with tenofovir[58]. A case of lichenoid eruption with eosinophilia associated with tenofovir therapy was also described[59]. A tenofovir hypersensitivity syndrome, consisting mainly of a maculopapular rash on the face, extremities and trunk, has been reported in nine HIV-infected patients[60].

1.3.8 Abacavir associated adverse reactions

Abacavir is an NRTI approved for use as part of a combination antiretroviral therapy. The most significant skin reaction associated with abacavir is hypersensitivity reaction. It has been reported to occur in patients ranging from 2.3% to 9% [59]. Abacavir hypersensitivity is a reversible, life-threatening, immune-mediated systemic reaction that generally occurs within the first 6 weeks of exposure to medicine[60]. Symptoms most commonly associated with a hypersensitivity reaction are fever (80%), rash (70%), gastrointestinal effects (50%), lethargy or malaise (40% to 60%) and upper or lower respiratory effects (18% to 30%). Overall, 98% of the cases included either fever or rash or both [61].

Rechallenge with abacavir following a hypersensitivity reaction is contraindicated. Fatal hypotension has occurred in patients who have been rechallenged[62]. Abacavir should not be re-started in patients who developed SJS because of the possibility that the event was a hypersensitivity reaction rather than SJS[63]. TEN has been reported in association with abacavir therapy.

1.3.9 Emtricitabine associated adverse reactions

Emtricitabine is a once-daily NRTI used to prevent the replication of HIV and hepatitis B virus. Emtricitabine is structurally similar to lamivudine, differing only in the addition of fluorine. A study of minor emtricitabine intolerance in treatment-stable patients who switched from lamivudine to emtricitabine was reported in Spain[64]. The most commonly reported adverse events in emtricitabine clinical trials were headache, nausea, diarrhea and skin rashes (pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash). These cutaneous adverse reactions were generally of mild or moderate intensity;

only 1% of the patients were discontinued from treatment because of rash[65] .Skin discoloration, which is typically reported as hyperpigmentation, usually affects either the palms of the hands or the soles of the feet and was observed in 10 (3.5%), 14 (6%) and 5 (2%) emtricitabine recipients with an overall incidence of 3.4%. Five patients (17%) of these 29 reported skin discoloration events, which resolved during continued treatment with emtricitabine was reported in Spain.[66]

In contrast to Abacavir, it is almost exclusive to patients of African origin [67]. However, no patients, regardless of race, perceived this benign event as a significant disability and none discontinued treatment as a result of hyperpigmentation[66]. This condition occurs more frequently in children, with a frequency of 32%.

1.3.10 Lamivudine-associated adverse reactions

Lamivudine has relatively few adverse effects and is well tolerated. Unlike other nucleoside analogues, lamivudine is not likely to be incorporated into mitochondrial DNA[68]. The most common adverse effects of lamivudine that were reported in dose-ranging clinical studies were diarrhea, malaise, fatigue, headache, and sleep disturbances[69]. However, there are anecdotal reports of a variety of nonspecific central nervous system adverse effects that recur on rechallenge[70]. Hematologic toxicity and peripheral neuropathy are rarely associated with lamivudine.[71]

1.3.11 Stavudine –associated adverse drug reactions

Stavudine is structurally similar to zidovudine but has a different adverse effect profile. Sensory peripheral neuropathy is a primary dose-limiting toxicity similar to the neuropathy associated with didanosine and zalcitabine. The incidence of the adverse drug reaction is dose-related; the highest frequency is associated with dosages of 4–8 mg/kg/d, which are much higher than the recommended dosage of ~1 mg/kg/d[72]. One-year rates of peripheral neuropathy associated with dosages of 0.1, 0.5, and 2 mg/kg/d were 6%, 17%, and 37%, respectively, while the cumulative dose was not associated with development of peripheral neuropathy; Symptomatic patients typically have tingling, burning, and pain in the lower extremities, especially at night[73]. Symptoms usually begin to diminish and/or resolve within 1–9 weeks after stavudine therapy is discontinued. It can be difficult to distinguish between HIV-induced peripheral neuropathy and medicine-induced peripheral neuropathy.

The diagnosis is often made on clinical grounds, and, if it is medicine-induced peripheral neuropathy, the symptoms usually resolve when therapy is discontinued. Other adverse effects associated with stavudine that may or may not be dose-related are asthenia, headache, malaise, insomnia, abdominal pain, and modest increases in liver transaminase levels .[74]

1.3.12 Zidovudine-associate adverse drug reaction

Although over years there has been a decrease in the recommended dose of zidovudine from 1500 mg/day to 600 mg/day, which has improved tolerability. Bone marrow suppression has been the most severe adverse effect, which causes anaemia and/or neutropenia[75.] However, the most common adverse effects are nausea, malaise, myalgias, insomnia, and headache[75]. Bone marrow suppression appears to be more common in those patients with advanced disease and is related to the dose and duration of treatment. In patients with $CD4^+$ cell counts >100 cells/ml, hematologic effects occur in 2%–14% of patients; however, the incidence is much greater among patients with $CD4^+$ cell counts <100 cells/ml[76]. Anaemia can occur as soon as 1–2 months after zidovudine is started but is more likely to develop after 2–4 months of therapy[75]. Zidovudine-induced anaemia appears to result from thymidine triphosphate deficiency leading to inhibition of stem cell maturation[77.] Although zidovudine adverse effects are dose-related, patients who have developed toxicity should not have their dose reduced to improve tolerability. This action could lead to sub-therapeutic levels of zidovudine and potentially to HIV medicine resistance.

1.4 Prevalence of adverse events associated with antiretroviral treatment

The Swiss HIV Cohort Study was a prospective cohort study of individuals with HIV-1 who were followed up in one of seven Swiss clinics[78]. Patients were identified by their type of antiretroviral regimen. Patients who had changed their regimen in the last 30 days were excluded from the study. During the visit, physicians completed a questionnaire based on classification used by the AIDS Clinical Trials group on adverse events.

The results of the study indicated that 47 % of patients had clinical adverse affects from antiretroviral combination therapy. Nine percent (9%) of effects were graded as serious or severe. Twenty-seven percent (27%) of laboratory results showed adverse effects, and 16%

of these were rated serious. The more medicines taken in combination, the lower the HIV levels but the higher the likelihood of side effects[78].

1.4.1 Commonly reported antiretroviral adverse reactions in Tanzania

A study revealed that anaemia, liver toxicity, skin rash and peripheral neuropathy were the most reported ADRs[79]. The same study concluded that, in both Dar es Salaam and Mbeya patients developed ARV related ADRs which were similar to those reported elsewhere.

1.5 The statement of the research problem

Although adverse drug reactions from these medicines are known worldwide, as a matter of fact, adverse reactions vary among various populations (genetics) and geographical locations[80]. With this in mind, data that are derived from within the country are more plausible for; patients monitoring, pharmaceutical planning and decision-making than those borrowed from another country. In response to that, a general study to document the commonly reported ADRs in Tanzania was done in Dar es Salaam and Mbeya regions[79]. Although the study did not indicate which sex and ages were more affected by ADRs but found the adverse reactions that were most common among patients included neuropathy, anaemia, liver toxicity and skin rashes. However, this study reported adverse effects from stavudine based combination which was a default first line at that time but due to its higher adverse effects, currently stavudine based combination is no longer initiated. Therefore, a new default combination which was not given first priority before, it is now practiced which include zidovudine, lamivudine and efavirenz (hereafter called new default first line). Similarly, this combination has its substitutes which include nevirapine, tenofovir and emtricitabine. The last two substitutes were not determined for their adverse effects. Therefore this study intends to determine the ARVs regimen safety profile by ADRs prevalence, severity and see which sex and ages were more affected. Furthermore, compare results of ADRs prevalence against old default and new default modified regimens data.

The results of the study will help clinicians in ADRs risks patients monitoring, provide information to National AIDS Control Program for treatment guidelines review, Tanzania food and drug authority for control, pharmaceutical planning &decision making.

1.6 Rationale:

Knowing information of antiretroviral ADRs prevalence and its severity provides vital information for monitoring of the risks and benefits of the medication to HIV/AIDS patients using ARVs new default (AZT/3TC/EFV) first line and its modified combinations. Again provides the information on the rate of known side effects and occurrence of rare ADR. This is also pertinent information for treatment guidelines review, regulatory authority for control, pharmaceutical planning &decision making

1.7 Broad objective:

To assess prevalence and severity of adverse drug reactions among adult patients using new default first line and modified antiretroviral combinations in Mbeya region, Tanzania.

1.7.1 Specific objectives:

i. To determine prevalence and severity of ADRs associated with new default first line and compare prevalence with those of old default first line combination.

ii. To determine and compare Prevalence and severity of ADRs associated with modified and new default first line combinations in a period 2010 to 2011

iii. To determine prevalence and severity of ADRs by sex and age of patients under new default first line and modified combinations in a period of 2010 to 2011.

