

The Prevalence And Patterns of Drug Related Problems Associated With Anti Retroviral Drugs In The Management of Hiv/Aids Patients At Ndola Central Hospital In 2016.

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ABSTRACT

Background: Antiretroviral therapy has posed multiple risks and challenges particularly in resource constrained African countries. This is due to the chronic nature of HIV/AIDS disease and hence its therapy, the use of combination therapy and also because therapeutic options and treatment guidelines continue to evolve. The increase in access to new essential medicines such as ARVs and the ARV regimen complexity and challenges increase the potential for drug related problems.

Objective: To determine the prevalence and patterns of drug related problems associated with anti retroviral drugs in the management of HIV/AIDS patients at Ndola Central Hospital in 2016.

Methodology: A cross sectional study design involving 310 randomly sampled HIV positive patients admitted to the internal medicine wards of Ndola Central Hospital was conducted. The actual/potential patient specific ARV drug related problems were identified and classified according to the Pharmaceutical Care Network Europe (PCNE) V5.01 for drug related problems. The ARV drug classes associated with the drug related problems were also determined as well as the intervention rate against these drug related problems. This was achieved by review of patients' files and drug charts over a period of two months. The data from the research was analyzed using SPSS 20.0 version. Descriptive and inferential statistics such as frequency tables, percentages and chi square tests were performed.

Results: Out of 300 patients involved in the study, 31% had drug related problems associated with antiretroviral drugs in the management of HIV/AIDS patients. The prevalence of each Drug related problem in the management of HIV/AIDS patients were adverse drug event (40%), Non-compliance (40%) and no drug initiation (20%). The drug related problems associated with Anti retroviral drugs in the management of patients with HIV/AIDS that were identified are adverse drug event, Non-compliance and no drug initiation. Only the ARV drug class NRTIs, was significantly associated with adverse drug event and Non compliance with p values= 0.03 and 0.011 respectively. 24% was the rate of intervention to prevent or resolve drug related problems associated with HIV/AIDS patients.

Conclusion: The Drug related problems that were identified as associated with anti retroviral drugs in the management of HIV/AIDS patients with their respective prevalence's are adverse drug event (40%), Non-compliance (40%) and no drug initiation (20%).

The study further established that all the ARV classes (NRTIs, NNRTIs and PIs) are significantly associated with Non Compliance while only the ARV class NNRTI is significantly associated with adverse drug event, in the management of patients with HIV/AIDS.

The results of the study also showed that there was a low rate of intervention to prevent or resolve drug related problems associated with HIV/AIDS patients (24%).

Key word: Drug related problems, Anti retroviral drugs, HIV/AIDS.

The scope of pharmacy practice now embraces more modern patient-focused and outcome-oriented pharmaceutical care than the traditional product-oriented roles such as compounding, supply and dispensing medications (Joda and Nwaokomah, 2011 cited in Oqua, *et al*, 2013). King and Fomundam, 2010 cited in Oqua, *et al*, 2013 p.2) describe Pharmaceutical care as the responsible provision of medication-related care in order to achieve definite outcomes that improve a patient's quality of life. A drug related problem (DRP) or Adverse drug event (ADE) is defined as an event or circumstance that involves a patient's drug treatment that actually, or potentially interferes with the achievement of an optimal positive health outcome (Bhalla *et al*, 2003; Roxburgh and Degenhardt, 2008). Pharmacists, through identifying actual or potential DRPs, play a key role in preventing and resolving drug related problems and make interventions or recommendations to the patient or other healthcare providers, appropriately, in order to resolve such problems (Abah *et al*, 2014). This

role is particularly important when providing pharmaceutical care to HIV infected persons given the complex nature of drug therapy for HIV and other co-morbidities or opportunistic infections experienced by HIV/AIDS patients (Gallant et al, 2011; Oqua et al, 2013). WHO (n.d cited in Strengthening Pharmaceutical Systems (SPS) Program, 2011) estimates that worldwide more than 50 percent (%) of all medicines are prescribed, dispensed, or sold inappropriately, while 50% of patients fail to take their medicines correctly. In Africa—4.5–8.4% of all hospital admissions were related to ADRs, 1.5–6.35 of patients were admitted as a direct result of ADRs; and 6.3–49.5% of all hospitalized patients developed ADRs. Moreover, 45% of ADRs accounted for the most frequent reason for treatment modification and interruptions in patients on ART (Tumwikirize, 2011; Jaquet, 2011 cited in Strengthening Pharmaceutical Systems (SPS) Program, 2011).

No study has been documented in Zambia to determine the burden of drug related problems in Antiretroviral therapy. If the current scenario continues, antiretroviral therapeutic switches may ensue, leaving fewer alternative treatment options for future switches, leading to the use of more expensive regimens, which in turn escalates the cost of health care delivery. Also, resistance to ARVs and other drugs used to treat opportunistic infections may occur with resultant poor treatment outcomes or even death. Ultimately, loss of confidence in the health system by patients takes place (Strengthening Pharmaceutical Systems (SPS) Program, 2011).

A study by Abahet *al*, 2014 in Nigeria documented the patterns of drug related problems as untreated indication (49.3%) as the most common type of DRP, such as failure to initiate ART when eligible or suboptimal treatment for hepatitis B co-infection. This was followed by therapeutic failure (25.9%) and drug toxicity (22.9%). The United States of America (USA) estimated that ADEs are the fourth to sixth leading cause of death. Also, the contribution of ADEs to the cost of the health system is estimated at \$177.4 billion in 2000, which is huge (Strengthening Pharmaceutical Systems (SPS) Program, 2011). Literature is sparse on studies evaluating DRPs in the management of HIV/AIDS and the impact on ARV resistance and adherence to treatment in sub-Saharan Africa. In developing countries, most cases of Adverse drug events (ADEs), adverse drug reactions and medication errors are not detected. Scant data are available on the global burden of DRPs and ADRs associated with new medicines such as ARVs and there is increasing evidence on the surveillance of medicines related problems, particularly in Africa with the vulnerable population receiving treatment for HIV/AIDS (Strengthening Pharmaceutical Systems (SPS) Program, 2011). Current authors have recommended further studies to determine the burden of DRPs associated with ARVs particularly in Africa (Strengthening Pharmaceutical Systems (SPS) Programme (2011)). Therefore, the purpose of this cross sectional study was to identify and determine the patterns and prevalence of drug related problems associated with ARVs in patients with HIV/AIDS admitted at Ndola Central Hospital in Zambia.

