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Adverse drug reactions among AIDS patients receiving antiretroviral treatment at Kampala International University Teaching Hospital, Uganda

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Abstract
Background: In Uganda, a well-established system for monitoring disease progression and treatment outcomes is in place, especially through the national HIV control program. Despite the presence of a well established monitoring system, monitoring of ADRs remains a significant problem. Available data on adverse drug reactions associated with antiretroviral use in the health care setting is limited, hence indicating the need for ART safety surveillance in healthcare settings.
Method: Data was collected from 250 HIV patients receiving ART at KIU-TH. Occurrences of ADRs, gender, age, ART regimen, response to ADR and treatment duration were obtained from questionnaires given to the patient. Data on how the clinic staff manages ADRs was collected through an interview.
Results: Out of 250 patients, 60.8% experienced at least one ADR, 41.2 % were male. 65.2% were on TDF/3TC/EFZ. 2% reported skipping medication over periods of time due to occurrence of an ADR. 24.8 % of patients experiencing ADR were on treatment for more than two years.
Conclusion: Age, the duration that the patient had been on treatment and the ART regimen used were associated with occurrence of ADRs. ADRs were more likely to occur after two years of treatment, hence long term monitoring of ADRs in patients is recommended. Further research on the occurrence of ADRs in AIDS patients in other facilities in the countries and even in the African region is also recommended in order to come up with solutions that can help address the issue. Such adverse effects of AIDS drugs have in some cases been shown to have negative treatment outcomes in patients.

Keywords: adverse drug reactions, AIDS patients, Uganda, treatment regimens

1. Introduction

Human Immunodeficiency Virus, the virus that causes Acquired Immunodeficient Syndrome (AIDS), has proven to be one of the most challenging health problems (Srikanth *et al*., 2012) [25]. At the end of 2014, approximately 36.9 million people were living with HIV/AIDS; 2.6 million of the infected were children. An estimated 2 million people became newly infected, and about 1.2 million died due to AIDS-related illness in 2014 (UNAIDS Gap Report. 2014). The increased access and availability of antiretroviral therapy has transformed HIV into a manageable chronic disease and prolonged survival (Shet *et al*., 2014) [24]. As seen with any long-term treatment, drug-related toxicities pose a major concern, as they lead to increased morbidity and affect patient adherence (Shet *et al*., 2014) [24]. The occurrence of adverse effects is mainly affected by the combination regimen used to manage HIV (Jha *et al*., 2015) [10].

Despite the gains made in the treatment of HIV using ARV's, adverse reactions to the ARV's remain a significant public health concern (Mehta, 2011) [14]. Adverse drug reactions continue to be a critical limiting factor to the success of treatment of HIV patients using ARV therapy (Domingo and Lozano, 2011) [6]. In Uganda, a well-established system for monitoring disease progression and treatment outcomes are in place, especially through the national HIV control program. Despite this, monitoring of adverse drug reactions among HIV patients remains inadequate (Ndagije *et al*., 2015) [19]. This inadequate monitoring has persisted despite the fact that the prevalence of HIV infection in Sub-Saharan African countries is higher than in developed countries. As seen in most long-term therapies, ARVs have been observed to produce ADRs and toxicities that range from mild to life-threatening with short-term or long-term effects. These multi-drug regimens also have a major problem of drug-drug interactions which can lead to increased toxicities (Shet *et al*., 2014) [24]. Antiretroviral drugs have been reported to cause adverse effects. The occurrence of adverse drug effects is one of the most common reasons among patients to switch or discontinue medication; thus occurrence of ADRs significantly affect medication adherence (Srikanth *et al*., 2012) [25].