1.7.2 Null hypotheses to be tested:

i. The prevalence of ADRs from new default first line combination is the same as the old default first line combination

ii. Modified combinations of the new default first line have the same ADRs prevalence as the new default first line combination.

iii. Male and female equally induced with antiretroviral adverse drug reactions

1.7.3 Research questions:

i. Does prevalence of ADRs associated with new default first line in 2011 less than those of 2006 from old default first line combination?

ii. How is prevalence of ADRs associated with modified new default first line combination in a period of 2010/2011 compared with those of new default first line combination?

iii. How do ADRs from new default first line and its modified combinations differ between sexes and ages?

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study area

The study was carried out in Mbeya region. The selection of location was purposely done to enable the researcher to collect adequate data. The region rates second in the country after Dar es Salaam in HIV prevalence, conceivably there is large number of HIV patients and therefore the likelihood of getting different categories of ADRs was high. Secondly, within the region, the referral, regional and eight district hospitals are providing ART services, and therefore the likelihood of getting adequate and diverse data was more certain. Thirdly, with the support of United State Department of Defense the Southern Highland zone has been assisted in developing HIV information system. This database was expected to avail the necessary data for the study.

2.2 Study population

The study involved patients' files under new default first line and modified combinations with an exclusion of those under or switched from stavudine based combinations. Furthermore, the study excluded pregnant women and HIV/AIDS patients below the age of 15 years old.

2.3 Study design

The study was descriptive cross-sectional that assessed prevalence and severity of ADRs associated to the dispensed new default first line based combination (zidovudine, lamivudine and efavirenz) and its modified combinations from nevirapine, tenofovir and emtricitabine as abbreviated in Annex 1. The ADRs of the new default and modified combinations were compared with previous raw data[79].

The new default first line combination and its subsequent modified combinations some came into operation since 2010 and therefore, the study covered a period starting from 2010 to 2011. The data for this study was collected retrospectively from patients' files receiving treatment from Mbeya referral, regional and three district hospitals (Mbozi,

Mbarali and Rungwe) in the region. The hospitals receive free ARVs from the Government medical stores department.

2.4 Period of study

The study period was between April 2012 and July, 2012

2.5 Sampling and sample size

The study population involved patients under new default first line and modified combinations receiving ART services from Mbeya referral, region and Mbarali, Rungwe and Mbozi district hospitals. The study population for each regimen was obtained by identifying particular patients' files regimens from the above mentioned hospitals. Actually, each patient's file contained a care and treatment clinic form number two (CTC 2) in which clinicians documented the reported ADRs. Therefore, the study sample was a total of sampled patients' files under different regimens.

The sample size of patients' files for each study regimen was calculated using the following expression[81].

$$n = \frac{Z^2 pq}{e^2}$$

Where

n = desired sample size for each combination;

z = the value of the standard variate at 95 per cent confidence level (1.96)

p = sample proportion of the target population (i.e. users of a particular combination) - It was determined by counting patients under each combination and then computing its proportion against the population. The value of p for each combination was established through a pre-test study as 0.761 for AZT/3TC/EFV and 0.239 for AZT/3TC/NVP

$q = 1 - p$.

e = an error (assumed to be 0.05)

Using the sample size formula, the sample size for each regimen was calculated and the raw data of ADRs were collected from patients' files that were under the study period

(January, 2010 to December 2011). Data of two years were considered enough to give the pattern of ADRs from each treatment[79].

Prior to the study, a pre- test study was conducted at Ifisi designated district hospital, in Mbeya rural council. During pre-test, a total of 176 (134 for AZT/3TC/EFV and 42 for AZT/3TC/NVP) patients files under new default first line and modified respectively were identified from the hospital. The number of patients on each regimen were used to calculate the sample proportion (Ps).When P- was known, then from the sample size formula q= 1-p.Given z = 1.96 and the acceptable error (e) of 5%, an estimated sample size for each regimen was calculated.

Furthermore, the contribution of hospital to a particular sample size regimen depended on the weights of the number of patients receiving ARVs services from respective hospitals. In order to get the weights of each combination, first, a total number (*y*) of patients' files under new default first line or modified regimen from the sampled hospitals was determined. Secondly, from each hospital, a total number of patients' files under each combination (*x*) were determined and used to calculate the proportionate. Thirdly, a weight for each combination (w_i) was determined using the following expression:

$$W_i = \frac{x}{y} * n$$

Eventually, the calculated sample for each combination and hospital was then attained by random selection of patients' files receiving a particular combination from a particular hospital.

The total sample size was 639.The sample size of AZT/3TC/EFV ($n_{1=280}$) regimen was accordingly contributed from study hospitals based on their proportionate number of patients as follows; Mbeya referral (104), Regional (71), Mbozi (48),Mbarali (34),Rungwe (23). Similarly for AZT/3TC/NVP($n_{2=}280$) ; Mbeya referral (73), Regional (67), Mbozi (20),Mbarali (101),Rungwe (19) and a study population for TDF/FTC/EFV(79) ; Mbeya referral (46), Regional (10), Mbozi (16),Mbarali (7),Rungwe (0),while other regimens were (2) patients under each regimen (i.e. TDF/FTC/NVP and TDF/3TC/EFV) at Mbeya referral hospital only and TDF/3TC/NVP none. Because of inadequate sample size for

TDF/FTC/NVP, TDF/3TC/EFV and the absence of patients under TDF/3TC/NVP, these last three regimens were dropped.

2.6 Inclusion criteria

- Records of adult patients(15years of age and above) on new default first line ARVs and its modified combinations from January, 2010 to December 2011.This criterion was based on the fact that patients of that age could provide plausible report to health providers rather than children whose reports of adverse reaction (s) depended on their caregivers.

2.7 Exclusion criteria

- Patients on old default first line combination or those who started with old and switched to new default first line or its modified
- Pregnant women

2.8 Data collection and analysis

2.8.1 Prevalence and severity of antiretroviral ADRs emanating from new default first line combination after two years of use (i.e. January 2010 to December 2011).

2.8.1.1 Prevalence of ADRs emanating from new default first line combination.

The total number of HIV/AIDS patients' files under new default first line combination in the study period (January to December, 2011) was identified at each hospital. The pre-determined sample size required for the study from individual hospitals was obtained by random selection from the identified total number of files of HIV/AIDS patients under new default first line from each hospital. From each hospital, you have total number of patients' files and the sample size for each facility was known. Randomly the sampling stage was calculated and hence the required number obtained randomly. ADRs were tallied as they appeared in the period of study using a table (Annex 2). First of all, the data was collected from individual hospitals and then was eventually summed up to get the overall prevalence in Mbeya region.

The ADRs prevalence (P, %) was calculated using the following expression [82].

$$P(\%) = \frac{Number\ of\ observed\ ADRs}{Total\ sampled\ cases\ under\ one\ regimen} x100$$

Significance of the difference between results from this study and results from previous data[79] was determined using chi-square test with level of significance α=0.05.

$$x^2 = \sum_{All\ cells} \frac{(O-E)^2}{E}$$

Where,

O = the Expected frequency (from this study)

E= the observed frequency (from the previous raw data)

The degree of freedom was determined using the following expression.

$$df = (Number\ of\ rows - 1) * (Number\ of\ columns - 1)$$

Where expected values were less than 5, Fisher exact test was used.

Fisher's exact test:

A matrix of two variables(X and Y) with ^{m} and ^{n} observed respective states was formed. In the formed matrix (m × n), the entries ^{a}ij represent the number of observations in which $x = i$ and$y = j$. The row and column sums R_i and C_j was respectively calculated and the total sum of the matrix(N).The conditional probability of getting the actual matrix was calculated using the row and column sums expression[83].

$$P_{Cutoff} = \frac{(R_1!R_2!\dots R_m!)(C_1!C_2!\dots C_n!)}{N!\prod_{ij} a_{ij}}$$

The all possible matrices of non-negative integers consistent with the row and column sums $R_i$and C_j were calculated. The sum of the conditional probabilities was equal to 1. The P-value of the test was computed by the sum of all *P*-values which were $\leq P_{cutoff}$ and then compared with the level of significance α=0.05

2.8.1.2 Severity of ADRs emanating from new default first line combination

The sampled files that were selected for prevalence of ADRs under new default first line combination were also used for the study of severity (minor and serious). Data of minor and serious ADRs were obtained from patients' files and tallied accordingly as minor or serious.

A serious adverse event was defined as one when the patient outcome has one of the following eventualities: death, life-threatening, hospitalization, disability (i.e. significant-impairment, damage or disruption in the patient's body function/structure) [8], while minor effects were those which get better as the treatment continues or could be easily treated. Data collected was coded and entered into Statistical Package for Social Sciences (SPSS) version 16 software to determine descriptive statistics and corresponding graphs. Annex 3 was used to capture the severity of ADRs in patients under the treatment of new default first line combination.