I. METHODOLOGY

This chapter includes the following: study design, study setting, data source, study population, inclusion/exclusion criteria, sample size/sampling method, variables, data collection/data collection tools, data consolidation/analysis/interpretation, and ethical considerations. The main objective of this study was to determine the prevalence and patterns of drug-related problems at Ndola Central Hospital, Zambia. The main concerns of the study include the identification of the actual/potential patient-specific drug related problems, the drugs involved in these drug-related problems and the intervention rate against DRPs.

2.1 Study Design

The study was designed as a cross sectional study based on objective 1, 2 and 4 as it aimed at just describing the trend of the drug related problems and the intervention rate towards these drug related problems.

2.2 Study Setting

The study was carried out at Ndola Central Hospital, Zambia. Ndola Central Hospital is a public tertiary hospital located on the Copperbelt Province in Zambia. The study was conducted in the Department of Internal Medicine and Admission ward. The following comprise the Internal Medicine wards: Male Medical Ward West, Male Medical Ward East, Female Medical Ward West and Female medical Ward East.

2.3 Duration of the study

Data was collected over a period of 2 months.

2.4 Data source and study population

The study involved review of patient files and drug charts to assess the occurrence and type of DRPs. Information on current Medication was obtained from the patients' Charts while that of past Drug history, diagnosis, symptoms/complaints/causes of hospitalization was obtained from the patients' files.

A pharmacotherapeutic team consisting of a Pharmacist (researcher), a senior Registrar and consultant physician in Medicine reviewed data and established the causal relationship between the drug and subsequent problem. The researcher then recorded the intervention conducted by the physicians in order to prevent the potential DRP or resolve the actual DRP.

Eligibility for Antiretroviral therapy was determined based on Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

2.5 Inclusion criteria

- Patients with HIV/AIDS on HAART or Eligible for HAART.
- All patients aged above 18 years with a length of hospital stay ≥ 24 hours
- Patients must be admitted to admission and Internal Medicine wards of NCH.
- Files of patients admitted to admission and Internal Medicine of NCH.

2.6 Exclusion criteria

- Patients without HIV/AIDS.
- Patients aged < 18 years with a length of hospital stay < 24 hours.
- Patients admitted to Surgical, Obstetrics & Gynaecology and Labour wards.
- Files of patients admitted to Surgical, Obstetrics & Gynaecology and Labour wards.
- Obese patients because some ARVs can cause obesity.
- Cases involving drug abuse, alcoholism, suicide attempts.

2.7 Sample size determination

At 95% confidence level, and a Prevalence of 72% according to a studies done by Synder *et al* (2011); Yehia *et al* (2012); Merchen *et al* (2011) and a precision of $\pm 5\%$, a sample size was calculated as follows:

$$n = \frac{Z^2 P (100-P)}{e^2}$$

Where n is the sample size

P is the prevalence 72%, and

Z (1.96) is area under curve for confidence level of 95%

e is the marginal error which is 5 in this case.

Therefore $n = 1.96^2 \times 72 (100-72)/5^2 = 310$.

2.8 Sampling Method

The patients, files were randomly sampled using excel.

The study sample was from one sample frame: Patients' records.

2.9 Variables

Table.1: Variables

Variable Name	Definition	Type of Variable	Scale of Measurement
Prevalence each of DRP in HIV	Number of patients with at least 1 specific type of DRP (numerator) divided by the total number of patients with drug related problems included in the study (denominator) admitted to internal Medicine and admission	Categorical	Frequency

	wards of NCH.		
DRP	Drug-related problems will be defined as Adverse drug reactions, non-compliance, sub-therapeutic dose, supra-therapeutic dose, drug-interactions etc according to Pharmaceutical Care Network Europe V5.01 of 2006 (Appendix A).	Categorical 1=under treatment 2=overtreatment 3=non-compliance 4=adverse drug reaction, etc.	Frequency
Drugs associated with drug-related problems	Drugs will be grouped as drug classes according to their mechanism of actions as outlined in the British National Formulary (BNF) e.g., ARV classes such as Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Fusion Inhibitors and other drug classes used to treat other co-morbidities will be grouped together as other drugs.	Categorical 1=Nucleoside Reverse Transcriptase Inhibitors 2=Non-Nucleoside Reverse Transcriptase Inhibitors 3=Protease Inhibitors 4=Fusion inhibitors.	Frequency
Actions/Intervention(rate) to prevent or resolve DRPs	The percentage of patients with DRPs	Categorical 1=drug stopped 2=Additional	Frequency

	provided with interventions during the study period will be calculated as the “number of patients provided DRPs interventions during the study period divided by the number of patients who were documented to have DRPs during the study period x100”	drug given 3=dose of drug reduced 4=drug changed, etc.	
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The drug regimens that were assessed include 1st and 2nd line treatment regimens for HIV/AIDS which Ndola central Hospital offers.

The study only focused on drug related problems associated with ARVS.

2.10 Data collection

Initial screening, was carried out by the researcher for each ward , recording demographic details, presenting complaints, diagnosis, disease states, drug therapy at the time the patient was enrolled in the study. Data was abstracted from patients’ records (files and charts) and will include laboratory results during admission.If there were any uncertainties about information in the medical records, extra information was obtained from care providers involved. Patients were not interviewed. The patients/records were given codes and the gender and age of the patients were noted.All information for each suspected DRP was collected by the researcher and was presented in form of an individual case review. Review of files was done twice a week for each patient included in the study as some patients develop DRPs during their stay in the Hospital. The case review was reported based on information obtained from the case notes, medication chart and nursing notes. The case reviews were then sent in batches to each member of the reviewing panel (pharmacotherapeutic team). Varying numbers of patients (one to three) considered not to have a DRP will be included in each batch of 25 case reviews. Two of the three reviewers were blind to the DRP/non DRP status of cases.

Each panelist reviewed the cases independently of the other panel members. For each patient, the reviewer decided whether a DRP exists definitely, possibly or not at all. They then classified the DRP and then associated the drug(s) to the subsequent DRP. The researcher then recorded the rate of action or Intervention undertaken in order to prevent or resolve such a DRP.A causal relationship between a suspected drug and a DRP was also established as definite, probable or unrelated. At the time of the study, the researcher alerted the attending doctors when a DRP was identified, so that it could be incorporated in the treatment of the patients. For a DRP to be defined as such required the agreement of at least two out of three members of the panel.