Various populations in different geographical locations have shown a wide variability in drug metabolic capacity due to variation in the gene expression of metabolizing isoenzymes. This is an issue of concern because most antiretroviral drugs used in developing countries have been validated in developed countries, whereas the vast majority of HIV-infected people live in developing countries (Subbaraman *et al*., 2007) [26]. There is also variability in the spectrum of adverse effects associated with antiretroviral treatment between developed and developing countries. This is due to several reasons which include the economic constraint in many developing countries limit the accessibility of different options of antiretroviral drugs, thus making very few drugs responsible for very many toxicities and adverse effects. (Kumarasamy, 2004) [11] Secondly, there is a prevalence of comorbid conditions such as malnutrition, anemia; antituberculosis therapy and use of herbal medicine has been

seen to influence the incidence of adverse effects (Mills *et al*., 2005) [15].

Factors like gender and age also predispose individuals to adverse effects of ARV drugs, as seen in women using nevirapine. Women using nevirapine are more likely to develop Stevens-John syndrome, skin rashes, and hepatotoxicity than male patients (Srikanth *et al*., 2012) [25].

Adverse drug effects differ depending on the class of antiretroviral drug used, and these classes include; Nucleoside reverse- transcriptase inhibitors, Non-nucleoside inhibitors, Protease inhibitors, Integrase inhibitors, Nucleotide reverse transcriptase inhibitors and Fusion/entry inhibitors (Montessori *et al*., 2004) [18]. There are frequent but mild adverse effects that occur during the start period of most antiretroviral drug regimen, including fatigue, headache, nightmares associated with efavirenz and more commonly gastrointestinal effects such as nausea, diarrhea and bloating (Montessori *et al*., 2004) [18]. One study has shown that a small proportion of HIV patients using protease inhibitors based regimens develop new onset of diabetes mellitus which is clinically similar to diabetes mellitus type 2. However another study found that insulin resistance may also be associated with HIV infection in patients not taking PI-based therapies, and maybe the direct action of HIV on β cell function and insulin secretion (Montessori *et al*., 2004) [18].

Lipodystrophy was first described in 1998, and the main features were lipoatrophy in the face, limbs, and buttocks, accumulation of fat on in the abdomen and breast, dorsal cervical spine. This is also referred to as the buffalo hump (Montessori *et al*., 2004) [18]. Hyperpigmentation in the skin and nails has been reported in HIV patients on ART and those, not on therapy. So it's hard to distinguish the etiology of hyperpigmentation. However, drug-induced nail hyperpigmentation is usually reversible but may take several years to recover melanin production (Rueben, 2012).

Nucleoside analogs were the first drugs approved for use in the management of HIV/AIDS. The common adverse effects in this class include lactic acidosis, hepatic steatosis. Commonly used NRTIs in Uganda are zidovudine, lamivudine, emtricitabine, abacavir (Ndagije, 2015) [19]. Zidovudine-associated adverse drug reactions include bone marrow suppression which is the most severe ADR. Bone marrow suppression often leads to anemia. It is related to the dose and duration and is more common in patients with advanced disease (Suthar *et al*., 2012; Dietrich *et al*., 2004) [27]. More common adverse effects are a headache, insomnia, fatigue, and nausea. Zidovudine adverse effects are dose related, but patients with adverse effects should not taper down their dose to improve tolerability as this can lead to resistance to zidovudine or sub-therapeutic levels (Minzi, 2009) [16]. Lamivudine has fewer side effects and is relatively well tolerated; most common adverse effects include sleep disturbances, fatigue, headache and diarrhea (Dando and Scott, 2005) [4]. Emtricitabine is structurally similar to lamivudine; they only differ in the addition of fluorine. The most commonly reported adverse effects are; nausea, headaches, skin rashes ranging from pruritic to urticaria. (Pollock *et al*., 2006) [21].

