Detection and Management of Adverse Drug Reactions Related to Antiretroviral Drugs among HIV/AIDS Patients in Kiambu Sub-County, Kenya

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The objective of this study was to establish the detection, prevalence and management of various adverse drug reactions associated with antiretroviral drugs occurring in patients attending Comprehensive Care Centre (CCC) of Kiambu District Hospital. The study was a cross sectional survey where the patients included were those attending the CCC on a monthly basis. The results revealed that 65.2% of the patients had experienced symptoms suggestive of adverse drug reactions (ADRs). Of these, 67.2% did not associate the symptoms to the medicines they were taking but rather to the AIDS syndrome. The most prominent reaction was peripheral neuropathy at 0.395 (0.344-0.447 at 95% confidence interval) while the least common was hepatotoxicity. Whereas 71.5% could tell the frequency of the daily dosage, 92.1% did not know the names of the medicines they were taking but could describe them by shape and colour. There was a significant association between occurrence and reporting of ADRs and age (P<0.001), weight (P=0.001), marital status (P=0.016), occupation (P<0.001), religious participation (P<0.001) and education level (P<0.001). Although the health care providers displayed adequate knowledge in management of these reactions, they complained of inadequacy of the current reporting tool (MOH 257) in capturing ADRs. The patients were ill equipped in recognising the ADRs.

Key words: Adverse drug reactions, occurrence, detection, management

INTRODUCTION

The prevalence of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) in Kenya currently stands at 7.1% among adults aged 15-64 years [1]. Approximately 1.5 to 1.7 million Kenyans are infected with HIV/AIDS [2]. The introduction and availability of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality [3]. Antiretroviral therapy (ART) is the most effective intervention for prolonging survival of people with the AIDS. When taken regularly, it is associated with 90% reduction in deaths caused by AIDS. As at the end of May 2011, there were 482,572 patients on ART, comprising 441,116 adults and 41,456 children [4].

Many factors interfere with adherence to antiretrovirals (ARVs), the most important being adverse drug reactions (ADRs). It is difficult to estimate their extent because most ADRs go unreported. In a study conducted in France, 2067 adults aged 26-67 years attending outpatient health centre for check-ups, 14.7% gave reliable histories of ADRs [5]. Studies done in Uganda by Forna [6] have shown that 40% of patients, out of a study population of 1037, developed clinical toxicities while a similar one done in Kenya reported even higher incidence ranging from 48% to 65% of ADRs [7].

Although ARVs are freely available in most government and mission hospitals, up to 25% of patients discontinue therapy within the first 8 months due to treatment failure, toxic effects or lack of adherence [8]. While the development of new antiretroviral drugs still continues, efforts have been made to maximize the effectiveness of currently available treatments including attempts to better understand and manage the ADRs [3]. Adverse drug reactions of ARVs and other drugs have been shown to be among the top ten leading causes of mortality among people

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living with HIV/AIDS (PLWHA) despite the fact that most ADRs are preventable [9].

As of December 2008, there were 3721 patients both adults and children reporting to the Comprehensive Care Centre (CCC) of Kiambu District Hospital. Only 917 of these patients were on ARVs even though the statistics indicated that adult population that required ARVs in the district was 981 [10]. Although HIV/AIDS care and treatment is now being offered in most health facilities in the Kiambu Sub-County, no study about detection, prevalence and management of ADRs had been carried out hence there was a need to undertake such a study.

AIDS is incurable, and to control the viral load to a degree where occurrences of opportunistic infections are minimized so that the patient leads a comfortable life, the ARVs have to be taken for a lifetime. Many patients on ARVs experience psychological torture because instead of feeling better, the drugs make them feel worse or get into irreversible disabling conditions due to occurrence of ADRs. The detection and management of any ADRs is therefore vital.

The ADRs appear in everyday outpatient practice but estimates of the true incidence are difficult since many of these reactions go unreported. There are many gaps in HIV management, not only because the treatment is relatively new but also because of poor documentation and untimely reporting of ADRs [11]. The use of ART is relatively new and tests carried out in animals are often insufficient to predict human safety. Therefore information about rare but serious adverse drug reactions, chronic toxicity and use in special groups (children, the elderly, pregnant women and lactating mothers) is often incomplete or unavailable.

The present study was therefore aimed at finding the prevalence of ADRs in patients attending the CCC, how knowledgeable the patients and the health care providers were about ADRs, the factors affecting the detection and management of ADRs and the management strategies undertaken to control these reactions.

