ADVERSE DRUG REACTIONS TO ANTI-RETROVIRAL THERAPY: A CROSS SECTIONAL OBSERVATIONAL STUDY

Dr. Yogananda Rajashekarachar¹, Dr. Manoj Kumar Mudigubba²*, Dr. Pathan Amanulla Khan³, Dr. Nagendra Gowda MR⁴, Dr. Bharathi Doddlu Raghunathnaidu¹ and Sowmya M¹

¹SJM College of Pharmacy, Chitradurga, Karnataka State, 577502, India.
²Department of Pharmacy Practice, TVM College of Pharmacy, Bellary, Karnataka State, India.
³Anwar-ul-uloom College of Pharmacy, Hyderabad, India.
⁴Basaveshwara Medical College Hospital and Research Centre, Chitradurga, Karnataka State, 577502 India.

ABSTRACT

Human immunodeficiency virus/Acquired Immune Deficiency Syndrome is a fatal illness which leaves the victim to a lot of life threatening Opportunistic infections, Neurological disorders, malignancies. Objectives: To evaluate the incidence, risk factors associated with adverse drug reactions (ADRs) and analyze these adverse drug reactions by using naranjos scale questionnaire among patients on antiretroviral drugs. Materials and methods: A Cross-sectional Observational study was carried out in People Living with HIV& AIDS attending antiretro viral therapy centre in a Chitradurga district, Karnataka state, India for a period of six months. A total of 599 patients were enrolled into the study. Chi square test was used to detect the association status of different variables. Results: Our study results shows that, a total of 599 [100%] patients were enrolled in to the study, out of them 155 [25.9%] came across with adverse drug reactions. The incidence of ADR was 1 in every 6 patients on antiretro viral therapy with in a period of 6-12 months. Major risk factors considered in this study were age, gender, CD4 count, treatment regimen, duration of treatment, tobacco smoking and alcohol. Conclusion: Adverse drug reactions were more likely to occur in the
first one year of treatment. Close monitoring with in this period is required to prevent occurrence of severe adverse drug reactions and can improve medication adherence.

**KEYWORDS:** Adverse drug reaction, ART, PLHAs, HIV/AIDS, Incidence, Risk factors.

**INTRODUCTION**

Human immunodeficiency virus/Acquired Immune Deficiency Syndrome is a fatal illness which leaves the victim to a lot of life threatening opportunistic infections, neurological disorders, malignancies.\(^1\) Living with HIV/AIDS not only hampers physical health but also mental and social well being. It is not only a simply virus that causes disease but also a social and historical event that impacts how others reacts towards the people living HIV/AIDS (PLHA).\(^2\) Antiretroviral drugs (ARVs), which can significantly delay the progression from HIV to AIDS – have been available in developed countries since 1996. Unfortunately, as in many resource-poor areas, access to this treatment is limited, in India an estimated 2,85,000 people were receiving free ARVs in 2009.\(^3\) According to WHO’s treatment guidelines (2010), which recommend starting treatment earlier, revised estimates may indicate that only around 1 in 4 people in need of HIV treatment are currently receiving it.\(^4\) The introduction of highly active antiretroviral therapy has led to a significant reduction in HIV/AIDS-related morbidity and mortality.\(^5\) Presently drugs belonging to classes of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease Inhibitors, fusion Inhibitors, entry Inhibitors - CCR5 co-receptor antagonist and HIV integrase strand transfer inhibitors are approved by Food and Drug Administration for treatment of HIV.\(^6\) Unfortunately, up to 25% of patients discontinue their initial highly active antiretroviral therapy regimen because of treatment failure (inability to suppress HIV viral replication to below the current limit of detection, 50 copies/ml), toxic effects or noncompliance within the first 8 months of therapy.\(^7,8\) While development of new antiretroviral agents continues, efforts to maximize the effectiveness of currently available treatments include attempts to better understand and manage adverse effects. Each antiretroviral medication is associated with its own specific adverse effects or may cause problems only in particular circumstances. Similarly, class-specific adverse effects may occur.\(^9\) The studies have reported that the incidence of adverse drug reactions (ADR) due to anti retroviral therapy (ART) ranges from 11 – 35.9%. The incidence of severe ADR is around 10%. The long term ADRs include peripheral neuropathy and lipodystrophy associated with stavudine, anaemia due to zidovudine and hepatotoxicity, rash associated with nevirapine. The hepatotoxicity incidence
has been reported to be around 16% due to nevirapine and 8% due to efavirenz. The incidence of anemia ranged from 3-12% due to Zidovudine.\textsuperscript{10} However, the studies about adverse drug reactions especially in people living with HIV/AIDS who are on antiretro viral therapy are fewer in India and almost absent in this part of the country. Hence it was decided to take up this research in order to study the incidence and risk factors for adverse drug reactions especially in PLHAs on antiretroviral therapy.