Abacavir is mainly associated with a hypersensitivity reaction, which is a reversible, life-threatening, an immune-mediated systemic reaction that occurs within the first weeks of using the drug. Symptoms that are associated with the reaction involve fever, fatigue, and gastrointestinal effects. Abacavir should not be restarted in patients who had Steven Johnson Syndrome because there is a possibility that the occurrence was a hypersensitivity reaction rather than SJS or Toxic Epidermal Necrosis (Dando and Scott, 2005; Montero *et al*., 2005) [4, 17]. Nucleotide analogs used in the management of HIV/AIDS include tenofovir disoproxil fumarate, adefovir, and cidofovir. The most documented adverse reaction associated with this class are renal toxicities including proximal renal tubule cell dysfunction and acute renal failure (Lockhart *et al*., 2007) [12]. Efavirenz is mainly associated with skin rashes that vary from mild to moderate and are exhibited through skin eruption or pruritic erythema. In some occasions, the rash could develop as mouth ulcerations. Previous studies have reported efavirenz induced photosensitive reactions, whereby the rash appeared only in the sun-exposed areas. Steven Johnson Syndrome and nightmares have also been linked to using efavirenz (Yoshimoto *et al*., 2004; Colebunders *et al*., 2004) [31, 3].

Nevirapine is another NNRTI that is used as a part of a combination therapy. It is associated with severe liver damage; hepatotoxicity and hepatic impairment. There have been reports whereby cases of liver damage have led to liver failure and concurrently death in people using nevirapine. Liver problems do not have a definite onset during the treatment duration as they occur at any time, although the highest risk has been documented to occur within the first 18 weeks of treatment. Patients with abnormal liver function tests or hepatitis B or C before starting to use nevirapine have shown a greater chance of experiencing liver problems. Skin rash is the most common adverse effect of nevirapine, and it can vary from mild to severe to life-threatening reactions. It can happen at any time, but a study in Netherlands reported that risk is highest during the first six weeks of treatment with nevirapine (Baylor & Johann-Liang, 2004; Dietrich *et al*., 2004) [1].

Protease inhibitors include lopinavir, ritonavir, nelfinavir, fosamprenavir, tipranavir and amprenavir. The most common adverse effects include lipodystrophy syndrome, insulin resistance, hyperlipidemia, hyperglycemia and abnormal distribution of fat (Wehmeyer *et al*., 2014) [30]. Lopinavir and ritonavir are commonly used as a combination because they exhibit excellent efficacy. The common undesired effects associated with the combination are gastrointestinal disturbances and elevation of serum lipids (Minzi, 2009; Wehmeyer *et al*., 2014) [16, 30].

2. Material and Methods

The study was carried out at the HIV clinic in Kampala International University-Teaching Hospital. The study population was the HIV patients receiving treatment at the above hospital. A total of two hundred and fifty patients participated in the study. Demographic information such as gender, age at clinic visit, age at diagnosis, was obtained from the patients using a questionnaire.

Information on the regimen the patient was receiving was documented from patient's records and the regimens sub-grouped accordingly. Data on the types and severity of ADRs was obtained from the patient through face to face interviews with the patients and the HIV clinic staff.

Information on the other drugs that the patients may have been using was documented in a questionnaire. Data on how the patients respond to the ADRs was also collected from the patients during the interview. Information on how the HIV clinic staff manages the reported ADRs was also collected during interviews with the staff.

The data collected was entered into MS Excel package 2013 version.
The most commonly occurring ADRs were determined from the data collected and classified in relation to the regimen.

Ethical considerations
Ethical approval to conduct the study was obtained from the Institutional Ethics and Review Board of Kampala International University-Western Campus. Permission to conduct the research at the ART clinic was obtained from the superintendent of the ART clinic. Consent was obtained from each patient both verbally and in writing before any data was collected from them. Confidentiality was maintained on all the data that was collected.

3. Results

Gender
The total number of patients experiencing ADRs was 152/250 (60.8%) More female patients (87) experienced ADRs as compared their male counter parts (65) representing 34.8% and 26% respectively. Figure 1 illustrates these findings.