METHODS

Research design

A cross sectional survey was conducted in which 354 patients on ARVs attending Kiambu District Hospital's CCC were interviewed over a period of 8 weeks between September and November 2008. Primary data was collected by interviewing patients and health care providers at the CCC.

Variables

Dependent variable – adverse drug reactions.
Independent variables – sex, age, weight, marital status, occupation, religion, educational level, perception of ADRs, knowledge of ADRs, detection and management of ADRs.

Sampling technique and sample size determination

The Kiambu Sub-County had a population of 1,623,282 persons according to the August 2009 census results with a population growth rate of 2.56% per annum [12]. The HIV/AIDS pandemic is a major health problem with a prevalence of 34% which is the highest in the Kiambu County. The most affected age group was 25-34 years with the females being the greatest hit. Up to 60% of bed occupancy in the hospitals was due to AIDS or related cases [13].

The sample size was calculated using a sample size determination formula [14] as follows:

$$n = \frac{z^2 pqD}{d^2}$$

Where: n=the desired sample size when population is more than 10 000; Z=standard normal deviation (1.96) at 95% CI; p=the proportion of the target population estimated to have ADRs=0.3 [15]; q=1-p=0.7; d=error margin (taken to be 5% for this study); and D=the design effect=1.

Hence a minimum of 323 patients were selected to be included in the study. During the actual data collection 354 respondents were

willing to participate. Patients on ARVs to be interviewed were selected by convenient sampling. Informed consent was obtained from the patient or the care giver before the interview could be conducted. Information regarding the social demographic characteristics, ADRs symptoms and diet recall was collected using a structured questionnaire. Data was analysed using Statistical Package for Social Sciences (SPSS) software version 11.50. Chi square test for independence of association between independent variables and occurrence of ADRs was performed. For statistical tests, a P value of less than 0.05 was considered to be significant.

RESULTS AND DISCUSSION

Prevalence of ADRs symptoms

The AIDS syndrome is associated with many complications including occurrence of opportunistic infections. Each antiretroviral medication is associated with specific adverse effects although some effects occur only in special circumstances e.g., co-morbid infections or other medications the patient may be taking. Table 1 shows the common ARVs and their adverse drug reactions. This was extracted from Kenya Clinical Manual for ART providers (2004) [16].

Table 1: Adverse drug reactions of antiretrovirals

Drug	Adverse effects
Nucleoside reverse transcriptase inhibitors	
Zidovudine	Bone marrow suppression (anaemia and/or neutropenia), nail hyperpigmentation, myopathy, hepatic toxicity, lactic acidosis, nausea, headache
Stavudine	Peripheral neuropathy, lipodystrophy
Lamivudine	Well tolerated. Occasional nausea, headache. May be associated with hepatitis
Abacavir	Hypersensitivity reactions (rash, fever, GIT symptoms), nausea, headache, rash
Tenofovir	Lactic acidosis, hepatotoxicity, nausea, vomiting, diarrhoea, flatulence
Didanosine	Pancreatitis, peripheral neuropathy, GIT intolerance
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine	Rash, hepatotoxicity
Efavirenz	CNS disturbances, dizziness, somnolence, insomnia, confusion, teratogenic, hepatitis, rash
Protease inhibitors	
Ritonavir	GIT intolerance, taste perversion
Lopinavir/ritonavir	GIT symptoms, taste perversion, hepatitis
Nelfinavir	Diarrhoea, nausea, vomiting

At the time of study, the following agents were recommended for use in the public health facilities: abacavir (ABC), didanosine (ddI), efavirenz (EFV), lamivudine (3TC), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), nevirapine (NVP), stavudine (D4T), tenofovir (TDF) and zidovudine (AZT). The recommended first and second line regimens for adults and adolescents were as follows: First line regimen: D4T (or AZT) + 3TC + NVP (or EFV). The second line regimen: TDF (or ddI) + ABC + LPV/r (or NFV) [16]. Table 2 summarizes the symptoms suggestive of ADRs [15] and Table 3 the prevalence of the ADRs suggested from the reported symptoms.