DRPs were individually identified and classified in seven categories as follows:

1. Unnecessary drug therapy: drug therapy is unnecessary because there is no clinical indication;
2. Needs additional drug therapy: additional drug therapy is required to treat or prevent a medical condition;
3. Ineffective drug: drug is not effective in producing the desired response;
4. Wrong dose: dosage too low to produce the desired response or dosage results in undesired effects;
5. Adverse drug reaction: drug causes an adverse drug reaction;
6. Non-compliance: the patient is not able or willing to take the drug regimen appropriately and
7. Drug-drug or drug-food interaction: there is a manifest or potential drug-drug or drug-food interaction.

Actions or Interventions were defined as ARV Initiation, patient counseling with regard to prescribed drug regimen, Medication changes such as ARV substitution, drug discontinuation, dosage adjustment, addition of a new drug, etc.

2.10 Data collection tools

All information for each suspected DRP was collected by the researcher from the patients' medical records and was presented in form of an individual case review. A pharmacotherapeutic team reviewed the cases and established the occurrence of a DRP, the causal relationship between the drug and subsequent problem, the rate of intervention taken to prevent a potential DRP or to resolve the actual DRP will be noted.

2.11 Data consolidation, analysis and interpretation

2.11.1 Quality evaluation

The identifiable DRPs were classified according to the Pharmaceutical Care Network Europe Version V5 (1) of 2006 (Appendix A).

In order for an event to qualify as a DRP, at least two conditions must exist:

- (i) A patient must be likely to experience disease or symptomatology; and
- (ii) These conditions must have an identifiable or suspected relationship with drug therapy.

2.12 Statistical Analysis

The focus was on descriptive analysis for objectives 1, 2 and 4.

Inference analysis was used to show association for objective 3. Chi square was used to show association between the Variables ARV classes and the subsequent DRP.

The Statistical Package for Social Sciences (SPSS) version 20.0 was used for all statistical calculations.

The variables were coded on SPSS data sheet and analyzed using descriptive analysis and inference or statistical analysis (Table 2).

Table. 2: STATISTICAL ANALYSIS

Prevalence of each DRP	Categorical	Frequency or percentage
DRP (e.g., under dose, overdose, missed dose, adverse drug reactions, non-compliance, under treatment, over-treatment, drug-interactions).	Categorical	Frequency or Percentage
Rate of Intervention	Categorical	Frequency or percentage

2.13 Ethics Consideration

Permission was sought from Ndola Central Hospital Management to carry out the study at the institution. Clearance by ERES Converge IRB was sought. The research results will only be released to designated authorities. Patients willing to participate in the research were required to sign a consent form. Confidentiality was assured as no names were captured and the patient files were given codes. Medical files were not taken away from the hospital premises to avoid mix up. All information regarding the study will be kept with passwords in the Pharmacy department and will be destroyed two (2) years after publishing the study.

II. RESULTS/FINDINGS

3.0 Introduction

This chapter presents the analysis and interpretation of the collected data from the research. There were 310 data collecting tools that were used to collect data from the ART inpatients. The data collecting tools were in English and Bemba for easy understanding during collection. Out of the 310 data collection tools, 300 of them were filled in and about 10 were returned for incomplete data in the files. 3 health workers namely a Pharmacist and 2 Clinicians were involved in the collection of data from the patient files.

3.1 Data analysis and interpretation

The data from the research was analyzed using SPSS 20.0 version. Descriptive and inferential statistics such as frequency tables, percentages and association or correlation tests were performed. In the data analysis, Chi square test was used to compare relationships between the variables drug related problems and ARV drug classes.

3.2 Socio-demographic characteristics of the patients

In this section the socio-demographic characteristics of studied patients as respondents was presented. The socio-demographic factors considered included the name of the medical ward, Age, Gender, Current regimen and how long on current regimen.

3.83.2.1 Name of the medical wards

The patient’s files were assessed from the 4 inpatient medical wards at Ndola Central Hospital. The results indicates that the majority 109(36.3%) of the patient files were from Male medical ward east, followed by 82(27.3%) patients from Male medical ward west, 64(21.3%) from Female medical ward west and the rest 45(15.1%) from Female medical ward east (Table 3).

Table.3: Name of medical ward where the in-patient files were studied

Name of medical ward	Frequency	Percent (%)
Female medical ward west	64	21.3
Male medical ward west	82	27.3
Female medical ward east	45	15.1
Male medical ward east	109	36.3
Totals	300	100.00

Table.3 shows the names of medical ward where the in-patient files were studied.

3.2.2 Age of the in-patients studied

The Mean Age =**2.70**

The Median Age =**3.0 (40-50) years**

Standard deviation=**0.883**

The majority 127(42.3%) of the of the studied inpatients were between the age of 40-50 years, followed by those who were between the age of 29-39 years 91(30.3%), 55(18.3%) were above 50 years and the rest were between the age of 18-28 years 27 (9.1%) (Figure 1).

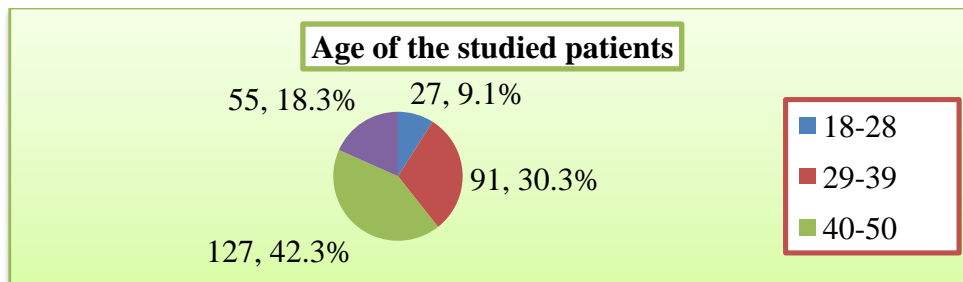


Figure.1: Age of the in-patients studied

The figure above shows that the majority of the patients (42.3%) studied, were aged between 40 and 50 years.

3.2.3 Gender

Out of the 300 in-patient files studied, Many were of the male gender about 200(67%) while the rest 100(33%) were of the female gender (Figure 2).