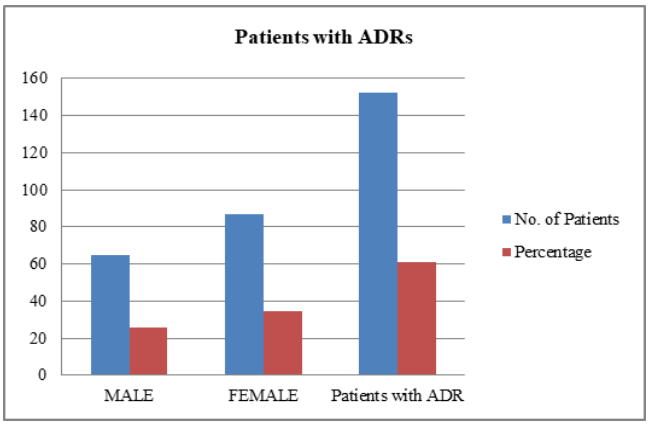

Fig 1: Distribution of ADRs among male and female patients

Duration of treatment
Among the patients experiencing ADRs, 62 were on ART for more than two years, 42 were on ART for a period of between one and two years, 10 were on ART for a period of between six and twelve months, 38 were on ART for a period of less than six months. Figure 2 illustrates these findings.

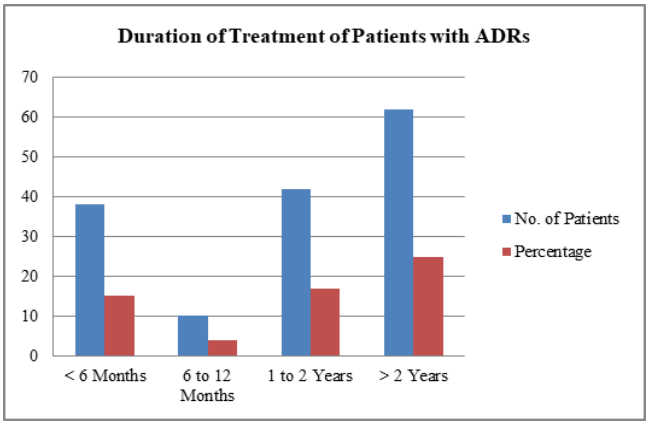

Fig 2: Treatment period and its association with ADRs

Age
Among the patients experiencing ADRs, the ones in the age group of 19 to 35 years had the highest number of ADR incidence with 69 patients (27.6%).

Prevalence of all ADRs
The most common ADR was nausea (26.4%) followed by fatigue (14.4%), diarrhea (13.2%) and skin rash (12.8%). The less commonly occurring, but significant ADRs were TEN (1.2%), peripheral neuropathy (4.4%), vomiting (4.0%) and loss of appetite (2.0%) and others. Figure 3 illustrates these findings.

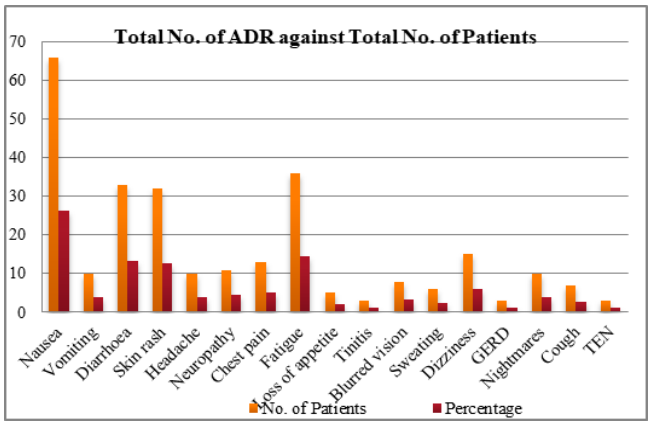

Fig 3: Commonly occurring ADRs among the patients

ADRs reported in tenofovir disoproxil fumarate. Lamivudine and efavirenz based regimen
65.2% of the respondents were using TDF+3TC+EFV regimen. The most common ADR was nausea with 29.4% of the patients experiencing it, followed by fatigue (16.0%), diarrhea (12.9%) and skin rash (11.7%). TEN and peripheral neuropathy were also reported with 1.2% and 3.2% incidence respectively other ADRs included cough, headache, vomiting, chest pain, loss of appetite, sweating, tinnitus, blurred vision, dizziness, GERD, and nightmares. Figure 4 illustrates these findings and other reported ADRs from TDF based regimen.