Table 2: **Symptoms of adverse drug reactions to antiretrovirals**

Adverse drug reaction	Symptoms reported
Pancreatitis	Abdominal cramps, nausea, vomiting
Lactic acidosis	Generalized weakness, abdominal cramps, nausea, vomiting, diarrhea, shedding of mucus membranes, rapid breathing
Hepatotoxicity	Yellow skin, pain in groin
Gastrointestinal effects	Abdominal cramps, nausea, vomiting, flatulence, heartburn, constipation
Central nervous system effects	Anxiety, depression, blurred vision, drowsiness, hallucinations, nightmares, insomnia
Hypersensitivity	Mild rash, severe rash, itchy rash, rash with blisters, shedding of skin, shedding of mucus membranes
Hyperglycemia	Increased thirst, increased hunger, frequent urination, diarrhoea at night
Anaemia	Generalized weakness, tiredness
Lipodystrophy	Loss of fat from face, buttocks, limbs
Peripheral neuropathy	Burning sensation, numbness, tingling

Table 3: Prevalence of adverse drug reactions

Adverse drug reaction	Number of respondents with the ADR	Prevalence (95% CI)
Peripheral neuropathy	140	39.5% (34.4 - 44.7%)
Hypersensitivity	89	25.1% (20.6 - 29.7%)
Pancreatitis	62	17.5% (13.5 - 21.5%)
Hyperglycaemia	51	14.4% (10.7 - 18.1%)
Lipodystrophy	26	7.3% (4.6 - 10.1%)
Anaemia	18	5.1% (2.8 - 7.4%)
GIT	3	0.8% (-)
Lactic acidosis	1	0.3% (-)
Hepatotoxicity	1	0.3% (-)

ADR = Adverse drug reaction; CI = Confidence interval.

Peripheral neuropathy occurred in 39.5% of the respondents in this study. A related study done in Nyeri, Kenya [3] had shown that 2.7% of females and 5% of males on stavudine developed peripheral neuropathy. The difference could be due to the fact that the study done in Nyeri considered only the drug stavudine, while this study considered the NRTI in general suggesting that there could be more than one drug responsible for development of peripheral neuropathy. HIV as a disease contributes to the pathogenesis of neuropathy symptoms which are clinically indistinguishable from toxic neuropathies caused by ARVs. It is therefore difficult to dissect out relative contribution of disease-associated and drug associated neuropathies [17].

Hypersensitivity reactions were reported by 25.1% of the respondents. Hypersensitivity reactions are 100 times more common in HIV-

1 infected patients than in general population [16]. With use of nevirapine, 13% of patients will present with mild to moderate rash [18]. A study done in Nyeri, Kenya revealed that 4% of patients on nevirapine developed skin rash and this reaction was more common in the females than in the males [3]. On the other hand, pancreatitis symptoms occurred in 17.5% of the respondents. Previous studies have shown that up to 7% of patients develop pancreatitis with the use of these drugs [19]. However, it has also been shown that patients in advanced stages of the syndrome or those with a history of alcohol consumption are at a higher risk of developing pancreatitis [19].

Hyperglycaemic symptoms were reported in 14.4% of the cases. Protease inhibitors which could predispose a patient to hyperglycaemia [20] were not available at the CCC pharmacy at the time of this study. The result of the hyperglycemic symptoms observed in this study could be due to a problem of nutrition or altered glucose metabolism. Lipodystrophy symptoms appeared in 7.3% of the respondents of this study. These results differ with a study done in Rwanda which revealed a prevalence of 34% of lipodystrophy in patients receiving ARVs for more than 72 weeks [21]. Anaemia was reported in 5.1% of the cases. The findings of this study agree with those of Carr [21] who reported that 5 to 10% of patients taking zidovudine developed anaemia during the first three months of therapy.

Gastrointestinal symptoms were reported in only 0.8% of the respondents in this study. These symptoms were mild and transient and disappeared with continued use of the drugs [22]. Hepatotoxicity adverse effects symptoms only appeared in 0.3% of the respondents. These results differ from those of Becker [23] who reported that 6% of patients on long term HAART therapy developed hepatotoxicity. The discrepancy could be due to the fact that the CCC of Kiambu District Hospital has been in existence for a relatively short period of time with only 17.8% of the respondents having been on treatment for more than 36 months (Table 5). Nevirapine has been associated with severe hepatotoxicity but liver damage can occur with all the three classes of approved ARVs [19]. Consistent with its rarity, lactic acidosis symptoms occurred in only one patient (0.3%) in this study. Though rare, the condition is life threatening [24].