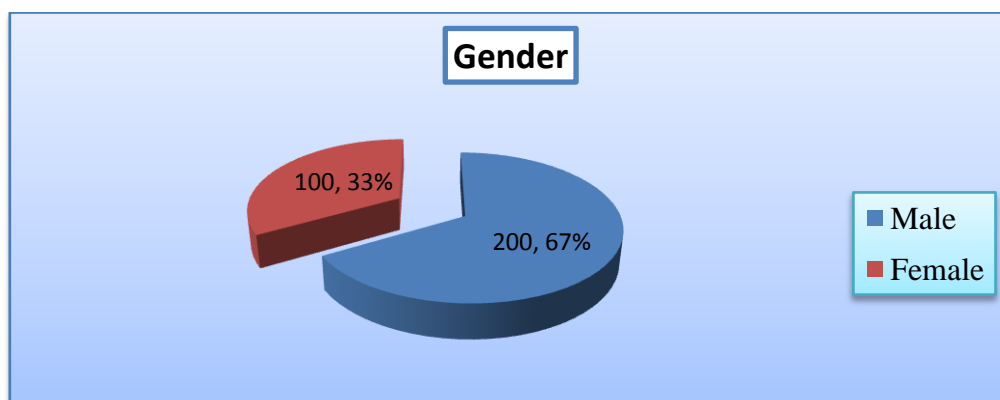


Figure.2: Gender of the in-patients studied

Figure 2 shows that the majority of the patients studied (200.7%), were male.

3.2.4 Current regimen

The current regimen most patients studied on were Atripla 164 (54.7%), followed by those who were not HAART 118(39.3%) and the rest 9(3%)were on ABC/3TC/LPV and Truvada/ Atazanavir respectively.

3.2.5 How long on current regimen (Period on current regimen)

Mean=1.29

Standard deviation=0.686

The majority were not yet on HAART or were on pre-art 146 (48.7%), followed by those were between 1-6 months 127(42.3%), above 12 months 18(6%) while the rest were between 7-12 months 9(3%) on the current regimen (Table 4).

Table.4: Current Regimen and How long on current Regimen

Current Regimen	Frequency	Percent (%)
Atripla	164	54.7
ABC/LPV	9	3.0
truvada/Atazanavir	9	3.0
Not on HAART	118	39.3
Totals	300	100.00
How long on Current Regimen		
1-6 months	127	42.3
7-12 months	9	3.0
Above 12 months	18	6.0
Not on HAART	146	48.7
Totals	300	100.00

Table 4 shows the current Regimen and how long on current Regimen of the patients studied on.

3.3. Prevalence of Drug Related Problem associated with ARVs.

The overall prevalence of drug related problem associated with ARVs was at 94(31.25%). This represents a high prevalence of drug related problem associated with ARVs (Figure 3).

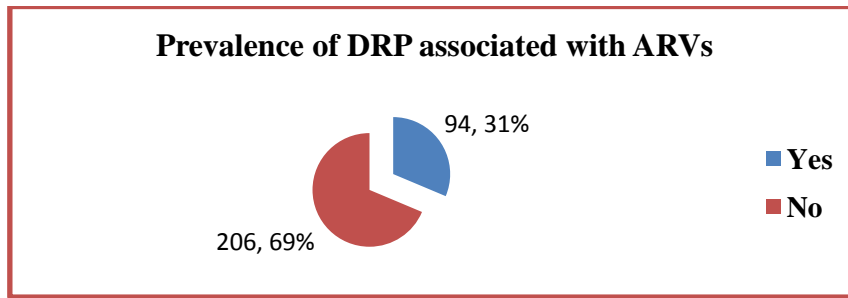


Figure .3: Prevalence of DRP associated with ARVs

Figure 3 shows the Prevalence of Drug Related Problems associated with ARVs at 31 %.

3.3.1 Category of the presence of a drug related problem associated with ARVs

Out of 300 inpatient files studied, the majority 204(68%) had no drug related problem associated with ARVs, followed by 22(66%) who had definitely a presence of Drug related problem, while the rest 10(30%) had a possibly the presence of a drug related problem Figure 4).

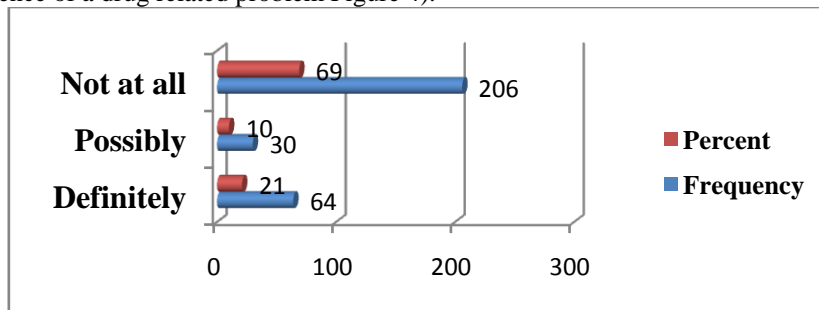


Figure.4: Category of the presence of a drug related problem associated with ARVs

3.4 Drug related problem associated with ARVs.

The common type of drug related problems associated with ARVs were adverse drug event 38 (40%), non-compliance representing 38 (40%) and no drug initiation 18 (20%) (Figure 5).

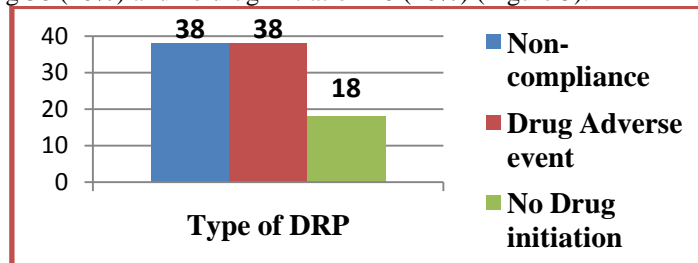


Figure.5: Prevalence of each Drug related problems associated with ARVs

3.4.1 Classes of ARVs associated with drug related problem in HIV/AIDS patient

The classes of ARVs associated with drug related problems in the management of HIV/AIDS patients was Non-Nucleoside Reverse Transcriptase inhibitors representing 47 (50%) patients, followed by Nucleoside Reverse Transcriptase inhibitors and Protease inhibitors representing 42(45%) and 5(5%) patients respectively (Figure 6).

