Prevalence and Severity of Adverse Drug Reactions among Adult Patients Using Antiretroviral New Default and Modified Default First Line Regimens in Mbeya Region, Tanzania

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A comparative study of the prevalence of adverse drug reactions due to zidovudine/lamivudine/efavirenz (new default first line) and zidovudine/lamivudine/nevirapine (modified default first line) regimens was done in Mbeya Region, Tanzania. The new default first line regimen was found to be safer than the modified default first line regimen. This study provides antiretrovirals safety profiles and potential information for patient health management planning and decision making.

Key words: Antiretroviral regimens, adverse drug reactions, prevalence

INTRODUCTION

Sub-Saharan Africa is heavily affected by Acquired Immune Deficiency Syndrome (AIDS) which is caused by Human Immunodeficiency Virus (HIV) [1,2,3,4]. The Government of Tanzania responded against HIV/AIDS infection by provision of free antiretroviral (ARV) medicines to patients in 2004, Mbeya Region being among the beneficiaries of this programme. The ARV medicines used in the programme since then include zidovudine, didanosine, lamivudine, abacavir, nevirapine, efavirenz, lopinavir, ritonavir, saquinavir and stavudine in various regimens. Although adverse drug reactions (ADRs) from these medicines are known worldwide, they vary among various populations and geographical locations [5]. Therefore, data that is derived from one country does not necessarily apply to another. In recognition of this fact, a general study to document the commonly reported ADRs in Tanzania was done in Dar es Salaam and Mbeya Regions [6].

The study by Minzi *et al*. reported ADRs from stavudine-based regimen which was a default first line at that time but due to its serious adverse effects, it is no longer used. A new default regimen of zidovudine, lamivudine and efavirenz is used. Its substitutes include nevirapine, tenofovir and emtricitabine. The last two substitutes were not evaluated in the previous study because they were yet to be introduced into the programme. The change in the first line ARVs regimen and introduction of two substitutes in the regimen necessitates a follow up study to determine their adverse effects.

The purpose of this study was to determine the ARVs regimen safety profile by ADRs prevalence and severity, and also determine which gender and age groups are more affected. In addition, the study compares the ADRs prevalence data between the old default, the new default and the modified ARVs regimens. The results of the study will help clinicians in monitoring ADRs in their patients and provide information to National AIDS Control Programme to assist in the review of treatment guidelines.

MATERIALS AND METHODS

The data reported in this study was collected retrospectively from Care and Treatment Clinic form number two (CTC-2) inserted in patients' files receiving treatment in one referral, one regional and three district hospitals in Mbeya Region.

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Sampling and sample size

The study population involved patients under new default first-line and modified regimens receiving antiretroviral therapy (ART) services from Mbeya Referral Hospital, Mbeya Regional Hospital and Mbarali, Rungwe and Mbozi District Hospitals. The study population for each regimen was obtained by identifying particular patients' files from the above mentioned hospitals. Each patient's file contained a CTC-2 in which clinicians documented the reported ADRs. Therefore, the study sample was the total of sampled patients' files under different regimens.

The sample size of patients' files for each study regimen was calculated using the following expression [7].

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

Where:
n = desired sample size for each regimen.
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 regimen) - It was determined by counting patients under each regimen and then computing its proportion against the population. The value of p for each regimen 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 = 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 in the study period (January 2010 to December 2011). Data of two years were considered enough to give the pattern of ADRs from each treatment option.

A pre-test study was conducted at Ifisi District Hospital within Mbeya Rural Council. During the 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 regimens, respectively, were identified from the hospital. The number of patients on each regimen was used to calculate the sample proportion (Ps). Using the sample size formula $q = 1-p$, z = 1.96, and the acceptable error (e) of 5%, an estimated sample size for each regimen was calculated.