This study also sought to know whether the patient had experienced other (emerging) side effects not specifically mentioned in the research tool. The respondents reported: abdominal distension, cough, general wasting, increased blood pressure, joint pains, missed monthly periods, otitis media, sneezing and itching of the throat. The distribution is as shown in Table 4. Some of these side effects had been noted by Highleyman as newer adverse effects which are coming into fore as HAART combination therapy continued to be used for longer periods of time [22]. We suggest that these effects be grouped with the other side effects of ARVs but further studies be conducted so as to associate these effects with a particular drug.

Table 4: Emerging side effects

Adverse drug reaction symptoms	Number of respondents	Percentage
Abdominal distension	2	0.6
Cough	1	0.3
General wasting	1	0.3
Increased blood pressure	1	0.3
Joint pain	1	0.3
Missed monthly periods	1	0.3
Otitis media	1	0.3
Sneezing/itching of throat	1	0.3
Total	9	2.7

Frequency of ADRs

Out of 354 respondents, 231 (65.2%) were found to be experiencing symptoms associated with ADRs while 123 had never experienced any symptoms suggestive of ADRs in the course of their use of ARVs. These symptoms were experienced singly or in combination. These results are shown in Figure 1. The occurrence of ADRs can vary dramatically among different people, with some experiencing one ADR or a combination of ADRs [8].

Patient's knowledge of ARVs and ADRs

This was assessed by asking the respondents the names of the medicines they were taking, when they started the medication and the frequency of the daily dosing. The results were as shown in Table 5.

Table 5: Duration on antiretroviral therapy

Duration (months)	Frequency	Percentage
≤ 12	134	37.9
13-24	93	26.3
24-36	59	16.7
> 36	63	17.8
Not indicated	5	1.4
Total	354	100

A Chi square measure of association indicated that there was no significant association between the duration on ARVs and occurrence of ADRs (P=0.207) as shown in Table 6.

Table 6: Association between duration on antiretroviral therapy and occurrence of adverse drug reactions

Duration on ARVs (months)	ADR occurred	No ADR	Total
≤ 12	49 (40.2%)	85 (37.4%)	134 (38.4%)
13-24	37 (30.3%)	56 (24.7%)	93 (26.6%)
24-36	21(17.2%)	38 (16.7%)	59 (16.9%)
> 36	15 (12.3%)	48 (21.1%)	63 (18.1%)

ARVs = Antiretrovirals; ADR = Adverse drug reaction; P value = 0.207.