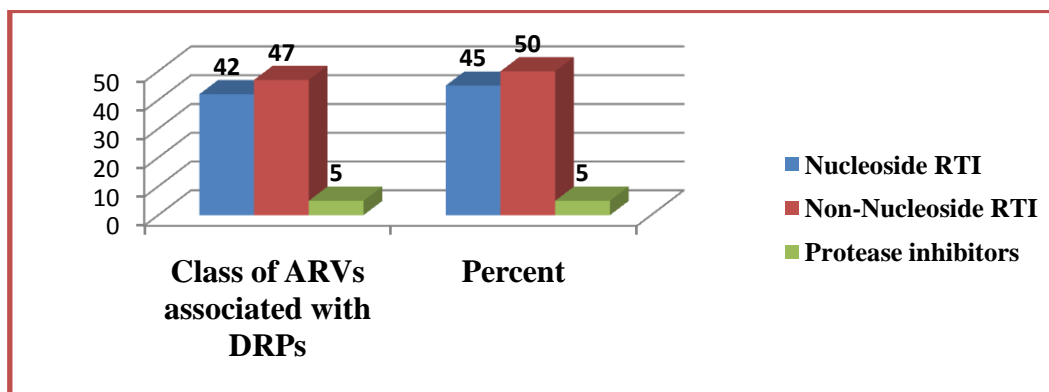


Figure.6: Classes of ARVs associated with drug related problem in HIV/AIDS patient

The figure above shows that Nucleoside RTIs were most associated with drug related problems.

3.6 Anti retroviral drug classes associated with drug related problems in HIV/AIDS patients.

Chi-Square test statistic (χ^2)

Chi-square test examines the relationship between two variables at nominal and discrete level in quantitative or qualitative research. The Chi-square test offers an alternate method of testing the significance of difference between two proportions. It has the advantage that it can also be used when more than two groups are being compared. The test compares the actual frequencies with the expected outcomes or how close they match or differ from the expected distribution and whether two variables are independent or not. In this study if the p-value is less than 0.05 ($p < 0.05$) significance level, then there is a significant association between the variables drug related problem and ARV drug class, while if the p-value is greater than 0.05 ($p > 0.05$) significance level, then there is no association between the variables. (Park K, 2011 p.789). Chi square and cross tabulation was used to answer the above question and the results were as follows:

3.6.1 Association between Nucleoside Reverse Transcriptase inhibitors and drug related problems in HIV/AIDS patients

Relationship between Nucleoside Reverse Transcriptase inhibitors and adverse drug event

The p-value (0.03) is < 0.05 significance level. There is a significant association between Nucleoside reverse transcriptase inhibitors and drug adverse event (Table 5).

Table.5: Relation between Nucleoside Reverse Transcriptase inhibitors and adverse drug event

Test-statistic χ^2	Value	Df	Asymp.Sig.(2-sided)
Pearson Chi-square	8.810	1	0.03

Table.5 shows an association between Nucleoside Reverse Transcriptase inhibitors and adverse drug event with p value=0.03, with Pearson chi square.

Relationship between Nucleoside Reverse Transcriptase inhibitors and Non- compliance

The p-value .011 < 0.05 significance level. Therefore, there is a significant association between Nucleoside reverse transcriptase inhibitors and Non-compliance (Table 6).

Table.6: Relation between Nucleoside Reverse Transcriptase inhibitors and Non- compliance

Test-statistic χ^2	Value	Df	Asymp.Sig.(2-sided)
Pearson Chi-square	6.388	1	.011

Table.6 shows an association between Nucleoside Reverse Transcriptase inhibitors and Non- compliance with p value=0.011, with Pearson chi square.

Relationship between Nucleoside Reverse Transcriptase inhibitors and No drug initiation

The *p*-value .982 > 0.05 significance level. Therefore, there is no significant association between Nucleoside reverse transcriptase inhibitors and No drug initiation (Table 7).

Table.7: Relation between Nucleoside Reverse Transcriptase inhibitors and No drug initiation

Test-statistic χ^2	Value	df	Asymp.Sig.(2-sided)
Pearson Chi-square	.001	1	.982

Table.7 shows no association between Nucleoside Reverse Transcriptase inhibitors and No drug initiation with p value 0.982, with Pearson chi square.

3.6.2 Association between Non-Nucleoside reverse transcriptase inhibitors and drug related problems in HIV/AIDS patients.

Relationship between Non-Nucleoside reverse transcriptase inhibitors and adverse drug event

The *p*-values (.674) > 0.05 significance level. Therefore, there is a significant association between Non-Nucleoside reverse transcriptase inhibitors and adverse drug event (Table 8).

Table.8: Relation between Non-Nucleoside Reverse Transcriptase inhibitors and adverse drug event

Test-statistic χ^2	Value	df	Asymp.Sig.(2-sided)
Pearson Chi-square	0.177	1	.674

Table 8 shows no association between Non-Nucleoside Reverse Transcriptase Inhibitors and adverse drug event with p value 0.674, with Pearson chi square.

Relationship between Non-Nucleoside reverse transcriptase inhibitors and Non compliance

The *p*-values (.401) > 0.05 significance level. Therefore, there is a significant association between Non-Nucleoside reverse transcriptase inhibitors and Non-compliance (Table 9).

Table.9: Relation between Non-Nucleoside Reverse Transcriptase inhibitors and Non-compliance

Test-statistic χ^2	Value	df	Asymp.Sig.(2-sided)
Pearson Chi-square	.707	1	.401

Table 9 shows no association between Non-Nucleoside Reverse Transcriptase Inhibitors and Non- compliance with p value 0.401, with Pearson chi square.

Relationship between Non-Nucleoside reverse transcriptase inhibitors and No drug initiation

The *p*-value (.294) > 0.05 significance level. Therefore, there is no significant association between Non-Nucleoside reverse transcriptase inhibitor and No drug initiation (Table 10).

Table.10: Relation between Non-Nucleoside Reverse Transcriptase inhibitors and No drug initiation

Test-statistic χ^2	Value	df	Asymp.Sig.(2-sided)
Pearson Chi-square	1.099	1	.294

Table 10 shows no association between Non-Nucleoside Reverse Transcriptase Inhibitors and No drug initiation with p value 0.294, with Pearson chi square.