The contribution of each hospital to a particular sample size regimen depended on the weights of the number of patients receiving ART services from respective hospitals. In order to get the weights of each regimen, 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 regimen (x) were determined and used to calculate the proportion. Thirdly, a weight for each regimen (w_i) was determined using the following expression:

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

Eventually, the calculated sample for each regimen and hospital was then attained by random selection of patients' files receiving a particular regimen 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), Mbeya Regional (71), Mbozi (48), Mbarali (34) and Rungwe (23). Similarly for AZT/3TC/NVP ($n_2 = 280$): Mbeya Referral (73), Mbeya Regional (67), Mbozi (20), Mbarali (101) and Rungwe (19).

The study population for TDF/FTC/EFV (79) was distributed as follows: Mbeya Referral (46), Mbeya Regional (10), Mbozi (16), Mbarali (7) and Rungwe (0). The TDF/FTC/NVP and TDF/3TC/EFV regimens had two patients each at Mbeya Referral Hospital only while TDF/3TC/NVP had none. Thus, the last three regimens, namely TDF/FTC/NVP, TDF/3TC/EFV and TDF/3TC/NVP were dropped because of inadequate sample size.

Data collection

The total number of HIV/AIDS patients' files on new default first line regimen in the study period was identified at each hospital. The pre-determined sample size required from an individual hospital was obtained by random selection of files of HIV/AIDS patients under new default first line. ADRs were tallied as they appeared using tally tables. The ADRs prevalence (P, %) was calculated using the expression:

$$P(\%) = \frac{\text{Number of observed ADRs} \times 100}{\text{Total sampled cases under one regimen}}$$

The sampled files selected for prevalence of ADRs induced by new default first-line regimen were also used to study severity of ADRs (minor and serious). Examples of some of the ADRs are given in Table 1. The collected data was coded and entered into SPSS version 16 software to determine descriptive statistics and corresponding graphs. The significance of the difference between results from this study and those from previous studies were determined using Chi-square and Fisher's exact tests where applicable. The same method was applied in the determination of the prevalence and severity of ADRs induced by the modified default regimen.

Table 1: Severity of ADRs associated with use of new default first line regimen

Minor	Serious
Dry skin rash	Wet skin rash
Mild peripheral neuropathy	Severe peripheral neuropathy
Anaemia, HB 7.5 – 13 g/dl	Anaemia, HB <7.5 g/dl
	Liver toxicity

HB = Haemoglobin.

RESULTS AND DISCUSSION

The overall prevalence of ADRs for new default first-line (AZT/3TC/EFV) regimen and modified default first-line (AZT/3TC/NVP) regimen are shown in Table 2 and Table 3 respectively. The observed ADRs in the AZT/3TC/EFV regimen comprised of 1 case of mild anaemia, 3 cases of minor skin rash, 1 case of serious liver toxicity and 6 cases of minor peripheral neuropathy. For the AZT/3TC/NVP regimen, the observed severe ADRs included 2 cases of skin rashes, 1 case of peripheral neuropathy and 1 case of anaemia, while minor ADRs included 17 cases of peripheral neuropathy, 9 cases of skin rashes and 1 case of mild anaemia. Comparative overall prevalence rates of the ADRs in the two ARVs regimens are captured in Figure 1.

Table 2: Overall prevalence of ADRs from AZT/3TC/EFV new default first-line regimen

Adverse drug reaction	n	Overall prevalence (%)
Anaemia (HB ≤ 7)	1	0.36
Skin rashes (wet and dry)	3	1.07
Liver toxicity	1	0.36
Peripheral neuropathy (minor)	6	2.14

HB = Haemoglobin.