**MATERIALS AND METHODS**

A cross sectional observational study was undertaken to study the incidence and determinants of adverse drug reactions (ADR) in a district antiretroviral therapy centre, Chitradurga. The ethical clearance was obtained from institutional ethical committee, Basaveshwara Medical College and Hospital, Chitradurga. This study was conducted between January 2013 and June 2013 for a period of six months. All the cases who attended district ART centre in the study period were chosen randomly. For the purpose of the study adverse drug reaction case was defined as “Any response to antiretroviral therapy drugs which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of HIV/AIDS or for the modification of physiological function in PLHA\textsubscript{S} who were on ART”.

All the age groups and both sexes of PLHA\textsubscript{S} attending ART centre and who were ready to give consent to take part in the study were included. A total of 599 cases satisfied the inclusion criteria and constituted the study sample. An informed, written, bilingual consent was obtained before the study. A pre tested and pre designed questionnaire was administered to study subjects. The ADRs were scored by using standard Naranjo’s questionnaire. The questionnaire differentiates the adverse drug reactions in to the following categories like definite, possible, probable and unlikely.

**Statistical analysis:** The data thus obtained was compiled and analyzed using Statistical Package for Social Services (vs.18). A Chi square test was obtained to determine any significant difference between the ADR and non ADR groups and Categorical variables and Z test was used for Quantitative variables.

**RESULTS**

A cross sectional study was undertaken to study the incidence and risk factors of adverse drug reactions in the PLHAs who were on ART. A total of 599 subjects satisfied the inclusion and exclusion criteria and were included as the study subjects.
Fig. 1 Distribution of the study population according to occurrence of ADR

Fig.No.01. A total of 599 [100%] patients were on ART therapy and about 25.9% [155] developed adverse drug reactions.

χ² value = 0.569, df = 1, p value = 0.451

Fig.No.02 shows that, the male to female ratio was 1:0.9. More than half of the PLHAs in this study were male. The difference between the sex and occurrence of ADR was not significant.

χ² value = 12.592, df = 1, p value = 0.403

Fig. 3 Distribution of the PLHAs according to the smoking and occurrence of ADR
Fig.No.03 shows that distribution of study group according to Smoking and occurrence of ADR. Almost 20.0% of PLHAS had social history of smoking and there was a statistically significant difference between the smoking and occurrence of ADR. But majority of adverse drug reactions were identified in non-smokers.

Fig. 4 Distribution of the PLHAs according to alcohol and occurrence of ADR
$$\chi^2 \text{ value} = 16.819, \, df = 1, \, P \text{ value} = 0.403$$

Fig.No.04 shows that distribution of study group according to Alcohol and occurrence of ADR. Almost 23.9% of PLHAS had social history of alcohol and there was a statistically significant difference between the alcohol and occurrence of ADR.

Fig. 5 Distribution of the PLHAs according to initial ART Regimen with respect to occurrence of ADR
$$\chi^2 \text{ value} = 29.285, \, df = 12, \, p \text{ value} = 0.004$$

Fig.No.05 Over all 418 patients were given only ZLN, out of these 107 [25.6%] developed adverse drug reactions to this combination therapy. However there was significant association between ADR and initial ART Regimen at 0.05% level of significance.
Fig. 6 Distribution of the PLHAs according to suspected drug with respect to occurrence of ADR

$\chi^2$ value = 599.00, df = 15, $P$ value = 0.000

Fig. No.06 Almost 78 [50.3%] patients were given only AZT who developed anaemia as adverse drug reaction. However there was significant association between ADR and suspected drug at 0.05 level of significance.