3.6.3 Association between Protease inhibitors and drug related problems in HIV/AIDS patients

Relationship between Protease inhibitors and adverse drug event

The p -values (.984) > 0.05 significance level. Therefore, there is no significant association between protease inhibitor and adverse drug event (Table 11).

Table.11: Relation between Protease inhibitors and adverse drug event

Test-statistic χ^2	Value	df	Asymp.Sig.(2-sided)
Pearson Chi-square	.000	1	.984

Table 11 shows no association between Protease Inhibitors and adverse drug event with p value 0.984, with Pearson chi square.

Relationship between Protease inhibitors and non-compliance

The p -values (.339) > 0.05 significance level. Therefore, there is no association between protease inhibitor and non-compliance (Table 12).

Table.12: Relation between Protease inhibitors and non-compliance

Test-statistic χ^2	Value	df	Asymp.Sig.(2-sided)
Pearson Chi-square	0.915	1	.339

Table 12 shows no association between Protease Inhibitors and non compliance with p value 0.339, with Pearson chi square.

Relationship between Protease inhibitors and no drug initiation

The p -values (.223) > 0.05 significance level. Therefore, there is no significant association between protease inhibitor and no drug initiation (Table 13).

Table.13: Relation between Protease inhibitors and no drug initiation

Test-statistic χ^2	Value	df	Asymp.Sig.(2-sided)
Pearson Chi-square	1.483	1	.223

Table 13 shows no association between Protease Inhibitors and no drug initiation with p value 0.223, with Pearson chi square.

3.7 The rate of interventions to prevent or resolved Drug related problems associated with HIV/AIDS patients.

Overall 23(24%) was the rate of interventions to prevent or resolve drug related problems associated with HIV/AIDS patient while 71(76%) had No intervention to prevent or resolve a drug related problem. This result indicates that there was a low rate of interventions to prevent or resolve drug related problems associated with HIV/AIDS patients (Figure 7).

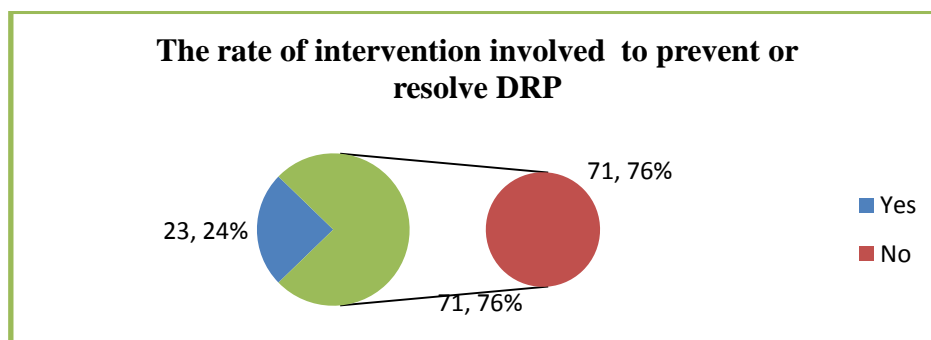


Figure.7: Rate of interventions to prevent or resolve drug related problems associated with HIV/AIDS patients.

This figure shows that the rate of intervention was 24%.

3.7.1 Type of drug intervention involved to prevent or resolve DRP

The interventions involved in preventing or resolving drug related problems in HIV/AIDS patients were change of drug 11(48%), followed by Adherence counselling 8(36%) and stopping of drug 4(16%) (Figure 8).

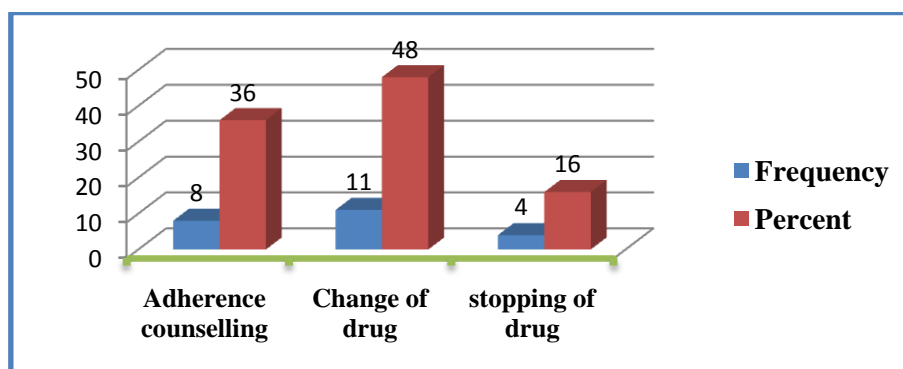


Figure.8: intervention involved in preventing or resolving drug related problem in HIV/AIDS patients.

The figure above shows that most of the interventions involved were change of drug (48%).

III. DISCUSSION

This study included patients living with HIV who were either already on combined anti retroviral therapy or not yet initiated on ART (on pre art). Of note, was the high prevalence rate (31%) of drug related problems associated anti retroviral drugs in the management of HIV/AIDS patients.

What is the prevalence of each Drug related problem in the management of patients with HIV/AIDS?

In this study, we provide evidence that the prevalence of drug related problems associated with anti retroviral drugs in the management of HIV/AIDS patients is high. The evidence is that 31% had drug related problems associated with ARVs. This result is comparable to a number of studies that documented the prevalence of ART administration DRPs in an inpatient setting as ranging from 25.8% to 72% of admissions for patients on ART (Synderet *al*, 2011; Yehiab`et *al*, 2012; Merchenet *al*, 2011) but higher than the result of the study done by Carcelero et al, (2011), that found the prevalence of antiretroviral related problems to be 21.7%.

The prevalence of each Drug related problem associated with anti retroviral drugs in the management of HIV/AIDS patients were adverse drug event (40%), Non-compliance (40%) and no drug initiation (20%) (Figure 5).The result of this study differs from several similar studies that documented the prevalence each of drug related problem associated with ARVs in the management of HIV/AIDS patients.

A prospective pharmacists' intervention study conducted by Ojeh *et al* (2015) shows that the most common type of DRPs was a drug omission (21.7%), followed by unnecessary drug (13.1%) and wrong drug indication(13.1%) respectively. Abahet *al* (2014) prospectively conducted a 1year descriptive study in Nigeria and documented the most common type of DRP as an untreated indication (49.3%), followed by therapeutic failure (25.9%) and drug toxicity (22.9%). In a prospective, observational, 1-year study done by Carceleroet *al* (2011) in Spain, the most common DRP was contraindicated combinations (drug-drug interactions) at 33.3%, followed by incorrect dose (low or high) at 16%, and dose omission at 15%.

