ABSTRACT

BACKGROUND
Botswana has a current prevalence of HIV infection at approximately 21.9% though in the age group of 20-45 years average prevalence is about 37%. The introduction of HAART (Highly Active Antiretroviral Therapy) which comprises combinations of at least 3 efficacious Antiretroviral drugs has shown effective suppressive rates and can improve quality of life. A certain proportion of patients may develop severe and even life-threatening side-effects and complications of therapy. METHOD: A retrospective study was carried out in a district hospital in Botswana for which data was collected from ADR Reporting form. Pharmacists record the ADR’s as reported either by the patient/care-giver/recent lab tests in case of Renal and Liver impairments. Data collection comprised of all reports made for the term 2015. Information collected included patient demographics, HAART, its initiation, co-morbidities, ADR suspected/reported and the change in treatment for the same. ADR assessment was carried out using the standard scales. RESULTS: A total of 66 patients were reported for Suspected ADR’s out of which there were 15 (22.7%) males and 55 (83.3%) females. Common ADR’s were Lipodystrophy, Renal Failure and in few cases were Psychosis, Gynaecomastia. Combivir (71%) was reported for most of them followed by Atripla (18%). ADR’s reported with co morbidities (15%) were less when compared to those with absence of any pre-existing conditions. Causality assessment showed ADR’s were Probable (63.6%), Possible (16.6%), and Unclassified (16.6%) while Severity accounted for 51.5% of cases being Severe (Grade -6) and 45.4% being Mild.

KEYWORDS: Adverse drug reaction, assessment, Antiretrovirals.
INTRODUCTION

Antiretroviral therapy (ART) is treatment of people infected with human immunodeficiency virus (HIV) using anti-HIV drugs. The standard treatment consists of a combination of at least three drugs (often called “highly active antiretroviral therapy” or HAART) that suppress HIV replication. Three drugs are used in order to reduce the likelihood of the virus developing resistance. ART has the potential both to reduce mortality and morbidity rates among HIV-infected people, and to improve their quality of life.\[^1\]

Unfortunately, the adverse effects of these drugs are of serious concern. Adverse reaction to antiretrovirals in HIV patients is a major cause of medication non-adherence, leading to treatment failure.\[^2\]

ADRs due to continuous exposure to antiretroviral drugs leave the caregiver with few options: decreasing the dosage of antiretroviral drugs thus compromising efficacy, withdrawing the offending drug and substituting it with another drug, or symptomatically treating the ADR. However, substituting the offending drug by the caregiver is difficult especially in resource limited settings because most HAART regimens exist as fixed dose combinations (FDC) of different drugs most of which are first line drugs with high toxicity profiles. The advent of new generation drugs with relatively low toxicity into the antiretroviral armamentarium is some hope that deleterious effects of HAART related ADRs in HIV patients would decrease. This hope still remains farfetched in resource limited settings where albeit the highest global HIV burden\[^3\]

Observing pharmacovigilance in order to detect, assess, understand and prevent adverse effects or any other drug-related problem is essential to ensure the safe use of ART now and in the future. It is important for HIV clinicians to develop a positive and pro-active attitude toward pharmacovigilance so that reporting adverse reactions become an accepted and understood routine.\[^4\]

Therefore this study is aimed at identifying the ADR’s along with their assessment and changes done to HAART therapy in presence of them.

METHODS

A retrospective study was carried out in a district hospital in Botswana. The data collection was made from the official Suspected ADR’s reporting form supplied by the Government of
Botswana for reporting ADR’s. The hospital has a separate Infection Diseases Control Centre which is centred around mainly HIV clinic and ARV pharmacy. Pharmacists record the ADR’s as reported either by the patient/care-giver/recent lab tests in case of Renal and Liver impairments. Data collection comprised of all reports made for the term 2015. Information collected included patient demographics, HAART, its initiation, co-morbidities, ADR suspected/reported and the change in treatment for the same. ADR assessment was carried out using the standard scales: CAUSALITY (WHO-UMC[5]), SEVERITY ((Modified Hartwig-Seigel).[6]

RESULTS
A total of 66 patients were reported for Suspected ADR’s which were then screened for their assessment of Causality and Severity using the scales. Table -1 shows Gender categorization being 15(22.7%) males and 55(83.3%) females of the study population. Ages of patients ranged from 20-90yrs from which most of them belonged to 40-50 yrs range (31.8%) is shown in Fig -1.

HAART initiation was also recorded and showed patients on therapy from 2000-2015 and further; most of the patients included in the study were found to have been initiated during the 2005-2010 term represented in Fig-2.