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

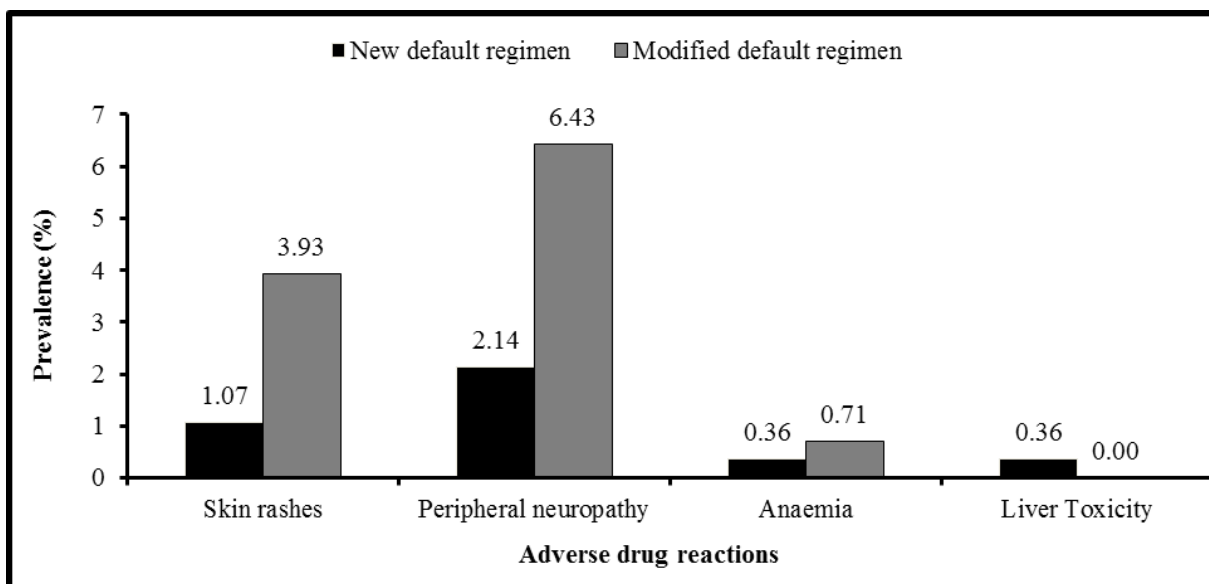| Adverse drug reaction	Frequency (%)	Overall prevalence (%)
Skin rashes	11 (35%)	3.93
Peripheral neuropathy	18 (58%)	6.43
Anaemia (HB ≤ 7)	2 (6%)	0.71

HB = Haemoglobin.

Figure 1. Comparison of prevalence of adverse drug reactions from new default regimen and modified default first line regimen.

The observed ADRs in this study were expected since they have been reported to be associated with the use of the new default first-line or its components [6,8,9]. For example, skin rash was reported to have occurred in patients receiving nevirapine-based regimen [8]. Zidovudine, which is a component in both regimens, has previously been shown to induce anaemia in patients [10]. Previous studies had shown that old default first line which contained stavudine is also associated with development of peripheral neuropathy [6].

However, the rates or extent of prevalence are different. Present results indicate that use of new default first line has significant reduction in the prevalence of ADRs ($P<0.001$) compared to old default first line [6]. For example, there is a notable reduction in the prevalence of 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%) in changing from old default regimen to the new default regimen. The difference in prevalence of ADRs in the two regimens could be attributed to substitution of stavudine and nevirapine in the old default regimen with zidovudine and efavirenz respectively in the new default regimen.

In the current study and as illustrated in Figure 2, peripheral neuropathy appeared to be the most common ADR followed by skin rash in both the new default and modified default regimens. The results from this study are in agreement with the findings reported in Nigeria that showed peripheral neuropathy followed by skin rash were the commonest ADRs in patients under AZT/3TC/NVP regimen [11]. However, comparison of the prevalence of ADRs induced by AZT/3TC/NVP and AZT/3TC/EFV regimens showed that the new default first line (AZT/3TC/EFV) regimen is significantly safer ($P<0.001$) than the modified regimen. Correspondingly, there is strong evidence that in clinical practice, general cutaneous reactions appear to be less common with the use of efavirenz-based regimens than nevirapine-based regimens and therefore efavirenz-based regimens are safer as in the new default first line [12].