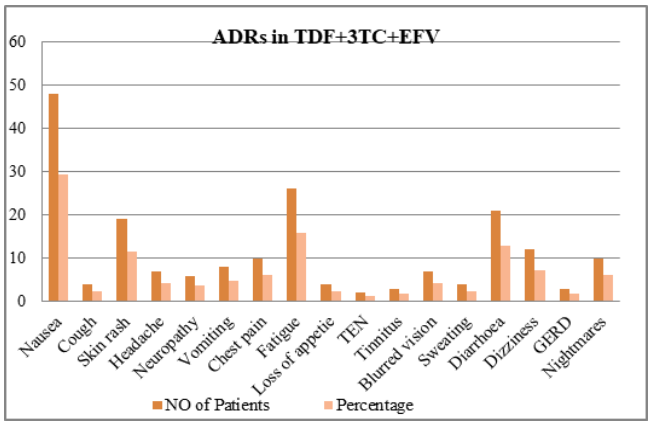

Fig 4: Commonly occurring ADRs in TDF+3TC+EFV

ADRs reported in lamivudine, zidovudine and efavirenz regimen
Thirty one patients were on 3TC+AZT+EFV regimen, the most common ADR was diarrhea and nausea contributing to 16.1% each. Other ADRs included; peripheral neuropathy, skin rash, vomiting, lack of appetite and dizziness. Figure 5 illustrates these findings.

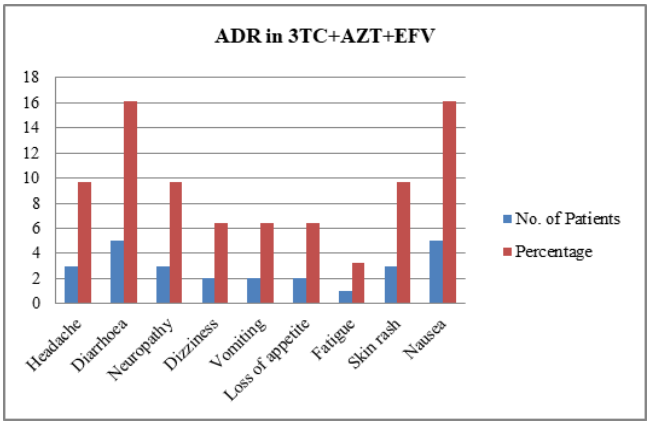

Fig 5: Commonly occurring ADRs in 3TC+AZT+EFV

ADRs reported in lopinavir/ritonavir and efavirenz regimen

Twelve patients were on LPV+RTV+EFV. The most common ADR was diarrhea with 50% prevalence. Skin rash and nausea followed with 33.3% prevalence each. Other ADRs were; fatigue, sweating and blurred vision. Figure 6 illustrates these findings.

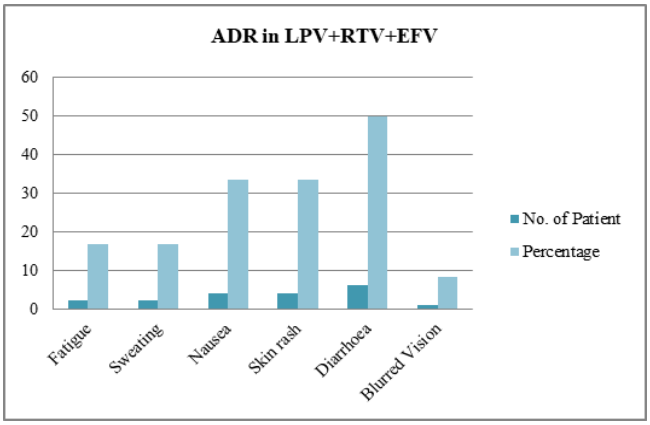

Fig 6: Commonly occurring ADRs in LPV+RTV+EFV

ADRs reported in lamivudine, zidovudine and nevirapine regimen

Thirty four patients were on 3TC+AZT+NVP. The most common ADR was Nausea with 23.5% prevalence followed by fatigue and skin rash with 17.6% prevalence each. Other ADRs reported included; itching, peripheral neuropathy, chest pain, dizziness. It is important to note that TEN was reported in this regimen with 2.9% prevalence (one patient). Figure 7 illustrates these findings.