2.8.2 Prevalence and Severity of ADRs emanating from modified new default first line combinations in a period of 2010 to 2011

2.8.2.1 Prevalence of ADRs emanating from modified new default first line combinations

Different total numbers of HIV/AIDS patients files under different modified new default first line combinations in the study period were identified at each hospital. The pre-determined sample size required for the study from individual hospitals was obtained by random selection from the identified total number of files of HIV/AIDS patients on each modified new default first line combination at each hospital. ADRs of based combinations were tallied as they appeared in the period of study. The data was collected from individual hospitals and then were eventually summed up for each based combination to get the overall prevalence of ADR for each based regimen in Mbeya region.

Significance of the difference between results, the modified combination and results from the new default first line combination was determined using chi-square at a level of α=0.05. The degree of freedom was determined using the following expression.

$$df = (Number\ of\ rows - 1) * (Number\ of\ columns - 1)$$

Annex 4 was used to capture ADRs which patients experienced as they continue to receive modified combinations of the new default first line.

2.8.2.2 Severity of ADRs emanating from modified new default first line combinations

The sampled files that were selected for prevalence of ADRs on modified new default first line combinations were also used for the study of severity. Data of ADRs were obtained from the patients' files and tallied accordingly as minor or serious. Data was coded and entered into SPSS version 16 software to determine descriptive statistics and corresponding graphs. Annex 5 was used to capture the severity of ADRs in patients under the treatment of the modified new default first line combinations.

2.8.3 Prevalence and severity of ADRs by sex of patients under new default first line and its modified combinations

2.8.3.1 Prevalence of ADRs by sex of patients under new default first line combination

The sampled files that were selected for prevalence of ADRs under new default first line combination were also used for the study of ADRS by sex. The observed ADRs from new default first line patients' files were tallied accordingly with their sex (i.e., male or female). To find out whether or not, there was association of ADRs with sex of patients. Using the observed frequencies, expected frequencies were calculated and then chi-square was determined to establish an association between primary (ADR) and secondary (sex) dependence variables at a level of α=0.05. The degree of freedom was determined using the following expression.

$$df = (Number\ of\ rows - 1) * (Number\ of\ columns - 1)$$

Annex 6 was used to capture ADRs by sex difference of patients.

2.8.3.2 Severity of ADRs by sex of patients under new default first line combination

The sampled files that were selected for prevalence of ADRs under new default first line combination were also used for the study of severity of ADRS by sex. The observed severity (minor and serious) of ADRs from patients files were tallied accordingly with their patients' sex (i.e. male or female). Data was coded and entered into SPSS version 16

software to determine descriptive statistics and corresponding graphs. Annex 7 was used to capture the severity of ADRs by sex of patients.

2.8.3.3 Prevalence of ADRs by sex of patients under modified new default first line combinations

The sampled files that were selected for prevalence of ADRs under different modified new default first line combinations were also used for the study of respective prevalence of ADRs by patients' sex. Data of ADRs occurrence from modified combinations were obtained from patients' files and tallied accordingly by patients' sex (i.e. male or female). To find out whether or not, there was dependence of ADRs on sex of patients was determined by using chi-square at level of α=0.05. The degree of freedom was determined using the following expression.

$$df = (Number\ of\ rows - 1) * (Number\ of\ columns - 1)$$

Annex 8 was used to capture ADRs by sex of patients.

2.8.3.4 Severity of ADRs by sex of patients under modified new default first line combinations

The sampled files that were selected for prevalence of ADRs under modified new default first line combinations were also used for the study of severity of ADRs by patients' sex. The modified new default first line had its own severity of ADRs. Data of minor and serious ADRs from modified combinations were obtained from patients files and tallied accordingly by patients' sex (i.e. male or female). Data was coded and entered into SPSS software to determine descriptive statistics and corresponding graphs. Annex 9 was used to capture the severity of ADRs by sex of patients.

2.8.4 Prevalence and severity of ADRs by age of patients under new default first line and modified combinations

2.8.4.1 Prevalence of ADRs by age of patients under new default first line combination

The sampled files that were selected for prevalence of ADRs under new default first line combination were also used for the study of ADRs by ages. The observed ADRs from new default first line patients' files were tallied accordingly with their ages (i.e.15-35years

referred as young or above 35 years referred as old). To find out whether or not, there was dependence of ADRs on ages of patients were determined by using chi-square at a level of α=0.05. The degree of freedom was determined using the following expression:

$$df = (Number\ of\ rows - 1) * (Number\ of\ columns - 1)$$

Annex 10 was used to capture the ADRs by ages in patients under the treatment of new default first line.

2.8.4.2 Severity of ADRs by ages of patients under new default first line combination

The sampled files that were selected for prevalence of ADRs under new default first line combination were also used for the study of severity of ADRs by ages. The observed severity (minor and serious) of ADRs from new default first line patients files were tallied accordingly with their ages (i.e.15-35 and above 35 years old). Data were coded and entered into SPSS software to determine descriptive statistics and corresponding graphs. Annex 11 was used to capture the severity of ADRs by ages of patients

2.8.4.3 Prevalence of ADRs by age of patients under modified new default first line combinations

The sampled files that were identified for study of prevalence of ADRs emanating from modified new default first line combinations were also used for the study of prevalence of ADRs by ages. For each modified combination, the observed ADRs from modified new default first line patients files were tallied accordingly with the patients' ages (i.e.15-35 and above 35 years old). To find out whether or not, there was dependence of ADRs on ages of patients was determined using chi-square at a level of α=0.05. The degree of freedom was determined using the following expression:

$$df = (Number\ of\ rows - 1) * (Number\ of\ columns - 1)$$

Annex 12 was used to capture ADRs by ages of patients.

2.8.4.4 Severity of ADRs by ages of patients under modified new default first line combinations

The sampled files that were selected for prevalence of ADRs by ages under modified new default first line combinations were also used for the study of severity of ADRs by patients' ages. For each modified combination, the observed data of severity of ADRs (i.e. minor and serious) were obtained from patients' files and tallied accordingly in ages of 15-35 and above 35 years old. Data was coded and entered into SPSS software to determine descriptive statistics and corresponding graphs. Annex 13 was used to capture the severity of ADRs by ages of patients

2.9 Ethical consideration

The ethical clearance (Annex 14) was obtained from the Directorate of Research and Publication Committee of Muhimbili University of Health and allied Sciences (MUHAS) while local permission was solicited from Southern Highland Zone Ethical Committee, Mbeya region.

CHAPTER THREE

3.0 RESULTS

As already pointed out, the study population involved HIV/AIDS infected patients who have never used stavudine based combination but were receiving new default first line and its modified combinations in the targeted hospitals. A total of 4,404 patients' files were found to be under treatment of the study regimens. Of the 4,404 patients, 1467, 1083, 593, 933, and 328 were receiving treatment from Mbeya referral, Mbeya regional, Mbozi District, Mbalali District and Rungwe District hospitals, respectively. On the other hand, among the 4,404 patients, 2629, 1692, 79, 2 and 2, were under treatment of AZT/3TC/EFV, AZT/3TC/NVP, TDF/FTC/EFV, TDF/FTC/NVP and TDF/3TC/EFV, respectively. No file reviewed had report on the use of TDF/3TC/NVP.

Sampling per weights of the number of patients in each hospital resulted into 223, 148, 84, 142 and 42 files being sampled from Mbeya referral, Mbeya regional, Mbozi District, Mbalali District and Rungwe District hospitals, respectively. Accordingly, samples of 280, 280 and 79 patient files were taken to represent those patients under AZT/3TC/EFV, AZT/3TC/NVP and TDF/FTC/EFV regimens, respectively. These samples were summed up to make a study sample of 639 patients' files. The sampled files were subjected to researcher's review, data collection and analysis. Results from the latter are presented in subsequent respective sub-sections.

3.1 Prevalence and severity of anti-retroviral ADRs emanating from new default first line.

3.1.1 The overall prevalence of ADRs from new default first lines

The use of new default first line combination (i.e., AZT/3TC/EFV) was found to be associated with ADRs' as presented in Table 1.

Table 1: Overall prevalence of ADRs from new default first line

S/No	ADRs	n'	Overall prevalence
1	Anaemia (below and above HB 7)	1	0.36%
2	Skin rashes (wet and dry)	3	1.07%
3	Liver toxicity	1	0.36%
4	Peripheral neuropathy (minor and severe)	6	2.14%

3.1.2 Severity of adverse drug reactions resulting from new default first line

Among the 280 HIV/AIDS patients' files studied under new default first line, 11 ADRs were observed in total. Amongst observed adverse reactions include; 1 case of serious liver toxicity,6 cases of mild peripheral neuropathy,3 cases of skin rash and 1 case of mild anaemia (i.e. hemoglobin above 7). Simultaneous continuation of regimen with a suspected ADR was a criterion for minor event while change of regimen was a criterion for serious ADR. A proportion of 0.09 of the ADRs observed from new default first line was serious.