Fig. 7 Distribution of the PLHAs according to Duration of treatment with respect to occurrence of ADR

$\chi^2$ value = 14.985, df = 5, $p$ value = 0.010

Fig. No.07 shows that almost 37.70 % of PLHAS had developed ADRs within 0-6 month’s duration of treatment followed by 30% PLHAS developed within the duration of 6-12 months. However there was statistically significant difference between the treatment duration and occurrence of ADR at 0.05 % level of significance.
Fig. 8 Distribution of the PLHAs according to CD4 count with respect to occurrence of ADR

Fig.No.08 shows that patients who were in the range of 200-500 CD4 Count were developed more [49.7%] ADRs than others.

Table.No.01 Distribution of PLHAs according to age group and ADR

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of adverse drug reactions [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 30 years</td>
<td>67 [43.2%]</td>
</tr>
<tr>
<td>31-40yrs</td>
<td>29 [18.7%]</td>
</tr>
<tr>
<td>41-50yrs</td>
<td>12 [7.7%]</td>
</tr>
<tr>
<td>51-60yrs</td>
<td>44 [28.4%]</td>
</tr>
<tr>
<td>&gt;60 yrs</td>
<td>3 [1.9%]</td>
</tr>
<tr>
<td>Total</td>
<td>155 [100%]</td>
</tr>
</tbody>
</table>

$\chi^2$ value = 6.465, $df$ = 4, $p$ value = 0.167, NS

Table.No.01 shows Almost 40% of the PLHAs were aged less than 30 years. Majority of adverse drug reactions identified less than 30 years of age group. However there was no significant difference between the occurrence of ADR and age group.

Table 02 WHO Clinical stage and occurrence of ADR

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Adverse drug reactions %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>32 [20.6%]</td>
</tr>
<tr>
<td>II</td>
<td>96 [61.9%]</td>
</tr>
<tr>
<td>III</td>
<td>24 [15.5%]</td>
</tr>
<tr>
<td>IV</td>
<td>3 [1.9%]</td>
</tr>
<tr>
<td>Total</td>
<td>155 [100.0%]</td>
</tr>
</tbody>
</table>

$\chi^2$ value = 0.731, $df$ = 3, $p$ value=0.603

Table.No.02 shows that distribution of study group according to the WHO Clinical stage and occurrence of ADR. 61.90% of adverse drug reactions were identified under stage-II
patients. However there was no statistically significant difference between the WHO Clinical stage and occurrence of ADR.

Table.03 Distribution of the PLHAs according to Changed ART regimen with respect to occurrence of ADR

<table>
<thead>
<tr>
<th>Changed ART regimen</th>
<th>Occurrence of ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0 [0.0%]</td>
</tr>
<tr>
<td>Yes</td>
<td>155 [98.1%]</td>
</tr>
<tr>
<td>Total</td>
<td>155 [25.9%]</td>
</tr>
</tbody>
</table>

Table.No.03 shows that, Out of total 599 [100%] HIV Positive patients, 158 patients were changed their regimen due to various reasons. Out of these 155 [98.1%] patients were changed their regimen due to development of adverse drug reactions.

Table.04 Distribution of the PLHAs according to respect male & female incidence of ADR’s

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>67.6%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>28.9%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>19.7%</td>
<td>19.0%</td>
</tr>
<tr>
<td>GI Toxicity</td>
<td>5.6%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

**Incidence:** Table.No.04 shows that incidence of each adverse drug reaction according to respect male and female. In all the reported anaemia cases females were accounting about 67.60 % and males were accounting about 58.30%, in the same of all reported peripheral neuropathy cases females were accounting about 28.90% and males were accounting about 21.40%, besides that all the reported Hypersensitivity reaction cases females were accounting about 19.70% and males were accounting about 19.00% and all the reported GI toxicity cases females were accounting about 05.6% and males were accounting about 9.5%.