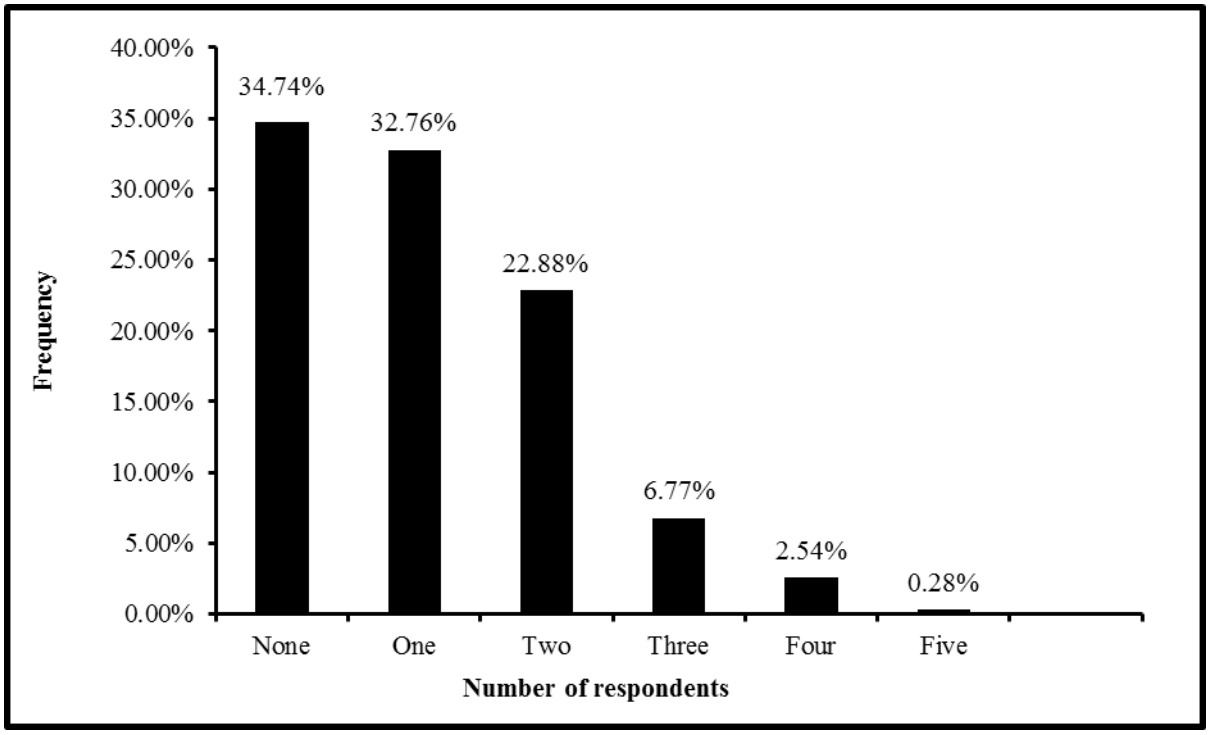

Figure 1: Frequency and number of adverse drug reactions.

Number of pills taken per day

The pills available in the CCC at the time of the study were the fixed dose combinations whereby patients took two pills in a day. Some patients reported to be taking one pill (9.69%), others two (72.08%), others three pills (10.54%) while others took more than three pills (7.69%). These results were also indicative of the level of adherence to ARVs: those who took two pills per day were adherent. For those who reported taking more than two pills in a day, it indicated that they did not distinguish which pills were ARVs and which ones were for opportunistic infections. This could be attributed to the patients' level of education, attitude towards medication and lack of knowledge of the medications used.

Names of the medicines taken

At the time of the study, the recommended ART standard regimen for adults and adolescents was a combination of stavudine (or zidovudine), lamivudine, nevirapine (or efavirenz) [16]. The medicines were dispensed as fixed dose combinations under the brand names Triomune® and Nevilast®. The results of the study revealed that most of the respondents 326 (92.1%) did not know the names of the medicines they were taking while 28 (7.9%) knew the names of their medicines. Many could however describe the medicines by shape and appearance. This could be due to the fact that names of most medicines are difficult to pronounce and remember. Most of the drugs available in the CCC were generics therefore they did not have a standardized shapes and colours.

Change of medication

The respondents were asked whether their medicines had been changed in the course of their treatment. Medications can be changed due to three main reasons: acute side effects, long term toxicities and virological treatment failure [11]. Only 10% of the respondents had encountered a medication change within the period of time they had been on ARVs. Twenty six of those whose medication had been changed could tell the reason for the change while five could not. The main reason for change was toxicity followed by occurrence of other infection and pregnancies. In general, most respondents felt that they had benefited from the use of ARVs and only a small percentage (1%) felt that they had not benefited. Such an attitude is expected to increase the level of adherence and make the patient more observant of adverse drug reactions.

Respondents association of ADRs with ARVs

Although respondents suffered symptoms indicative of ADRs, the majority did not relate the symptoms to the medicines but rather to the AIDS syndrome except in 25% of the cases.

Social demographic characteristics of respondents

The social demographic characteristics of the respondents were studied to determine the impact that they had on the occurrences, reporting and management of ADRs. It was found that gender did not significantly affect the occurrence and reporting of ADRs (P=0.477). Other findings are as shown in Table 7.

Nutrition and ADRs

The evaluation of dietary intake was conducted by three methods: food frequency, 24-h recall and a week diet history [26]. The results show that 78% of respondents had three meals in a day. These results concur with the fact that the majority of respondents (64.6%) were self-employed so could afford more than three meals in a day.

Recognition and management of ADRs: Health care provider's knowledge

Health care providers working at the CCC had not come into contact with patients presenting with hyperglycaemia, pancreatitis, hyperlipidaemia, and lactic acidosis. The other ADRs encountered were managed by change of regimen or treatment of symptoms as recommended in the Kenya Clinical manual for ART providers [16]. The results are as summarised in Table 8. Lipodystrophy was reported to be the most challenging ADR to manage, followed by peripheral neuropathy and hepatotoxicity.