3.2 Prevalence and Severity of ADRs associated with modified new default first line combinations in a period of 2010 to 2011

As already pointed out, AZT/3TC/NVP and TDF/FTC/EFV modified regimens resulting from substitution of individual medicine(s) in the new default first line were studied. The former was a result of substituting efavirenz in the new default first line with nevirapine while in the latter; zidovudine and lamivudine were substituted by tenofovir and emtricitabine, respectively. The observed ADRs from these regimens were reported in subsequent subsections.

3.2.1 Prevalence of ADRs resulting from AZT/3TC/NVP and TDF/FTC/EFV regimens

3.2.1.1 The prevalence of ADRs resulting from use of AZT/3TC/NVP regimen

From the cases studied, the patients under the use of AZT/3TC/NVP combination were induced with the following ADRS; skin rashes, peripheral neuropathy and anaemia. The observed ADRs' frequencies and overall prevalence were as shown in Table 2.

Table 2: Overall prevalence of ADRs from AZT/3TC/NVP modified default first line

ADRs	Frequencies	ADRs overall prevalence
Skin rashes	11 (35%)	3.93%
Peripheral neuropathy	18(58%)	6.43%
Anaemia	2(6%)	0.71%

3.2.1.2 The prevalence of ADRs resulting from use of TDF/FTC/EFV regimen

Although TDF/FTC/EFV patients were sampled, it was later found that patients under this combination in study area were not common and most of the patients' files belong to patients in transfer from other regions. However due to failure of reaching their background medical history of those in-transfer patients, they were excluded in the study. A total of 79 files of patients that were found to be under this regimen were all studied (100% sampling) and fortunately none had shown signs of ADRs. Notwithstanding, studies of France, Germany, United Kingdom and United states indicated that use of TDF/FTC/EFV had significantly low anaemia prevalence than AZT/3TC/EFV[84]. And, this suggests for the need to continue monitoring patients under this regimen to get conclusive results.

3.2.2 The severity of ADRs emanating from use of AZT/3TC/NVP and TDF/FTC/EFV

3.2.2.1 The severity of ADRs emanating from use of AZT/3TC/NVP

As pointed out above, of 280 patients files studied, it was observed that serious ADRs associated with the use of this combination included; 2cases of serious skin rash ,1 case of severe peripheral neuropathy and 1 case of severe anaemia. Minor observed cases included peripheral neuropathy which ranked the highest 17cases, followed by 9 cases of skin rash and 1 case of mild anaemia (i.e. hemoglobin > 7). Occurrence of severe skin rash in patients was not surprising since niverapine- a component in this combination, is said to cause severe skin rash[85].

3.3 Prevalence and severity of ADRs from new default first line and modified AZT/3TC/NVP combinations as a function of sex of patients

The sample of HIV/AIDS patients' files for AZT/3TC/NVP and AZT/3TC/EFV were randomly selected, the differences or equality was only obtained by chance

3.3.1. Prevalence of ADRs from new default first line as a function of sex of patients

The sampled files (280) were segregated by sex of the patient and in each sex; files were reviewed for ADRs. Table 3 shows numbers of patients found with and without ADRs in each sex category.

Table 3: Prevalence of ADRs from AZT/3TC/EFV as a function of sex of patients

SEX	With ADRs	Without ADRs	TOTAL
Male	2 (0.7%)	138	140
Female	9(3.21%)	131	140
TOTAL	11	269	280

3.3.1.2 Prevalence of ADRs from modified AZT/3TC/NVP combination as a function of sex of patients

Table 4 presents ADR cases between male and female patients under the use of this combination.

Table 4: Prevalence of AZT/3TC/NVP ADRs as a function of sex of patients

SEX	ADRs	Non-ADRs	TOTAL
Male	7 (2.5%)	113	120
Female	24(8.57%)	136	160
TOTAL	31	249	280

3.3.2 The severity of ADRs induced by AZT/3TC/NVP (modified) as a function of sex of patients.

The AZT/3TC/NVP induced ADRS distribution by sex of patients was as follows: 3 Females and 1 male for serious ADRs while on the other hand, 17 females and 10 males were for minor ADRs.

3.4 Prevalence and severity of ADRs as a function of age of patients under new default first line and modified combination in a period of 2010 to 2011

3.4.1 Prevalence of ADRs under AZT/3TC/EFV as a function of age of patients in a period of 2010 to 2011

Table 5 presents the results of prevalence of ADRs as a function of age of patients receiving new default first line

Table: 5 Prevalence of ADRs under AZT/3TC/EFV as a function of age of patients

Age	With ADRs	Without ADRs	TOTAL
15-35 yrs	5(1.79%)	86	91
>35yrs	6(2.14%)	183	189
TOTAL	11	269	280

3.4.2 Prevalence of ADRs under AZT/3TC/NVP as a function of age of patients in a period of 2010 to 2011

Table: 6 Presents the prevalence of ADRs under AZT/3TC/NVP as a function of age

Age	With ADRs	Without ADRs	TOTAL
15-35 yrs	8(2.86%)	94	102
>35yrs	23(8.21%)	155	178
TOTAL	31	249	280

3.4.2.1 Severity of ADRs as a function of age of patients under new default first line and modified combination (i.e., AZT/3TC/NVP) in a period of 2010 to 2011

The severity of ADRs under new default first line were as follows; 15 to 35 years (4), above 35 years (6) for minor and 15 to 35 years (0),above 35years (1) for serious. On the other hand, the severity of ADRs for AZT/3TC/NVP was 15 to 35 years (6),above 35 years (20) for minor and 15 to 35 years (0) and above 35 years(4) for serious ADRs

CHAPTER FOUR

4.0 DISCUSSION OF RESULTS

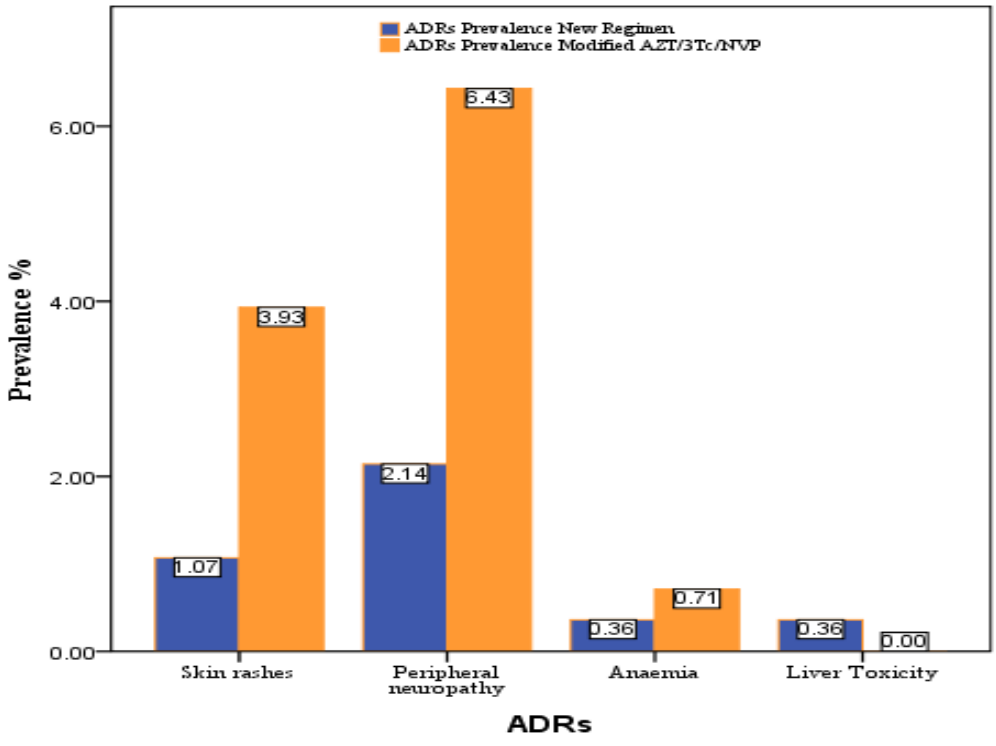
4.1 The overall prevalence of ADRs from new default first line (AZT/3TC/EFV)

The observed ADRs in this study were expected since they have been reported to be associated by the use of the new default first line or its components[79, 86, 87]. For example, skin rash was reported to have occurred in patients receiving nevirapine-based regimen [86]. Use of zidovudine, which is a component of the new default first line, induced anaemia in patients[88]. Furthermore, the use of old default first line which contains stavudine resulted in patients developing peripheral neuropathy[79]. Also, the use of new and old default first lines combinations have been reported to induce anaemia[89]. Essentially, the observed ADRs were documented in the forms (CTC 2-Annex 15) by clinicians during attending patients. These forms were inserted in each patient's file and the results observed were in line with previous data. However, the rates or extent of prevalence were different. From table 1, it is evident that when using new default first line, peripheral neuropathy was the most common ADR (2.14%) followed by skin rashes (1.07%) among the observed ADRs. The observed scenario was also reported [86].

