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Identification, assessment and reporting of suspected Adverse Drug Reactions (ADRs) to Anti-retroviral therapy (ART) and Anti-tubercular therapy (ATT) in a community care centre at Warangal

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ABSTRACT

Adverse effects of drugs are the main source of morbidity and mortality among the outpatients and inpatients. The objective of the study was to identify, assess and report suspected Adverse Drug Reactions in patients who are diagnosed with Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS) patients with and without Tuberculosis (TB). This was a prospective observational study conducted for a period of six months to explore the significant ADRs caused by Anti-Retroviral and Anti-Tubercular drugs in patients visiting community care centre at Warangal who are diagnosed with HIV-AIDS with or without Tuberculosis as co-infection. In our study we enrolled 144 patients and a total of 514 ADRs were identified in 125 patients. The most common ADR observed in our study was peripheral neuropathy in 61 patients, followed by vomitings, weakness, anorexia, myalgia, diarrhea and itching. The ART regimen Stavudine+Lamivudine+Efavirenz (STV+LMV+EFV) was found to be most commonly involved in about 138 ADRs,whereas the regimen Zidovudine+Lamivudine+Nevirapine (ZDV+LMV+NVP) was found to be having least incidence rate of ADRs. Causality assessment was made using WHO probability scale and Naranjo's Scale and 340 (66.14%) and 346 (67.31%) ADRs were classified into Possible respectively. Severity of ADRS were assessed using Hartwig scale and 376 (67.50%) ADRs were classified into Moderate and 138 (26.84%) into Mild ADRs. The findings of our study showed that a huge number of ADRs were experienced by the patients who are receiving ART and ATT which is a major cause for medication Non-compliance and discontinuation of the therapy. Therefore, close monitoring and reporting of ADRs is needed in these patients who are receiving ART and ATT.

Key words:
Adverse Drug Reaction, Anti-Retroviral Therapy, Anti-Tubercular Treatment, Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome (HIV-AIDS) and Causality.

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INTRODUCTION

Adverse drug reactions (ADRs) cause considerable mortality and morbidity[1]. ADRs are defined by the World Health Organization as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[2].

Globally, Adverse Drug Reactions (ADRs) account for 5% of all hospitalizations[3]. HIV stands for Human Immunodeficiency Virus and is different to AIDS, which is the advanced stage of HIV infection. This virus can be spread through infected blood, breast milk, semen, and anal or vaginal fluids contaminating the blood stream. This attacks the immune system by using the body's defence cells to replicate, simultaneously destroying the same cells that protect the body from illness. If HIV is not treated with antiretroviral treatment which works by preventing the virus from replicating - then the body is exposed to opportunistic infections which can cause serious illnesses[4, 5, 6]. In 2016 more than 36 million People had HIV globally. In 1990, the total number of deaths was estimated to be approximately 290,000; this increased to peak in 2005/06 at approximately 1.9 million. From then, the total number of deaths has been declined almost half, falling to around 1 million in 2016. Across this period, 15-49 year old have maintained the highest (and a consistent) share of around 74-75% of global deaths from HIV/AIDS[7].

India has the third largest HIV epidemic in the world with 2.1 million HIV people. In 2017, HIV prevalence among adults aged 15-49 years was estimated 0.2% [8, 9]Among them, 79% of people were aware of their status and 56% were on antiretroviral treatment (ART) [10]. NACO is the governing body responsible for formulating the policy and implementing programmes in India for the prevention and control of the HIV epidemic. In 2017, India adopted "test and treat" following WHO guidance, which means anyone testing positive for HIV is now eligible for treatment, regardless of their CD4 count [11]. Globally, 10million people were estimated to have developed TB in 2017, 27% of whom lived in India. India has the highest proportion of MDR/TB cases at 24% [12,

[13]. In HAART, a combination of antiretroviral drugs is used to bring about lasting suppression of HIV replication and thereby preventing the consequences of uncontrolled HIV infection in particular, the loss of CD4-cell-mediated immunity[14]. Global ART coverage for all patients living with HIV reached approximately 41% by March 2015[15]. ART significantly decreases mortality overall, but death rates are also highest in the first 3 months of ART due to ADRs [16].

First line ART for adults should consist of at least three drugs (2NRTI's and a NNRTI's or/and Integrase Inhibitor). After first-line therapy has failed, second-line ART is the next regimen used in sequence immediately. (Current NACO treatment guidelines recommend that the protease inhibitor (PI) class is reserved and characterizes second-line ART. Ritonavir boosted protease inhibitors (bPIs) are recommended and supported by two agents.) Increasing ART coverage leads to decreased TB cases. ART should be started in all TB patients with HIV, regardless of CD4 cell count[17]. Adherence to ART remains unsatisfactory due to multifactorial and dynamic process which raises considerable difficulties for long term follow-up [18].