Table.05 Naranjos causality assessment of ADR

<table>
<thead>
<tr>
<th>Naranjo scale category</th>
<th>Number of ADR</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>13</td>
<td>8.3</td>
</tr>
<tr>
<td>Possible</td>
<td>81</td>
<td>52.3</td>
</tr>
<tr>
<td>Probable</td>
<td>49</td>
<td>31.6</td>
</tr>
<tr>
<td>Unlikely</td>
<td>10</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Table.No.05 shows that out of all the reported ADRs, 81(52.3%) were assessed as possible.
DISCUSSION

The study was aimed to find out the incidence, and risk factors associating adverse drug reactions to anti-retro viral therapy in people living with HIV/AIDs who were attending Chitradurga district ART Centre, Karnataka. The study observed that significant ADRs associated with PLHAs in the local population of Chitradurga.

A total of 599 patients were enrolled in to the study, out of them 155 [25.9%] came across with adverse drug reactions. The incidence of ADR was 1 in every 6 patients on highly active antiretro viral therapy with in a period of 6 – 12 months. In this study, majority of ADRs were identified in the age group of less than 30 years [43.2%]. However, the prevalence was more in age group of 31 – 40 years [40.84%] as per the study conducted by the Akshaya et al.[12] Our study didn’t showed marked difference in reported ADRs between men [54.2%] and women [45.8%]. As per Eluwa et al, females [64.04%] were more prone to develop ADRs than males [35.96%].[13] And Bonfanti et al observed that women experienced significantly greater number of ADRs compared to men.[14]

About 96.1% patients who developed adverse drug reactions to anti-retro viral therapy, got HIV infection through heterosexual mode of transmission, in addition to that other route of transmissions like blood transfusion was around 1.9%, injection, mother to child and Male Sex to Male [MSM] had same percentage level [0.6%]. As heterosexuality is major mode of transmission in HIV infected people, the incidence of ADRs to antiretro viral therapy in these population were large. This shows no significant association with the adverse drug reactions.

CD4 Count is the most important parameter in assessing the disease severity of PLHAs. In our study, of the 599 patients 597 [99.7%] have undergone CD4 count ever. This shows that almost all the patients have gone through CD4 examination to assess their disease severity for better therapeutic treatment and outcome. In the same way when we found the relation between adverse drug reactions and CD4 count, 49.7%(77) of adverse drug reactions were developed to antiretro viral therapy in PLHAs who had come under the category of 200-500 cells/cu mm of CD4 count along with that 33.5%(52) of ADRs were developed in PLHAs of the category more than 500 cells/cu mm, 16.8%(26) of ADRs were identified in the range of less than 200 cells/cu mm of CD4 count. A study conducted by Eluwa et al [13] did not showed any association between CD4 cell count with ADRs, but Subbaraman et al study suggested that low CD4 count at treatment initiation is a risk factor for ADR.[15] By
comparing literature with our result we didn’t found a marked variation in the range of CD4 count with respect to ADR.

During the study period we found that prevalence of ADRs were more in non-smokers [80%] than smokers [20%]. When we gone in-depth to the prevalence of ADRs within the smokers, we found that predominant number of patients 31 [20.0%] out of 41 smokers had encountered ADRs. Statistical test showed that adverse drug reaction is dependent in other words there was significant association between ADR and smoking.

The prevalence of adverse drug reactions was more in non-alcoholics [76.1%] than alcoholics [23.9%]. The inter-individual variability’s in alcoholics with respective to ADRs had shown that 37 alcoholics developed adverse drug reactions out of 47 alcoholics. Statistical test showed that there was significant association between alcohol and adverse drug reaction.