Molinioet *al* (2014) in a study conducted in Brazil identified Adverse drug reactions as the most prevalent DRPs. The variation in the prevalence of DRPs between studies could be due to the following reasons: (i) the definition and methods used to identify the DRPs; (ii) the heterogenous estimates of the reported prevalence, and (iii) the risk factors associated with these DRPs.

What drug related problems are associated with Anti retroviral drugs in the management of patients with HIV/AIDS?

The drug related problems associated with Anti retroviral drugs in the management of patients with HIV/AIDS that were identified in our study are an adverse drug event, Non-compliance and no drug initiation. The result of this study is not in agreement with similar studies that reported and classified drug related

problems associated with ARVs. A study conducted by Ojeh *et al* (2015) identified and classified Drug related problems associated with ARVs as drug omission, unnecessary drug and wrong drug indication. Abahet *al* (2014) in Nigeria, however, identified and documented the most common type of DRPs as untreated indication, therapeutic failure and drug toxicity. Carceleroet *al* (2011) in Spain, identified and reported the most common DRPs as contraindicated combinations (drug-drug interactions), incorrect dose (low or high) and dose omission. Molinioet *al* (2014) in a study conducted in Brazil identified Adverse drug reactions as the most prevalent DRPs. The definitions and classifications of DRPs may influence the patterns of DRPs identified in various studies. The following are the subgroups of DRPs: adverse drug events (ADEs), adverse drug reactions (ADRs) and Medication errors (MEs). Some studies may have used only one or two of the subgroups of DRPs. But for the purpose of this study, we used the PCNE V5.01 for the classification of DRPs which was inclusive of all aspects of DRPs (ADEs, ADRs and ME).

What Anti retroviral drug classes are associated with drug related problems in the management of patients with HIV/AIDS?

In this study, we have shown that only the ARV class Nucleoside Reverse Transcriptase Inhibitor (NRTI) is significantly associated with adverse drug event and Non Compliance, in the management of patients with HIV/AIDS (Table 14). The findings of this study are not consistent with the findings of a study done in Kenya by Arika (2011) which documented that patients that were on ART was significantly associated with adherence (non compliance) ($\chi^2=12.111;1df; p<0.05$) regardless of the class. Using Pearson’s chi-square test and multivariate analysis (logistic regression) using STATA version 9.0, the study done by Arika (2011) further determined a statistically significant association between caregivers difficulty in adhering to own ARV medication and child’s adherence/non-adherence outcome with a $p<0.05$. The fact that NRTIs are often the ‘backbone’ of the cART makes them the most frequently prescribed class of ARVs. Moreover, the patterns and severity of DRPs may differ because of local environmental and genetic influences. In summary, the differences in the patterns of DRPs in the various studies are due to the fact that the causes of DRPs are multi factorial.

Table 14: Statistical relationship between the ARV drug class and drug related problems (Non compliance and Adverse drug event).

Class of ARV	DRP	P value
NRTIs	Adverse drug event	0.03
NRTIs	Non compliance	0.011

Table 14 shows the statistical relationship between NRTIs and drug related problems (Non compliance and Adverse drug event).

What is the rate of intervention to prevent or resolve DRPs in the management of HIV/AIDS?

Our results indicate that 24% was the rate of intervention to prevent or resolve drug related problems associated with HIV/AIDS patients (Figure 9). This intervention rate is low and is comparable to a study done by Abahet *al* (2014) that documented a 0.9% intervention rate of the population seen during the study period. However, this result is lower than that documented by other studies. A study by Aguet *al* (2014) documented that 98.3% of participants who had medication errors (DRPs) received interventions for the medications errors and 97.4% of the potential/actual DRPs were resolved. Another study by Chiampaset *al* (2015) observed that documented correction of DRPs for the clinical specialist was approximately 50%. Carceleroet *al* (2011) documented a 100% intervention in all the 60 DRPs detected. Under-reporting of interventions in our study may have been due to inadequate time during clinic to document each intervention. Under-reporting of interventions may also be due to the fact that only interventions accepted by the attending physician were documented. Besides, only interventions of greatest clinical importance and those most likely to result in favorable HIV clinical outcomes were documented in the study.

Limitations

The following limitations to the study were identified:

- A limitation to our study is that there were no HIV clinical specialists (Pharmacists and physicians) with training in HIV pharmacotherapy to play an important role in correcting DRPs.
- The small sample size, which limits the identification of other drug related problems associated with ARVs, other than the ones that were documented (e.g., adverse drug reactions, drug interactions,) that might also have been experienced by HIV/AIDS patients.
- The study only covered the department of Internal Medicine of the institution and only in patients had their records reviewed.

IV. CONCLUSION AND RECOMMENDATIONS

This chapter includes a summary of the key findings based on the objectives of this study and evaluation of the study in terms of the rate of intervention to prevent or resolve drug related problems associated with ARVs in the management of HIV/AIDS patients at Ndola central Hospital. The study findings raise a lot of concerns due to the high overall prevalence of drug related problems associated with anti retroviral drugs in the management of HIV/AIDS patients (31%). The Drug related problems that were identified as associated with anti retroviral drugs in the management of HIV/AIDS patients with their respective prevalence's are Adverse drug event (40%), Non-compliance (40%) and no drug initiation (20%). The study further established that all the ARV classes (NRTIs, NNRTIs and PIs) are significantly associated with Non Compliance while only the ARV class NNRTI is significantly associated with adverse drug event, in the management of patients with HIV/AIDS.

The results of the study also showed that there was a low rate of intervention to prevent or resolve drug related problems associated with HIV/AIDS patients (24%).

V. RECOMMENDATIONS

1. There need to train HIV clinical specialists (Pharmacists and physicians) in HIV pharmacotherapy that can play an important role in identifying and correcting DRPs associated with ARVs in the management of HIV/AIDS patients.
2. There is need to incorporate the identification and prevention/resolution of drug related problems associated with ARVs in the treatment guidelines for HIV/AIDS.
3. There is a need to strengthen or develop strategies that will encourage HIV/AIDS patients accept their sero-positive status and hence encourage compliance to the prescribed ARV regimens.
4. There is a need for further studies to be conducted that will look at factors that increase the risk of drug related problems associated with ARVs such as local environmental and genetic factors.