However, more interestingly, the use of new default first line has shown significant reduction in regimen ADR's prevalence ($P<0.001$) compared to old default first line [79]. Notably, there was reduction of ADRs prevalence as from old default to new default; in liver toxicity (5.88 %to 0.36%), skin rashes (4.07% to 1.07%), anaemia (2.38 to 0.36%) and peripheral neuropathy (2.38% to 2.14%). The difference in prevalence of the two regimen could have been attributed by substitution of stavudine with zidovudine and as well as of nevirapine with efaviranz in the new default first line combination. Stavudine is commonly known to cause peripheral neuropathy[72], while nevirapine causes skin rash[43]. Omission of stavudine and nevirapine in the new default first combination, indeed, was expected to produce positive results. Conceivably, there is no strong evidence to support the null hypothesis that the prevalence of ADRs from new default first line combination is the same as the old default first line combination and therefore, it was rejected.

4.2 The prevalence of ADRs resulting from use of AZT/3TC/NVP regimen

From Table 2, similar to new default first line, peripheral neuropathy appeared to be the most common ADR followed by skin rash. The results from this study were supported by findings reported in Nigeria that peripheral neuropathy followed by skin rash were the commonest ADRs in patients under this regimen[90]. However, when prevalence of ADRs induced in patients by this regimen were compared with those induced by new default first line, the new default first line appeared to be significantly safer (*P<0.001*) to its modified combination; as indicated in Figure 1. Plausibly, there is no strong evidence to support the null hypothesis that suggested that the prevalence of ADRs from AZT/3TC/NVP combination is the same as those from the new default first line combination and therefore, it was rejected. And accordingly, there is strong evidence that in clinical practice, general cutaneous reactions appear to be less common with the use of efavirenz-based than nevirapine-based and therefore efavirenz is as the best candidate at least by now in the new default first line[43].

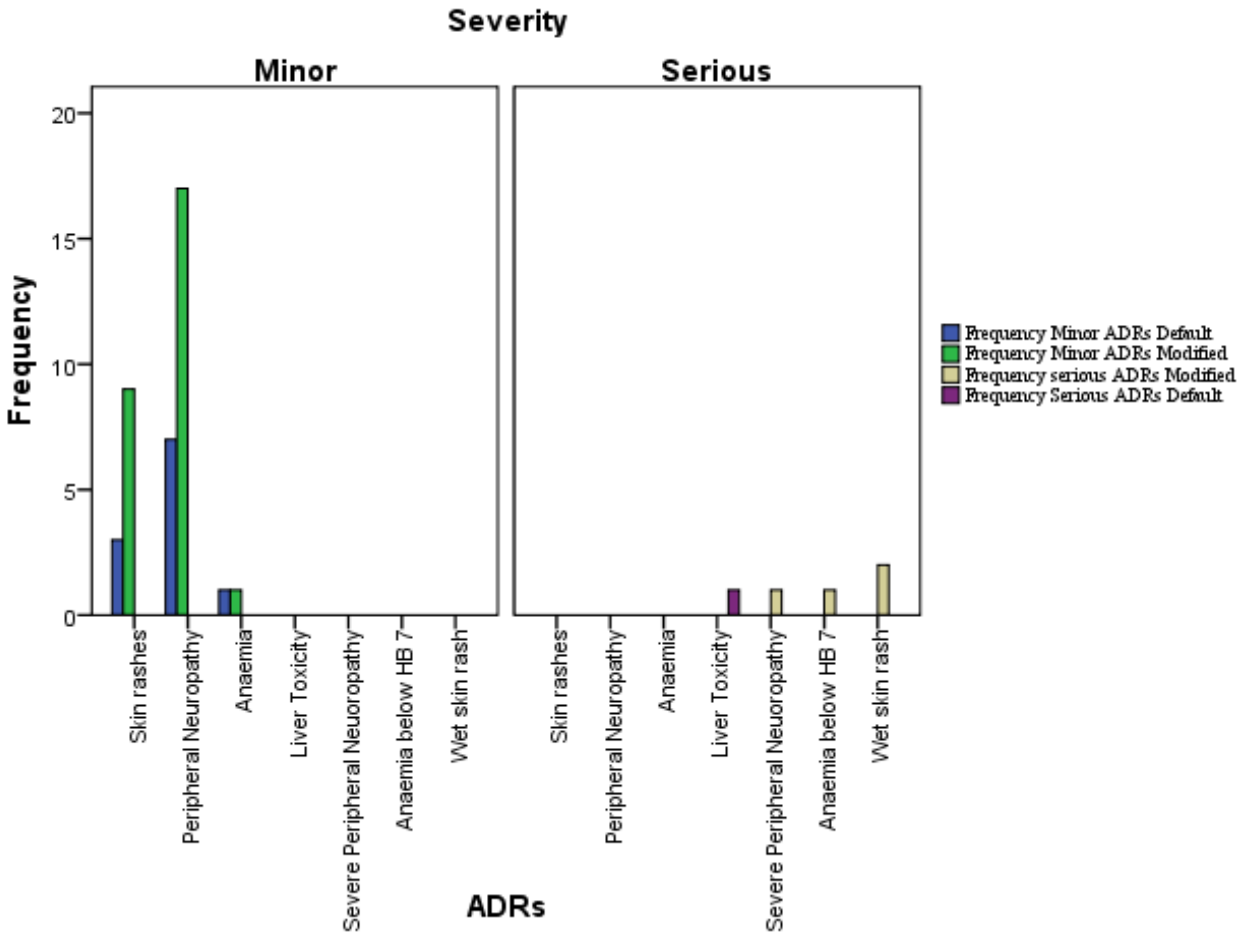


Source: Own data (2012)

Figure 1: Comparison of prevalence of ADRs from default and modified first line

4.2.1 The severity of ADRs associated with use of AZT/3TC/NVP

The Figure 2 below compares severities of ADRs between AZT/3TC/EFV (i.e., new default) and AZT/3TC/NVP (modified regimen). Looking at Figure 3 which indicates minor and serious ADRs cases, the new default first line appeared safer as compared to AZT/3TC/NVP with the exception of one case of liver toxicity which appeared when using AZT/3TC/EFV. This is supported by a study that indicated frequency of serious increased liver enzyme (ILE) in patients under efavirenz based ranges from 1 to 8% whereas in patients treated with nevirapine based, it ranges from 4 to 18%[91]. Therefore the one case occurrence of liver toxicity could be due to efavirenz in the regimen or could be an outlier since it was a single case out of 280 cases.



Source: Own data (2012)

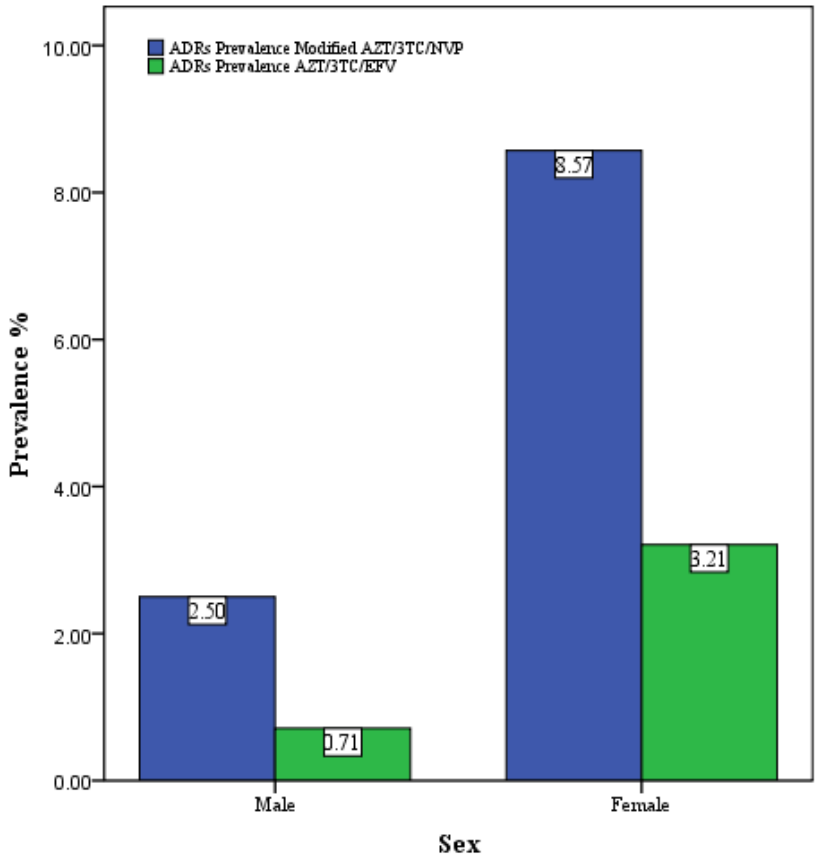
Figure 2: Frequencies of minor and serious ADRs in the study area