The study also reviewed distribution of ADRs based on the gender of the patients as shown in Figure 3. Out of 280 patients on AZT/3TC/NVP regimen, serious ADRs were noted in 1 male and 3 females while 10 males and 17 females had minor ADRs. This translates to prevalence of 2.5% in males and 8.57% in females. On the other hand, of the

280 patients on AZT/3TC/EFV regimen only 2 males and 9 females experienced ADRs, translating to prevalence of 0.71% and 3.21%, respectively.
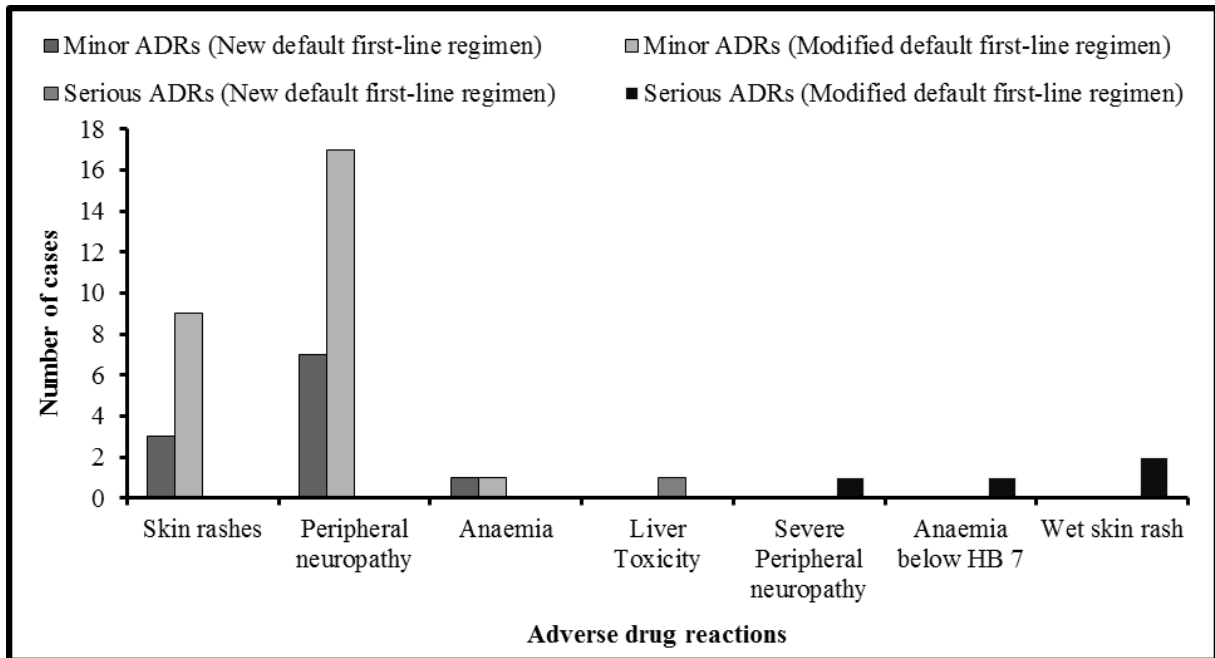

Figure 2: Frequencies of minor and serious adverse drug reactions in the study area.

Statistical analysis indicated that the two ARVs regimens induced ADRs in males and females differently ($p<0.05$), a finding that negates the null hypothesis. Differences in weight and body mass index between men and women might have played an important role to such results [14,15]. 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 [14,15]. In addition, gender 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 drug metabolism [16].

Analysis of the 280 patients' files under AZT/3TC/EFV regimen showed that 91 patients were between 15 to 35 years while 189 were above 35 years. Of these, 5 cases (1.79%) of ADRs were observed in the 15-35 years age bracket and 6 cases (2.14%) of ADRs in the

above 35 years age bracket. On the other hand, of the 280 patients' files under AZT/3TC/NVP regimen, 102 cases were in the 15-35 years age bracket while 178 cases were in the above 35 years age bracket. The distribution of ADRs in the AZT/3TC/NVP regimen was: 8 cases (2.86%) in the 15-35 years age bracket and 23 cases (8.21%) in the above 35 years age bracket. This ADRs distribution as a function of age is graphically represented in Figure 4.
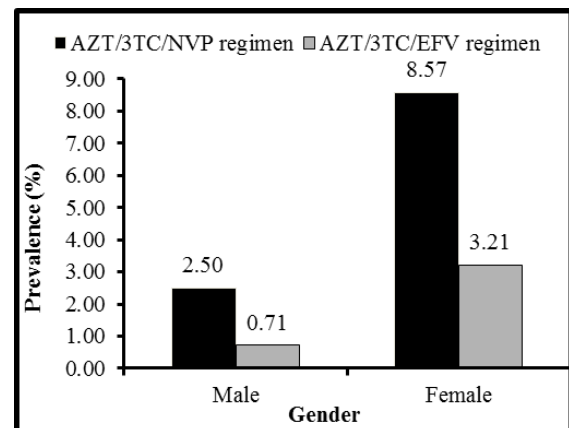

Figure 3. Prevalence of adverse drug reactions in male and female patients.