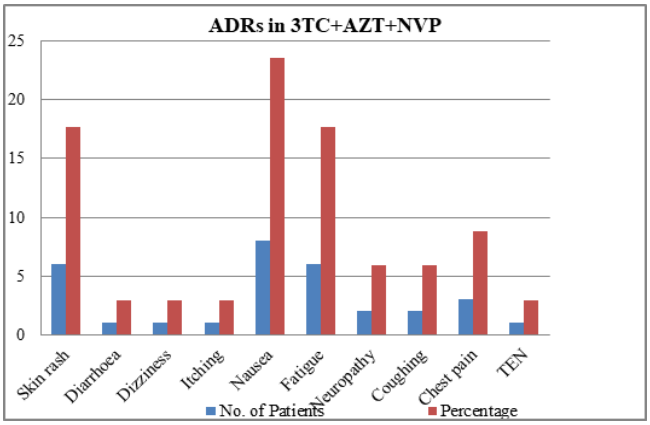

Fig 7: Commonly occurring ADRs in 3TC+AZT+NVP

ADRs reported in abacavir, lamivudine and efavirenz regimen

The abacavir based regimen (ABC+3TC+EFV) had the least number of patients (10) using it. There was no apparent common ADR since the ADRs were reported by 40% of the patients using this regimen and all had the same prevalence. These ADRs included; cough, fatigue, loss of appetite.

Patients' response to ADRs

Response to ADRs differed among the respondents. 20% of patients on ADRs resulted to self-medication, 8.6% sought medical attention, 13.2% responded by resting and sleeping. Patients who experienced excessive sweating resulted to taking hot showers, there were about 3.2% of patients with ADRs. Some patients who experienced skin rash, used creams and jellies to manage the ADR, 5.2%. 9.9% of the patients experiencing ADRs admitted to not doing anything. It is important to note that 3.2% of the patients on ADRs skipped medication due to severity of ADRs. 14.5% of the patients on ADRs did not have conclusive information on this subject. Figure 8 illustrates these findings.

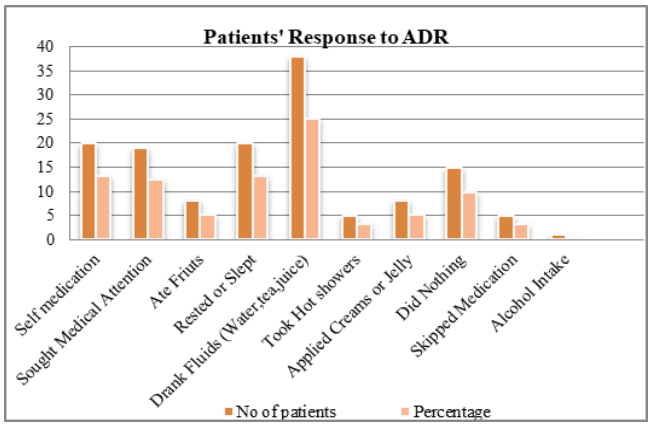

Fig 8: Patients' response to ADRs

Management of ADRs by the Clinical team

The HIV clinic staff manage severe ADRs by changing the regimen the patient is on. In a case where a patient presented with TEN, the patient was given a herbal supplement that helped improve the condition of the skin. Some ADRs were managed by counseling the patient on what to do. For *example, Patients who experienced diarrhea were told to* ensure they have a regular fluid intake, patients who experienced vomiting as an effect were told to seek medical attention.