4.3 Prevalence of ADRs from new default first line, sex of patients as a factor

From Table 3, of 280 cases reviewed, only two males and nine females were found with ADRs with prevalence of 0.71 and 3.21%, respectively. From these results, it has been shown that males and females induced antiretroviral ADRs differently ($p<0.05$) a finding that negates the null hypothesis. Studies indicated that female patients were more affected as compared to male patients [90, 92, 93]. These reports support the findings from this study. Differences in weight and body mass index between men and women might have played an important role to such results [94, 95]. It is also postulated that hormonal changes in women at puberty, during menstrual cycles, and at menopause may induce changes in medicine metabolism that is different from men. [94, 95] In addition, sex differences in fat accumulation that are more in females and the impact on medicine distribution might have also played a role, as may the genomic constitutional difference that exists between male and female and the way in which this difference affects the levels of various enzymes involved in medicine metabolism[96]

4.3.1 Prevalence of ADRs associated with use of AZT/3TC/NVP combination, sex of patients as a factor

Similar to a case presented in section 4.3 above, male and female induced ADRs differently ($P<0.05$). However, when prevalence from AZT/3TC/EFV combination was compared to those of AZT/3TC/NVP, the former appears safer (Figure 3).The causes of difference between prevalence of the two combinations could have been caused by the substitution made of efarvirenz in the new default first line combination with nevirapine. Generally, cutaneous reactions appear to be less common with efavirenz than with nevirapine as a component in new default first line[43]. For example, during the study, when reviewing files of patients under new default first line combination 3 cases of skin rashes were noted as opposed to 11 cases under AZT/3TC/NVP combination.

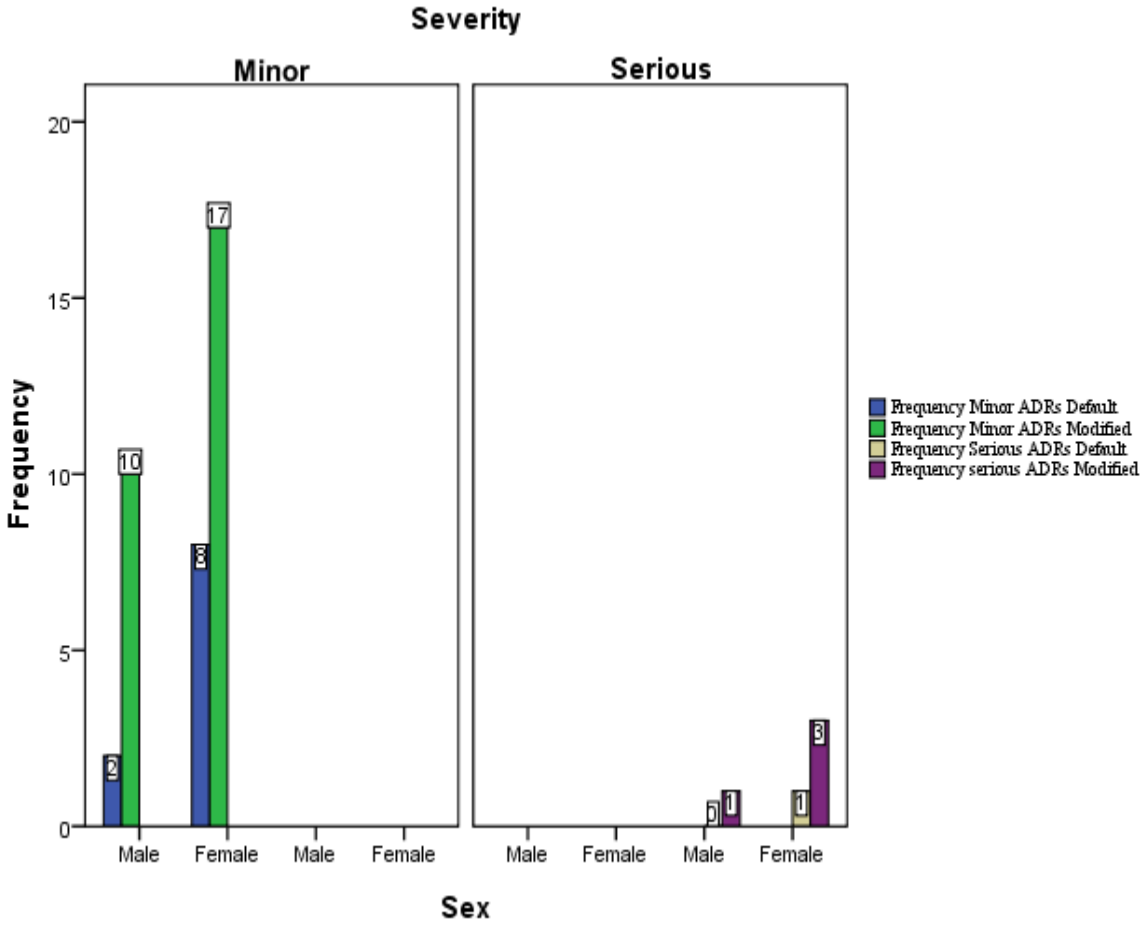


Source: Own data (2012)

Figure 3: ADRs prevalence between male and female patients

4.3.2 Severity of ADRs by sex of patients induced by new default first line and modified first line (i.e. AZT/3TC/NVP).

The new default first line in both cases (i.e. minor and serious) appeared to be safer than modified new default first line by inducing less ADRs in both male and female figure 4. It is also noted that ADR occurrence in (for both minor and serious) females is more than in males. Conceivably, as suggested by the analysis, male and female induced ADRs statistically significant ($p<0.05$) negating the null hypothesis which says male and female patients induced ADRs equally. This finding is in line with the study reported; that ADRs had statistically significant positive correlation with sex[94]. The same line of reasoning which was presented in section 4.3 above as to why women are more prone to ADRs still holds water in this case.



Source: Own data (2012)

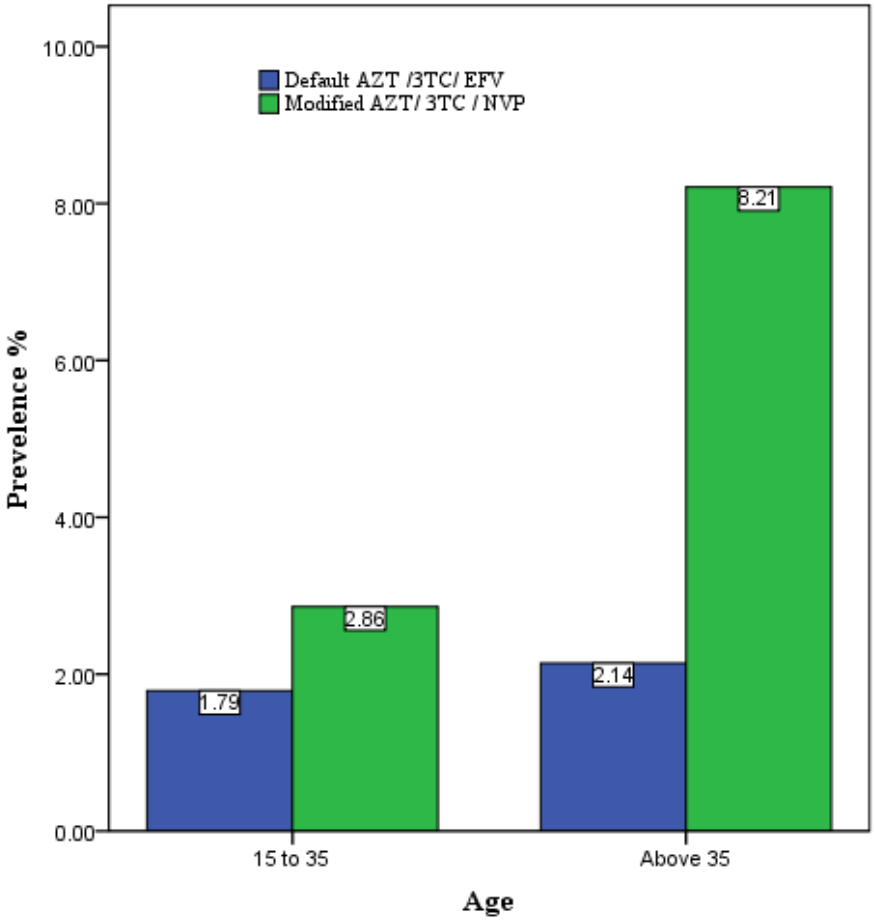
Figure 4: Frequencies of ADRs in male and female patients

4.3.3 Prevalence of ADRs as a function of age of patients under AZT/3TC/EFV (default) and AZT/3TC/NVP (modified) in a period of 2010 to 2011

From figure 5, it is observed that AZT/3TC/EFV induces ADRs differently to different age groups but insignificantly ($p>0.322$). This finding supports the null hypothesis which says young patients are as prone to ADRs as the old patients. Also these findings are being supported by other reported studies. [85, 94]

On the other hand, the effect of age on ADR's prevalence for patients under AZT/3TC/NVP combination was also found to be insignificant ($p>0.1$). However, the prevalence of 2.86% in young for AZT/3TC/NVP looks mathematically different from 8.21% of old patients found in the combination. The latter case suggests that, though

insignificant, further monitoring/research on the effect of age particularly on this regimen is required.