In our study population, more than half of all adverse drug reactions reported were in patients taking regimen containing zidovudine [AZT] and the major was anaemia [62.6%]. A finding suggested by Akshaya et al showed 16.9% of haematological abnormalities with zidovudine regimen containing anti retro viral therapy.\textsuperscript{[12]} The literature shown females were more to develop anaemia as adverse drug reactions to antiretro viral therapy. Here in this study 67.6% of adverse drug reactions to anaemia were identified in the females and 58.3% in males. In our study population 1/4\textsuperscript{th} of all adverse drug reactions were reported in patients taking stavudine [d4t] regimen i.e 11% adverse drug reactions were d4t induced peripheral neuropathy. Our findings are less than African settings like Cameroon in 2012 at Doulala general hospital showed a prevalence of peripheral neuropathy was 21.2%.\textsuperscript{[11]} When we did the inter-individual gender variability in peripheral neuropathy as an adverse drug reaction, we found that 28.9% of them were in females, followed by followed by 21.4% in males. Based on this we concluded that females are more prone to get peripheral neuropathy as an adverse drug reaction to antiretro viral therapy when compared to males. Of the total 155 adverse drug reactions reported, 16.1%(25) were nevirapine induced hypersensitivity reactions. Oshikoya et al\textsuperscript{[16]} study showed that nevirapine associated rashes [65.5%] were the commonest clinical adverse event in PLHAs to antiretro viral therapy. Upon the percentage gender distribution of hypersensitivity as an adverse drug reaction, we found no major difference in females [19.7%] and males [19.0%].
GI associated adverse drug reactions had a prevalence of 7.7%. In GI, nausea and vomiting were accounting about 3.2%. According to the percentage gender distribution of GI adverse effects, we found that males were a little more prone get GI associated adverse drug reactions when compared to females because of their social habitats like smoking and alcohol which increases the risk of getting these adverse drug reactions.

Since adverse drug reactions are the single most common reason for poor adherence to treatment, identifying risk factors for the occurrence of adverse drug reactions is of crucial importance to optimize the initial choice of antiretro virals before initiating therapy and to adapt the pace of surveillance to each unique situation. After meeting the criteria for the initiation of antiretro viral therapy, the physicians will start treating PLHAS with highly active antiretro viral therapy regimen. In our study of total 599 patients 418 patients have been prescribed with zidovudine [ZLN] as their initial ART regimen followed by stavudine+ lamivudine+nevirapine [SLN] and other highly active antiretro viral therapy regimens. After keenly observing the percentage of adverse drug reactions to initial treatment regimens in detailed “ZLN occupies first ranking 107 out of 418 initial ZLN prescriptions, next ranking goes to SLN, 32 prescriptions developed adverse drug reactions out of 124 who were initiated with this SLN regimen followed by zidovudine+lamivudine +efavirenz [ZLE], 4 out of 13 ZLE initial prescriptions, tenofavir+lamivudine+nevirapine [TLN] 2 prescriptions developed ADRs out of 22 TLN initial prescriptions.

After identifying the adverse drug reactions it is crucial important to assess severity of adverse drug reaction by using various standard scales. Here in our study we followed the standard Naranjo’s scale questionnaire for assessing their severity based on their scoring for each ADR. Out of all 155 adverse drug reactions, 153 were undergone causality assessment. When we did category wise 8.3%ADRs were assessed as definite, 52.3% ADRs were assessed as possible, 31.6% ADRs were assessed as probable, and 6.5% were assessed as unlikely.

**CONCLUSION**

The adverse drug reactions of antiretroviral therapy damages moderate to severe of various organ systems in PLHAs. The incidence of ADR was 1 in every 6 patients on antiretro viral therapy with in a period of 6 – 12 months. Close monitoring of patients within this time frame is thus imperative to prevent the occurrence of severe adverse drug reactions, improve adherence as well as improve documentation of ADRs. Risk factors  age group, Sex, CD4
cell count doesn’t show significant association with adverse effect and Smoking, Alcohol, treatment regimen, duration of treatment show significant association with adverse effect. Out of all 52.3% adverse drug reactions were assessed as possible by using naranjos causality assessment scale. Our study finding showed that there is a need of active pharmaceutical care with intensive monitoring of adverse drug reactions in people living with HIV-AIDs.

REFERENCE
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