REFERENCES

- [1] Abah IO, Ojeh VB, Faland KD, Darin KM, Olaitan OO, Agbaji OO. Pharmaceutical care outcomes in an outpatient human immunodeficiency virus treatment centre in Jos, Nigeria. *J Basic ClinPharma* 2014; 5:57-61.
- [2] Agu KA, Oqua D, Adeyanju Z, Isah MA, Adesuna A, Oliaeri SI, Ali PN, Ekechukwu N, Akpakwu AA, Sami T, Omeh IO, King RC and Wutoh AK. The incidence and Types of Medication Errors in Patients Receiving Antiretroviral Therapy in Resource Constrained Settings. *Plos One* 2014;9(1): e87338.
- [3] Carcelero E, Tuset M, Martin M, Lazzari E De, Codina C, Miro J, Gatell JM. Evaluation of antiretroviral-related errors and interventions by the clinical pharmacist in hospitalized HIV infected patients. *HIV Medicine* 2011;12 (8):494-499.
- [4] Chiampas T.D, Kim H, Badowski M. Evaluation of the occurrence and type of antiretroviral and opportunistic infection Medication errors within the inpatient setting. *PharmPract (Granada)* 2015;13(1):512.
- [5] Cipolle RJ, Strand LM, Morley PC. *Pharmaceutical Care Practice: The Patient-Centered Approach to Medication Management Services*. New York, NY: *McGraw-Hill*; 2012.
- [6] Conforti A, Constantini D, Zanetti F, Moretti U, Grezzan M, Leone R, (2012). 'Adverse drug reactions in older patients: an Italian observational prospective hospital study'. *Drug health. Patient Safety*. 4: 75-80.
- [7] Davies EC, Green CF, Mottram DR, Rowe PH, Pirmohamed M (2010). 'Emergency re-admissions to hospital due to adverse drug reactions within 1 year of the index admission'. *Br J. Pharmacol.*, 70(5):749-755.
- [8] Giwa A, Giwa HBF, Yukubu SI, Ajiboye WT, Abubakar D, Abe SA. J. Pharmacists' roles in optimizing pharmaceutical care for HIV/AIDS patients in University of Maiduguri Teaching Hospital, North-eastern Nigeria. *Pharmaco and Trop Ther* 2011;1(2):12-16.
- [9] Hamid AA, Ghaleb M, Aljadhey H, and Aslanpou Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. *Br J Clin Pharmacol*. 2014; 78(2): 202-217.
- [10] <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.
- [11] Arika LA (2011). *Care-giver factors associated with adherence to antiretroviral therapy in HIV infected children: A case of Thika District Hospital in Kenya*. A research thesis submitted in partial fulfillment of the requirement for the award of the degree of master of public health in the school of health sciences of the kenyatta university
- [12] Menéndez-Conde PC, Vicedo BT, Silveira DE, Accame CE (2011). 'Adverse drug reactions which provoke hospital admission'. *Farm. Hosp.*, 35, pp. 236-243.
- [13] Merchen BA, Gerzenshtein L, Scarsi KK et al. Evaluation of HIV-specialized pharmacists' impact on prescribing errors in hospitalized patients on antiretroviral therapy. In: Abstracts of the Fifty-first

- Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, 2011. Abstract H2–794, p. 101. American Society for Microbiology, Washington, DC, USA.
- [14] Molino CGRC, Carnevale RC, Rodrigues AT, Visacri MB, Moriel P, Mazzola PG. Impact of pharmacist interventions on drug-related problems and laboratory markers in outpatients with human immunodeficiency virus infection. *Therapeutics and clinical risk management* 2014; 10: 631-639.
- [15] National Coordination Council for Medication Error Reporting and Prevention (NCCMERP), 2013. About Medication Errors.
- [16] Obah IO, Ojeh VB, Falang KD, Darin KM, Olaitan OO, Agbaji OO. Pharmaceutical care outcomes in an outpatient human immunodeficiency virus treatment centre in Jos, Nigeria. *J Basic ClinPharma* 2014; 5:57-61.
- [17] Ojeh VB, Naima N, Obah IO, Falang KD, Ogwuche L, London I, Christiana D, Agaba P, Agbaji O. Patterns of drug therapy problems and interventions in ambulatory patients receiving antiretroviral therapy in Nigeria. *Pharm Pract (Granada)*. 2015;13 (2): 566.
- [18] Posthumus AA, Alingh CC, Zwaan CC, *et al* (2012). 'Adverse drug reaction-related admissions in paediatrics': a prospective single-centre study. *BMJ Open.*, 2 e000934.
- [19] Rodenburg EM, Stricker BH, Visser LE (2011). 'Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands.' *Br. J. Clin. Pharmacol.*, 71, 95–104.
- [20] Singh H, Kumar BN, Sinha T, Dulhani N (2011). 'The incidence and nature of drug-related hospital admission: a 6-month observational study in a tertiary health care hospital' *J. Pharmacol. Pharmacother.*, 2, 17–20.
- [21] Stausberg J, Hasford J (2011). 'Drug –related admissions and hospital acquired adverse drug events in Germany: a longitudinal analysis from 2003 to 2007 of ICD-10-coded routine data' *BMC Health Serv. Res.* 11:134.
- [22] Strengthening Pharmaceutical Systems (SPS) Program. 2011. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA:
- [23] Snyder AM, Klinker K, Orrick JJ *et al*. An in-depth analysis of medication errors in hospitalized patients with HIV. *Ann Pharmacother* 2011; 45: 459–68. *World Health Organization. Assuring Safety of preventive chemotherapy interventions for neglected tropical diseases. Practical advice for national programme managers on the prevention, detection and management of serious adverse effects. WHO*. 2011. P 1.
- [24] Yehia BR, Mehta JM, Ciuffetelli D *et al*. Antiretroviral medication errors remain high but are quickly corrected among hospitalized HIV-infected adults. *Clin Infect Dis* 2012; 55: 593–9.
- [25] Zuidlaren. *Pharmaceutical Care Network Europe (PCNE) Classification scheme for Drug-Related Problems V5.01.2006*; 1-4.