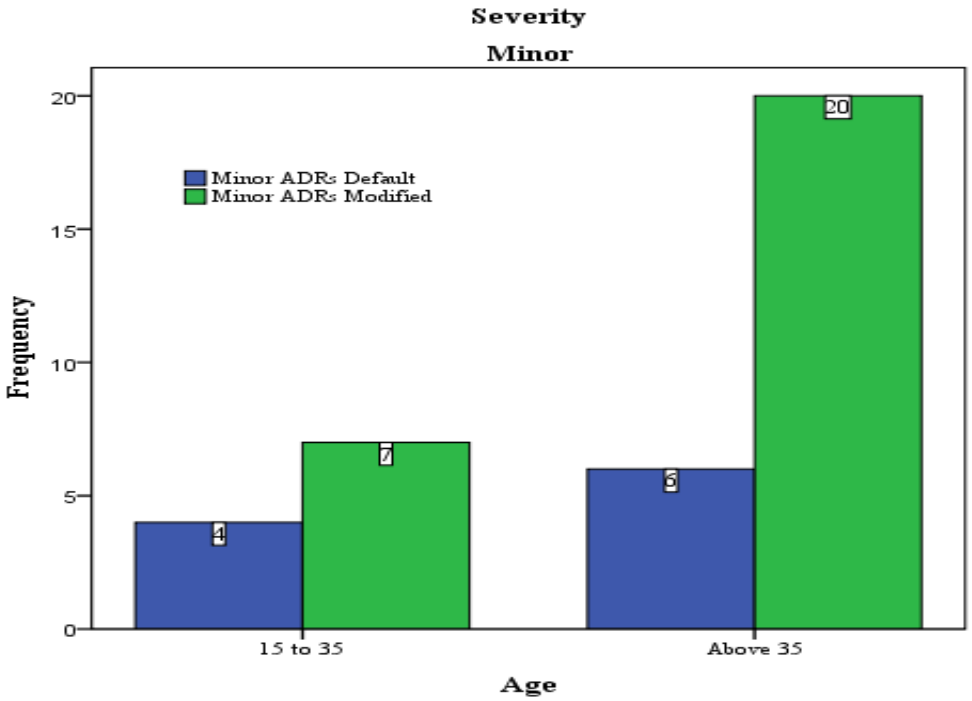


Source: Own data (2012)

Figure 5: Prevalence of ADRs in male and female patients

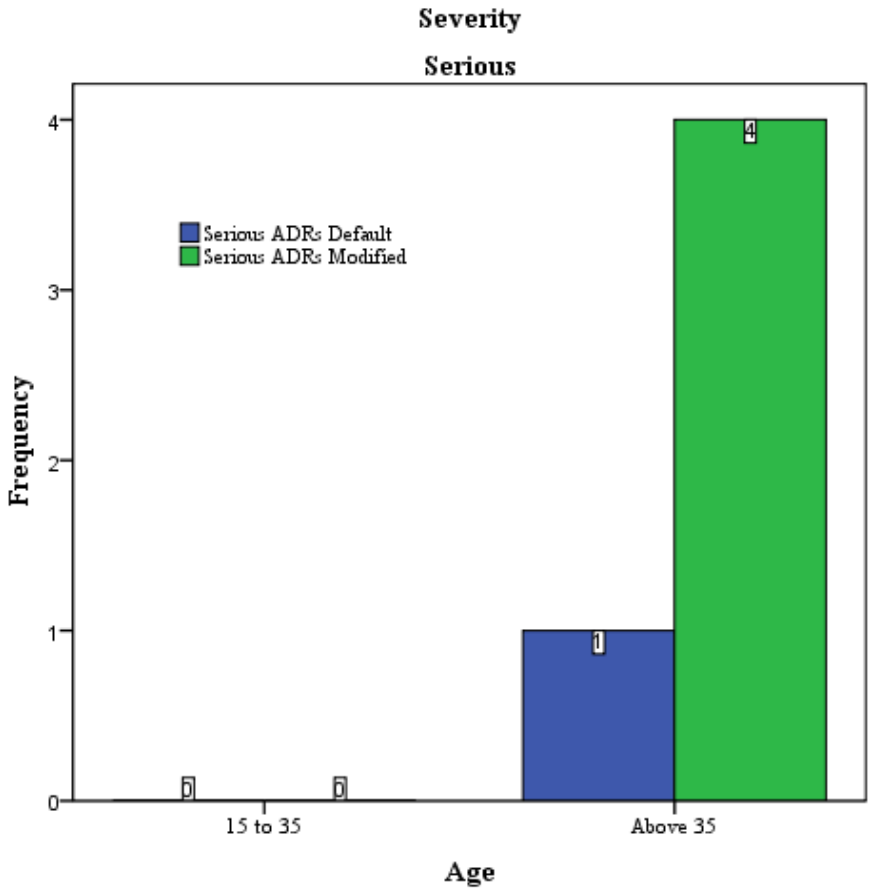
4.3.4 Severity of ADRs as a function of age of patients under AZT/3TC/EFV and AZT/3TC/NVP in a period of 2010 to 2011

Figure 6 and 7 below present frequencies of ADRs in patients between 15 and 35 years and those above 35 years old. As was observed above in section 4.4.3, mathematically, both regimens (i.e. new default first line and its modified combination) induce ADRs in patients by different severity. When the ADRs were segregated into serious and minor cases, old people seem to be more prone to both minor and serious ADRs than young patients but the statistical analysis indicated that ages in ADRs induced is insignificant.



Source: Own data (2012)

Figure 6: Frequency of minor ADRs, age of patients as a factor



Source: Own data (2012)

Figure 7: Frequency of serious ADRs, age of patients as a factor

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATION

5.1 CONCLUSION

- The ADRS that were found to have been induced in patients who are under the use of new default first line combination included anaemia, skin rashes, liver toxicity and peripheral neuropathy. The prevalence of these ADRs was 0.36%, 1.07%, 0.36 % and 2.14% for anaemia, skin rashes, liver toxicity and peripheral neuropathy, respectively. Also it was found that the use of new default first line combination showed significant reduction in ADRs prevalence compared to old regimen as reported in previous raw data. This suggests that the new default first line combination is safer to old default first line

  → On severity, only one case of serious liver toxicity was observed while the rest were minor cases. Amongst the minor cases observed; 6 cases of peripheral neuropathy, 3 cases of dry skin rash and 1 case of mild anaemia
- Of the five modified combinations that were proposed to be investigated in this study, only AZT/3TC/NVP was found to be in broad use. The ADRs that were found to be associated with the use of AZT/3TC/NVP regimen included anaemia, skin rashes and peripheral neuropathy. Prevalence of these ADRs was 0.71%, 3.93% and 6.43%, for anaemia, skin rashes and peripheral neuropathy, respectively. When these ADRs were compared to the prevalence induced by new default first line, the new default first line appeared to be significantly safer ($P<0.001$) to its modified combination.

  → On the continuum of severity of ADRs, both for minor and serious cases, the new default first line had a safer profile as compared to AZT/3TC/NVP. The exception was a single occurrence of liver toxicity which was observed in one out of 280 patients to have experienced it. To be conclusive, further monitoring of regimen regarding this ADR is required

- Of 280 patients who were receiving new default first line, two males and nine females were found with ADRs. On the other hand, of 280 patients who were

receiving modified first line, 7 males and 24 females were found with ADRs. The ADRs prevalence in males and females under new default first line were 0.71% and 3.21% respectively. Whereas the ADRs prevalence in males and females under modified combination was 2.5% and 8.57%, respectively. In both cases, statistical analysis indicated that males and females induced antiretroviral ADRs differently. Females were found to be more prone to ADRs than males.On the scale of ADRs severity, the new default first line appeared safer to modified combination by inducing less ADRs (both minor and serious) in both males and females.

- It was found that the age of patients was not a risk factor in inducing ADRs since the statistical analyses for data from both new default first line and modified combination indicated that difference in prevalence of ADRs among age groups were insignificant,

STUDY LIMITATIONS

- The absent of TDF/3TC/NVP in use and unpopular use of TDF/FTC/EFV, TDF/FTC/NVP and TDF/3TC/EFV limited their study of ADRs prevalence and severity in the study area.

- Concurrent use of opportunistic infection medicines could have affected the accuracy of the results.