Table 7: Factors that influence occurrence and reporting of adverse drug reactions: Social-demographic characteristics and chi-square association

Variables	ADR occurred		Total	P-value
	No	Yes		
Gender				
Male	44 (35.8%)	74 (32.0%)	118 (33.3%)	0.477
Female	79 (64.2%)	157 (68.0%)	236 (66.7%)	
Age (years)				
<14	24 (19.5%)	10 (4.3%)	34 (9.6%)	
14-24	8 (6.5%)	11 (4.8%)	19 (5.4%)	<0.001
>25	91 (74.0%)	210 (90.9%)	301 (85.0%)	
Weight (kg)				
<=40	24 (19.7%)	13 (5.7%)	37 (10.6%)	
41-50	14 (11.5%)	42 (18.0%)	56 (15.7%)	
51-60	47 (37.7%)	79 (34.6%)	126 (35.7%)	0.001
61-70	24 (19.7%)	64 (27.6%)	88 (24.9%)	
>70	15 (11.5%)	32 (14.0%)	47 (13.1%)	
Marital status				
Single	53 (43.1%)	69 (29.9%)	122 (34.5%)	
Married	50 (40.7%)	95 (41.1%)	145 (41.0%)	
Widowed	4 (3.3%)	22 (9.5%)	26 (7.3%)	0.016
Separated	16 (13.0%)	45 (19.5%)	61 (17.2%)	
Occupation				
Self employed	62 (50.0%)	166 (72.2%)	228 (64.6%)	
Salaried job	20 (15.8%)	22 (9.7%)	42 (11.8%)	
Child/student	30 (25.0%)	116 (6.6%)	46 (13.0%)	<0.001
Housewife	11 (9.2%)	27 (11.5%)	38 (10.7%)	
Religion				
Active	87 (70.5%)	178 (77.3%)	265 (74.9%)	
Non-active	20 (16.4%)	50 (21.4%)	70 (19.7%)	<0.001
Child	16 (13.1%)	3 (1.3%)	19 (5.4%)	
Education				
Pre-primary/children	20 (15.7%)	7 (3.1%)	27 (7.5%)	
Primary	66 (52.9%)	140 (61.1%)	206 (58.2%)	
Secondary	32 (25.6%)	72 (31.4%)	104 (29.4%)	<0.001
Post-secondary	7 (5.8%)	10 (4.4%)	17 (4.9%)	

ADR = Adverse drug reaction.

The health care providers did not consider the current reporting tool MOH 257 (comprehensive care clinic patient card) adequate for capturing all the ADRs. The card had only one line for reporting side effects in code form. They suggested that a section should be added to show when the regimen was changed and when a particular ADR was resolved.

Table 8: Diagnosis and management of adverse drug reactions

Condition	Diagnosis	Management
Anaemia	Observation, laboratory results	Change of regimen
Peripheral neuropathy	Observation Patient's report	Depending on severity, drop offending drug
Lipodystrophy	Observation Patient's report	Change from stavudine to tenofovir
Hypersensitivity	Observation Patient's report	Change of regimen
Hepatotoxicity	Observation Laboratory test	Change of regimen
Steven-Johnson's rash	Observation Patient's report	Change the causative drug (nevirapine or cotrimoxazole)
CNS disturbances	Patient's report	Change of regimen
GIT effects	Observation Patient's report	Management of symptoms

CONCLUSION

There was a high prevalence of ADRs symptoms: 65.2% of the patients using ARVs having experienced them. These symptoms occurred singly or in combination. Most of the patients did not report them to the health care providers so they were never managed or treated. The patients were unable to distinguish the ADRs symptoms from disease and they did not associate the symptoms with their medication. The occurrence and reporting of the ADRs symptoms was significantly affected by age, weight, marital status, occupation, religion and education level. Duration on ARVs and gender did not seem to significantly affect the occurrence or reporting of ADRs. The population studied was food secure and therefore no clear cut association between the diet and occurrence of ADRs.

The respondents reported side effects related to ARVs which had not been previously documented: namely abdominal distension, cough, missed monthly periods, sneezing and itching of throat. From the conclusions drawn from this study, we made the following recommendations: all Comprehensive Care Centres should have patient centred health education programs. The programs should include medication use counselling, detection and reporting of ADRs symptoms among other health related issues. Emphasis should be made to enable patients to distinguish those ADRs symptoms that are self-limiting from those that are potentially harmful and irreversible. Reporting of all symptoms should be encouraged. The health care providers working in the CCC should undergo continuous medical education in recognition and management of ADR symptoms. All health facilities providing HIV services should have well equipped laboratories and radiological tests to aid in the diagnosis and confirmation of ADRs.

There appeared some symptoms of drug reactions not previously noted and further investigation should be done to know whether these are new or emerging adverse drug reactions. Study of adverse drug reactions should be done not only for ARVs but also for the other drugs used to treat opportunistic infections since most of the information currently used in Kenya comes from developed countries. Research should be done to find standardized dosing regimens of ARVs that minimize the occurrence of ADRs and reduce the pill burden to the patient.

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