ART regimen followed in the hospital mainly showed the following combinations prescribed in accordance with the Botswana treatment Guidelines (2012):

- AZT(300mg)+3TC(150mg)+EFV(600mg) [Combivir & Efavirenz],
- AZT(300mg)+3TC(150mg)+NVP(200mg) [Combivir & Nevirapine],
- EFV(600mg)+FTC(200mg)+TDF(300mg) [Atripla],
- FTC(200mg)+TDF(245mg)+NVP(200mg) [Truvada & Nevirapine]
- LPV(200mg)/r(50mg) +3TC(150mg)+ABC(300mg) [Aluvia,Lamivudine &Abacavir]

Fig-3 shows the percentage of HAART prescribed to the study population.

Fig-4 represents the prevalence of ADR’S caused by the drugs used as part of the HAART regimens.

Fig-5 gives the incidence rates of common ADR’s reported by the patients.

Table-2 and Fig-6 outlines the drugs causing Renal failure.
Table-3 shows the different drugs causing Hepatomegaly

Table -4 represents the ADR’s mainly caused by Combivir therapy highlighting the ones caused by individual constituents also and the same is represented graphically in Fig-7.

Presence of co morbidities in patients with Renal Failure on Combivir regimen is shown byTable-5.

Data showed fewer patients with co morbidities and were mostly Hypertension, Diabetes Mellitus, Renal failure due to previous ART regimen, Pregnancy etc,

ADR’s reported with co morbidities (15%) were less when compared to those with absence of any pre-existing conditions.

Fig-8 shows the Lipodystrophy cases reported classified by their presence in the body.

Fig -9 is a summarising chart for depicting Atripla and its constituents causing the respective ADR’s.

Table-6 depicts the Causality assessment whereas Table-7 is showing Severity assessment

**Table-1: Gender Categorization**

<table>
<thead>
<tr>
<th>GENDER</th>
<th>Number(N=66)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15</td>
<td>22.7</td>
</tr>
<tr>
<td>Female</td>
<td>55</td>
<td>83.3</td>
</tr>
</tbody>
</table>

Fig: 1

SJS: Steven-Johnson’s Syndrome

Table-2

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>Number(N=25)</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV</td>
<td>17</td>
<td>68</td>
</tr>
<tr>
<td>TDF(ATR)</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>TDF(TRU)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>3TC</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Fig -6
Table 3

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>Number(N=6)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>ABC</td>
<td>1</td>
<td>16.6</td>
</tr>
<tr>
<td>TRU</td>
<td>1</td>
<td>16.6</td>
</tr>
<tr>
<td>EFV</td>
<td>1</td>
<td>16.6</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>ADR</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBV</td>
<td>Renal Failure</td>
<td>36.9</td>
</tr>
<tr>
<td>AZT</td>
<td>Anaemia</td>
<td>10.8</td>
</tr>
<tr>
<td>3TC</td>
<td>Lipodystrophy</td>
<td>58.6</td>
</tr>
</tbody>
</table>

Fig -7

Table 5

<table>
<thead>
<tr>
<th>RENAL FAILURE (CBV)</th>
<th>CO MORBIDITIES</th>
<th>Number(N=17)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>5</td>
<td>29.4</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>HTN +DM</td>
<td>3</td>
<td>17.6</td>
<td></td>
</tr>
<tr>
<td>NONE</td>
<td>8</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

Fig -8
Table-6: Causality Assessment Using WHO-UMC Scale

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>Number(N=66)</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable</td>
<td>42</td>
<td>63.6</td>
</tr>
<tr>
<td>Possible</td>
<td>11</td>
<td>16.6</td>
</tr>
<tr>
<td>Unclassified</td>
<td>13</td>
<td>19.6</td>
</tr>
</tbody>
</table>

Table-7: Severity Assessment Using Modified Hartwig-Seigels Scale

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>Number(N=66)</th>
<th>Percentage(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild(2)</td>
<td>30</td>
<td>45.4</td>
</tr>
<tr>
<td>Moderate(4B)</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Severe(4A)</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Severe(6)</td>
<td>34</td>
<td>51.5</td>
</tr>
</tbody>
</table>

DISCUSSION

The study was aimed at identifying the ADR’s, their prevalence and assessment of ADR’s using standard scales in a spontaneous reporting program. The main HAART regimen followed in most patients were found to be CBV/EFV followed by Atripla.

Results showed a higher incidence of ADR’s in females compared to males and this in accordance with study stating gender predisposition is a risk factor for ADR’s [7]. This is in contrary with findings by Eluwa et al. which reported that gender was not significantly associated with ADRs [8].