5.2 RECOMMENDATIONS

- Following plausible results, new default first line combination is safer and it is recommended for use to reduce ARVs induced ADRs..
- The National AIDS Control Programme in Tanzania should set a mechanism that ensures information of the availability of other ARVs combinations are well disseminated, timely so that the target groups could benefit from their potentials
- A study of TDF/FTC/EFV regimen adverse reactions to be continually monitored
- A further study is required to ascertain whether or not age of patient is a risk factor when receiving ARVs

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ANNEXES

Annex 1: Distribution of HIV/AIDS patients receiving new default and modified first line in the study settings.

No.	Regimens	Mby. ref.	Mby. reg	Mbozi District hospt.	Mbalali District hospt	Rungwe District hospt	Sub Total
1	AZT/3TC/EFV						
2	AZT/3TC/NVP						
3	TDF/FTC/EFV						
4	TDF/FTC/NVP						
5	TDF/3TC/EFV						
6	TDF/3TC/NVP						
	Total						

Annex 2: Adverse drug reactions resulting from new default first line combination

Name of health facility…….. Level of health facility ……

No.	Regimen	Skin rash	Peripheral neuropathy	Anaemia	Liver toxicity	Others
1	AZT/3TC/EFV					

Annex 3: Severity of adverse drug reactions resulting from new default first line combination

Regimen	Minor			Serious				
	Skin rash	Peripheral neuropathy	Anaemia	Neuropathy	Anaemia	skin rashes	Liver toxicity	others
AZT/3TC/EFV								

Key: **Minor** **Serious**

Mild peripheral neuropathy severe peripheral neuropathy, Death,

Dry skin rashes Wet skin rashes, Anaemia below 7 Hb,

Anaemia above 7 hemoglobin (Hb)

Annex 4: ADRs resulting from modified new default first line combinations

Name of health facility ……. Level of health facility…….

S.no	Regimens	Neuropathy	Skin rash	Anaemia	Central nervous system	Liver toxicity	Others
1	AZT/3TC/NVP						
2	TDF/FTC/EFV						
3	TDF/FTC/NVP						
4	TDF/3TC/EFV						
5	TDF/3TC/NVP						

Annex 5: **Severity of adverse drug reactions resulting from modified new default first line combinations**

Regimen	Minor				Serious				
	Dry skin rash	Mild peripheral neuropathy	Anaemia	Others	Peripheral neuropathy	Anaemia	skin rashes	Liver toxicity	Others
AZT/3TC/NVP									
TDF/FTC/EFV									
TDF/FTC/NVP									
TDF/3TC/EFV									
TDF/3TC/NVP									

Annex 6: ADRs resulting from new default first line combination as a function of sex of patients.

Name of health facility …… Level of health facility ……

SEX	ADRs	Non-ADRs	TOTAL
Male			
Female			
TOTAL			

Annex 7: Severity of ADRs resulting from new default first line combination as a function of sex of patients.

Sex	Minor	Serious	TOTAL
Male			
Female			
TOTAL			

Annex 8: ADRs resulting from modified new default first line combinations as a function of sex of patients.

Name of health facility……

SEX	ADRs	Non-ADRs	TOTAL
Male			
Female			
TOTAL			

Annex 9: Severity of ADRs from modified new default first line combinations as a function of sex of patients.

Name of health facility ……

Sex	Minor	Serious	TOTAL
Male			
Female			
TOTAL			

Annex 10: ADRs resulting from new default first line combination as a function of age of patients.

Name of health facility ……

Age in years	ADRs	Non-ADRs	TOTAL
15-35			
>35			
TOTAL			

Annex 11: Severity of ADRs resulting from new default first line combination as a function of age of patients.

Age in years	Minor	Serious	TOTAL
15-35			
>35			
TOTAL			

Annex 12: ADRs resulting from modified new default first line combinations as a function of age of patients

Name of health facility…… Level of health facility……...

Age in years	ADRs	Non-ADRs	TOTAL
15-35			
>35			
TOTAL			

Annex 13: Severity of ADRs from modified new default first line combinations as a function of age of patients.

Name of health facility ……. Level of health facility ……

Age in years	Minor	Serious	TOTAL
15-35			
>35			
TOTAL			

Annex 14: Ethical clearance for the study

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
DIRECTORATE OF POSTGRADUATE STUDIES

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Ref. No. MU/PGS/SAEC/Vol. VI/

18th April, 2012

Mr. William N.M . Reuben,
MSc. Pharmaceutical Management,
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED "SEVERITY AND RPEVALENCE OF ADVERSE DRUG REACTIONS AMONG ADULTS PATIENTS USING FIRST LINE DEFAULT AND MODIFIED ANTIRETROVIRAL COMBINATIONS IN MBEYA REGION, TANZANIA"

Reference is made to the above heading.

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

Thus ethical clearance is granted and you may proceed with the planned study.

Please liaise with bursar's office to get your research fund.

Prof. Z. Premji
DIRECTOR, POSTGRADUATE STUDIES

/emm
c.c. Vice Chancellor, MUHAS
c.c. Deputy Vice Chancellor – ARC, MUHAS
c.c. Dean, School of Pharmacy, MUHAS

Annex 15: Care and Treatment clinic-form 2

THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH AND SOCIAL WELFARE

NATIONAL HIV CARE AND TREATMENT

FACILITY NAME ______________________ FACILITY CODE ______________ DISTRICT __________________
UNIQUE CTC ID NUMBER ___________ HEALTH FACILITY FILE NUMBER ________________________________

NAME ________________________________ (first middle last) **SEX** M ☐ F ☐ **DATE BIRTH** ______________ (dd/mm/yy)
AGE _____________ YRS/MONTHS (circle "months" if age is less than 1 year and fill in age in months) **MARITAL STATUS** _________________ (see codes)

DATE OF FIRST HIV+ TEST _______ (dd/mm/yy)
PATIENT REFERRED FROM (tick appropriate)
- ☐ OPD
- ☐ STI
- ☐ MCH/PMTCT
- ☐ PLHA GROUP
- ☐ SELF REFERRAL (INCLUDES VCT)
- ☐ OTHER (SPECIFY) __________
- ☐ INPATIENT
- ☐ TB / DOTS
- ☐ HBC

PATIENT TELEPHONE NUMBER ______________________________
PATIENT ADDRESS
DISTRICT/DIVISION/WARD ______________________________
STREET/VILLAGE ______________________________
STREET/VILLAGE/HAMLET CHAIRMAN ______________________________
TEN CELL LEADER ______________________________
HEAD OF HOUSEHOLD ______________________________

VISIT DATE *check box for first visit; transfer in, write TI in margin*	WEIGHT (and HEIGHT/ LENGTH if <15 YRS)	WHO CLINICAL STAGE insert number	AIDS DEFINING ILLINESS, NEW SYMPTOMS, SIDE EFFECTS, HOSPITALIZED *see abbreviations or write in*	PREGNANT *Y/N, if Y, write in EDD*	FUNC-TIONAL STATUS *W, A or B*	TB STATUS *see codes*	COTRIM *Y/N*	DIFLUCAN *Y/N*	ARV STATUS *see codes*	ARV REASON *see codes*
__/__/__										
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If meds are picked up by a treatment supporter or other person, write the name of this person in the same row following the encounter date

CTC 2: PATIENT RECORD FORM

DRUG ALLLERGIES

TREATMENT SUPPORTER INFORMATION

NAME TREATMENT SUPPORTER ______________________________

TREATMENT SUPPORTER ADDRESS ______________________________

TREATMENT SUPPORTER TELEPHONE NUMBER ______________________________

COMMUNITY SUPPORT ORGANIZATION/GROUP ______________________________

PRIOR ARV EXPOSURE (tick appropriate)

- ☐ NONE
- ☐ PRIOR THERAPY (transfer in without records)
- ☐ PMTCT MONOTHERAPY
- ☐ PMTCT COMBINATION THERAPY
- ☐ TRANSFER IN (with records)

DATE CONFIRMED HIV+ _______ (dd/mm/yy)

DATE ENROLLED IN CARE _____ (dd/mm/yy)

DATE MED. ELIGIBLE ________ (dd/mm/yy)

DATE ELIGIBLE & READY _____ (dd/mm/yy)

DATE START ART ___________ (dd/mm/yy)

WHY ELIGIBLE (tick appropriate)

- ☐ CLINICAL ONLY
- ☐ CD4 COUNT/% ____(insert)
- ☐ TLC ____________(insert)

STATUS AT START ART: CLINICAL STAGE ____FUNCTION____WEIGHT_____CD4 ____

ARV COMBIN. REGIMEN *see codes/* No. of days dispensed	ARV ADHERE STATUS (if poor, reasons) *see codes*	RELEVANT CO-MEDS	CD4 COUNT/%	HB	ALT	ABNORMAL LAB RESULLTS/ OTHER	NUTRITION SUPPORT NEEDED Y/N	REFERRED TO *see codes, enter all that apply*	NEXT VISIT DATE	FOLLOW UP STATUS *see codes*	SIGNATURE OF CLINICIAN
									__/__/__		
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* for children, <6 CD4 %, otherwise CD4 count

(VERSION 0706)