4. Discussion

The most common ADR was nausea, followed by diarrhea, skin rash and fatigue this findings are contrary to findings from other studies carried out by Eluwa *et al* (2012) [8] and Masenyetse *et al* (2015) [13]. It is however important to note that nausea reported in this study was more associated with the drug in the regimen rather than as a disadvantage of the regimen formulation. However the occurrence of skin rash was comparable to results from Masenyetse *et al* (2015) [13] on patients on the same regimen (3TC+AZT+NVP). It is important to note that the variability in these two settings can be explained in the different regimen patients used, specifically TDF+3TC+EFV.

Gastrointestinal unwanted effects comprised of nausea, vomiting and diarrhea have been reported to be associated

with most antiretroviral agents. Gastrointestinal unwanted effects are also a cause of short-term discontinuation of treatment. (Montessori, 2004) [18].

Skin rash had an incidence of 12.8 percent. This is comparable to findings from a study by Sadiq *et al.* (2016) [23] Nevirapine has been documented by numerous reports to be associated with skin rash. Drug hypersensitivity in form of rash occurs with ARV therapy and has been closely associated with nevirapine, abacavir and efavirenz. (Patel, 2006) [20]

TDF+3TC+ EFV regimen showed the highest incidence of ADRs in this study whereby 65.2% of the patients were on this regimen. It is important to note that although TDF has been documented to cause kidney associated toxicities, no patient on this study said to have experienced symptoms relating to kidney injury (Forna *et al.,* 2007) [9].

This study found that women experienced a slightly higher number of ADRs compared to men; this is comparable to the findings of Bonfati *et al* (2000). It's been reported that women have a better health seeking behavior than men (Thompson *et al.,* 2016) [28]. Hence ART regimen – drug interaction could play a part in these findings.

Patients whose age was over 36 years had a higher incidence of ADR than those below 35 though it was not statistically significant. This is comparable to finding by Srikanth *et al* (2012) [25].

The likelihood of developing an ADR was highest after two years of ART treatment. Duval *et al*. (2004) [7] explained that early occurrence of ADR is an indication of intrinsic intolerance rather than time dependent toxicity. In relation to this study, the later occurrence of ADRs during treatment could be an indication of time dependent toxicity.

Patients' responses to ADRs had a wide variation. Drinking of fluids including water, tea and juices was the most common response with 25% incidence. Resting and sleeping followed with 13.2%. Some patients reported that they result to self medication 13.2%, this may lead to occurrence of other unwanted effects. Only 12.5% of patients sought medical attention. 3.3% reported that they skip they medication due to occurrence of these ADRs.

The clinical team at the HIV clinic managed presented ADRs by changing regimens if the occurrence was a severe. One occurrence was where a patient suffered from TEN and was using 3TC+AZT+NVP the regimen was changed to LPV+RTV+EFV after the patient recovered from TEN. Riedl *et al* 2003 proposed that the most important therapeutic intervention was to stop the drugs causing the ADR and if possible to replace them with an alternative that has a different chemical structure. The other means involved in managing ADRs are largely supportive and symptomatic (Riedl *et al.,* 2003) [22]. The clinical team managed an occurrence of TEN by using a herbal formulation on the skin, this was supportive by it alleviated the patient's symptoms, hence more research should be done on herbal formulations and their use in TEN management. The team also counseled the patients on what to do when certain ADRs occur. Patients who experienced diarrhea were advised to have regular fluid intake. Those who suffered vomiting were advised to seek medical attention. Vomiting may have an effect on treatment since one may vomit the drug thus leading to missing a dose or sub-therapeutic levels of the drug being utilized.

5. Conclusion

From the results of this study, we conclude that occurrence of ADR events are common in patients on antiretroviral therapy. Gastrointestinal adverse effects were the most common. ADRs were highly prevalent and were more experienced by patients above 36 years of age. The likelihood of developing an ADR was highest in patients who were on treatment for more than two years; this can be due to long-term toxicities or due to the HIV infection.

6. Acknowledgement

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