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 [14,17]. On the other hand, the effect of age on ADRs prevalence for patients under AZT/3TC/NVP regimen was also found to be insignificant (*p>0.1*). However, the prevalence of 2.86% in the younger patients for AZT/3TC/NVP looks mathematically different from 8.21% of old patients found in the regimen. The latter case suggests that, though insignificant, further monitoring/research on the effect of age particularly on this regimen is required.
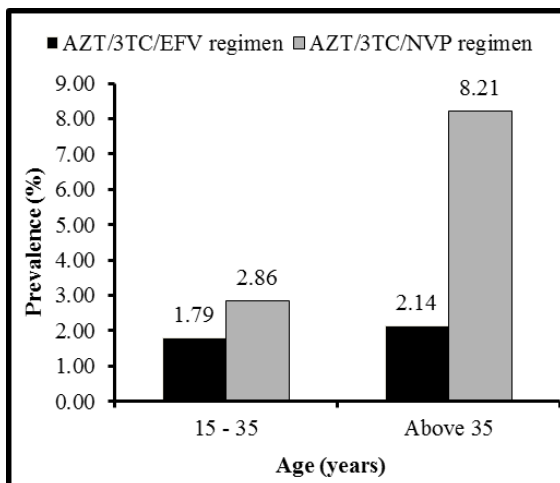

Figure 4. Prevalence of adverse drug reactions as a function of age of patients.

Comparison of the severity of ADRs between AZT/3TC/EFV and AZT/3TC/NVP regimens shows that the AZT/3TC/EFV regimen is safer than the AZT/3TC/NVP regimen with the exception of one case of liver toxicity that was observed in the AZT/3TC/EFV regimen. This is supported by a study that indicated high frequency of increased liver enzyme in patients under efavirenz-based regimen that ranges from 1 to 8% whereas in patients treated with nevirapine-based regimens, it ranges from 4 to 18% [13]. Therefore the observed one case of liver toxicity in this study could be due to efavirenz in the regimen or could be an outlier since it was a single case out of 280 cases.

CONCLUSION

The prevalence of ADRs in the new default first-line (AZT/3TC/EFV) regimen was 0.36%, 1.07%, 0.36% and 2.14% for anaemia, skin rash, liver toxicity and peripheral neuropathy, respectively. The new default first-line regimen showed significant reduction in the prevalence of ADRs as compared to old default first-line regimen. The prevalence of ADRs in the modified default first-line (AZT/3TC/NVP) regimen was 0.71%, 3.93% and 6.43% for anaemia, skin rash and peripheral neuropathy, respectively. Thus, comparatively, the new default first-line regimen appeared significantly safer than the modified first-line regimen (p < 0.001).

The prevalence of ADRs in the AZT/3TC/EFV regimen as a function of gender was 0.71% and 3.21% for males and females, respectively. Similarly, for AZT/3TC/NVP regimen, the prevalence was 2.5% and 8.57% for males and females, respectively. Statistical analysis indicated that the two regimens induced ADRs differently in males and females. Nevertheless, new default first-line regimen induced much less ADRs (minor and serious) than the modified first-line regimen in both males and females. Further, statistical analysis for both new and modified default first line regimens indicated that difference in prevalence among age groups were insignificant. Therefore age is not among the risk factors.

It is noteworthy to mention that the absence of TDF/3TC/NVP from the Tanzanian clinical market and unpopular use of TDF/FTC/EFV, TDF/FTC/NVP and TDF/3TC/EFV limited the study of the prevalence and severity of their ADRs in the study area.

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