Hospitalization for ADR’s was reported only for 1 patient who had SJS similarly as reported by Kenneth et al citing (<2%) of new hospitalization due to ADR [9].
Patients on Combivir and Nevirapine regimen reported higher incidence of ADR’s which is in accordance with the results stated by Leiketsang et al.\[10\]

Majority of the ADR’s were attributed to Combivir therapy wherein the individual constituents i.e. Lamivudine contributed to be causing Lipodystrophy whereas Zidovudine for Anaemia.

Certain cases also showed Renal failure(38.3%) while on Combivir although this can be interpreted in two ways: firstly presence of co-morbidities like Hypertension and Diabetes in individuals are predisposed to developing Renal impairment thereby Combivir alone cannot be reported for ADR in these situations and secondly Renal failure has also been reported in patients without co-morbidities showing slight chances that Combivir may also play a role.

As per standard drug information\[11\] related to Combivir and its role in Renal Impairment further study needs to be done as currently information provided does not support or substantiate the ADR causality, thereby making it Unclassified according to WHO-UMC\[5\] scale.

The study reported Anaemia (10.8%) showing similarity with results from Kenneth et al who also reported 4.3% cases while on Zidovudine\[9\] and other reports too suggested the same.\[12,13,14,15,16,17\] Blood transfusion was done in 2 of the patients reporting severe anaemia.Henry et al reported 3.8% of all ADRs of which anaemia (haemoglobin <7g/dl) was the most common and the most severe, all of which were associated to AZT-containing regimens.\[18\] Our findings are higher compared to that of Ivory Coast of 3.4% in 2006\[19\], but similar to that of a Malawian study in 2002\[20\], and a Senegalese study in 2007\[21\] where AZT-related anaemia were 7.8% and 6.3% respectively.

Lipodystrophy was caused by Lamivudine and accounted for 39.3% of ADR’s reported. This malfunction is supported by databases confirming the causality of Lamivudine to it. Most of them seemed to develop it after 2-3 years of HAART Initiation. Among the patients 54% showed general presence whereas 21% showed Lower extremities lipodystrophy. Reports also showed presence of dual types in a single individual like Buffalo Hump & Facial lipodystrophy/Lowe extremities. According to a Botswana study of 650 adults in 2007 Lipodystrophy was 16% of all ADRs\[22\], 34.2% in a Rwandan population of 409 adults in 2007.\[23\]
Atripla therapy reported about 18% of ADR’s which were mainly Hepatic impairment, Renal Failure and minimally Psychosis. Atripla constituents Tenofovir and Emtricitabine contributed majorly for Liver and renal ADR’s whereas Efavirenz mainly caused Psychosis (3%).

Causality assessment showed that ADR’s were belonging mainly to the following 3 categories: Probable (63.6%), Possible (16.6%), and Unclassified (16.6%).

Main concern lied in classifying Combivir associated renal failure as it lacked supporting justification and documentation from studies and databases alike.

Severity assessment revealed most mild ADR’s to be renal failure mostly based on their Creatinine clearance levels showing that they were in the initial stages although a few patients even reported Severe (4A) as they were belonging to the chronic stage. Lipodystrophy was assessed as Severe due to the drastic changes in weight of patients were reported thereby causing permanent harm.

Treatment for ADR’s was done accordingly based on the Botswana guidelines 2012 thereby showing compliance to the SOP’s. For ADR like Severe anaemia transfusion was done along with change in therapy.

Patients experiencing renal failure on Combivir were changed to Lamivudine and Zidovudine once dosing whereas for those experiencing Lipodystrophy, Truvada was initiated and in some Atripla.

AZT induced Anaemia patients were switched to Truvada and Nevirapine regimen. Atripla induced ADR’s showed change of therapy to Aluvia and Truvada respectively.

CONCLUSION
The retrospective analysis showed the system of spontaneous reporting done actively by the pharmacists in the hospital although a few of them maybe under-reported. Mainly classifying the ADR’s is of importance and training needs to be done to identify them promptly. Adequate lab reports were done to supplement the ADR’s of Renal and Hepatic impairments which is considered quite remarkable in monitoring and improving patient care. The reporting form can be made so as to include other criterions which allow for the assessment of ADR in a better, detailed manner.
ABBREVIATIONS

ADR: Adverse Drug Reaction
HAART: Highly Active Anti-Retroviral Therapy
ARV: Antiretroviral
CBV: Combivir
3TC: Lamivudine
AZT: Zidovudine
EFV: Efavirenz
NVP: Nevirapine
TRU: Truvada
ATR: Atripla
ALU: Aluvia

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