Side effects vary from person to person and are impossible to predict exactly how each individual will be affected. Several factors may predispose individuals to adverse effects of ART like Alcoholism or co-infection with viral hepatitis, medications with overlapping and additive toxicities [19, 20, 21, 22]. Most common opportunistic infection in HIV patients is 'Tuberculosis'. The risk of death in co-infected individuals is also twice that of HIV infected individuals without TB[23].

Treatment in these co-infected patients is problematic because of pill burden, Drug-Drug interactions and toxicity. This study is aimed at investigating the incidence of various ADRs related to antiretroviral and Anti-tubercular drug use in Community Care Centre (CCC),

India and finding out the incidence, the offending drug regimen and types of such ADRs, thus encouraging the health care professionals to provide better patient care by continuous monitoring of Anti-Rretroviral therapy, reporting of unusual and known ADRs and effective management of such conditions.

METHODOLOGY AND METHODS

Materials used

- Informed Consent Form
- Patient Data Collection Form
- ADR Documentation Form

The present study was conducted in Community Care Center (CCC) in-patient wards of a 70 bedded community care centre located in Warangal district of Andhra Pradesh. The present study is a prospective study. It was carried out for a period of 6 months. The data including demographics, drug usage pattern of patients were collected from the patients case notes, treatment chart, nurse notes, laboratory reports, out patient records etc. All the collected data was documented in a suitably designed data collection form developed for the study. All patients visiting the impatient department were reviewed intensively on daily basis. Demographic details of the patient, reason for admission, diagnosis, past medical history were documented in the data collection form. Patient/patient care takers were interviewed for the presence of any documented ADRs, All suspected ADRs were suitably assessed for Causality, Severity, Preventability and predictability.

Ethical Considerations

The ethical clearance for the study was approved by the Institutional Ethical Committee.

Inclusion Criteria

HIV patients with and without Tuberculosis co-infection of either gender referred to Community Care Center (CCC), Warangal were included in the study.

Exclusion criteria

- Patients under 12 years.
- Pregnant/ lactating females.
- Patients in which antiretroviral therapy has not yet started.
- Patients who were unable to respond to verbal questions.

Data Collection Form

Data collection form was designed to collect, document and analyze the data. Informed consent form was incorporated in the data collection form.

ADR Documentation Form

ADR documentation form contained the details regarding the patient demography, description of event, medications suspected, medication used prior to the reaction with their complete dosage regimen, co-morbidities, risk factors, allergic status, casualty category, severity, predictability, preventability, management of reported adverse reaction, outcome of management and follow up details.

List of tools used in this study

- WHO probability scale
- Naranjo's algorithm
- Severity scale
- Preventability scale
- Predictability scale.

RESULTS

The maximum number of patients that is 62 was in the age group 31-40 years and only 1 patient was above 60 years of age. The CD4 count of 110 patients was in between 100-500 cells/μL. Out of 144 patients 36 HIV and 26 HIV+TB patients were in age group 31-40 years and only 1 patient was above 60 years of age. 42 males were diagnosed with HIV+TB and 44 females were diagnosed with HIV alone

Table 1: Distribution of Patients

Age wise distribution of patients	Age	Number of patients	Percentage (%)
	12-20	3	2.08
	21-30	35	24.30
	31-40	62	43.05
	41-50	33	22.91
	51-60	9	6.25
	>60	1	0.33
CD4 Count in patients	**CD4 count**	**Number of patients**	**Percentage (%)**
	<100	19	13.19
	100-250	59	40.97
	250-500	51	35.41
	>500	15	10.41
Age wise distribution of HIV and HIV+TB patients	**Number of HIV+TB patients**	**Number of HIV patients**	**Percentage (%)**
0-20	0	3	2.08
21-30	15	21	25.00
31-40	26	36	43.05
41-50	20	14	23.61
51-60	2	7	6.25
>60	**0**	1	0.69
Sex wise distribution of HIV and HIV+TB patients	**Male**	**Female**	**Percentage (%)**
HIV+TB	42	20	43.75
HIV	37	44	56.25

ADVERSE DRUG REACTIONS

The number of patients who reported at least one ADRs were 125. Maximum number of ADRs 121 were reported in age group 21-40 years and only 3 ADRs were reported in patients above 60 years of age. The number of ADRs in males were 293 followed by 217 in females. Gastrointestinal system was majorly affected with 154 ADRs followed by Central Nervous System. Only 40 ADRs were reported related to Hematologic and Hepatic system.

Table 2: Distribution of ADRs

Incidence of Adverse drug reactions	Number of patients	Number of patients with ADRs	Percentage (%)
	144	125	86.08
Age wise incidence of ADRs	**Age Group**	**Number of ADRs**	**Percentage (%)**
	0-20	2	1.24
	21-40	121	75.16
	41-60	35	21.74
	>60	3	1.86
Sex wise incidence of ADRs	**Sex**	**Number of ADRs**	**Percentage (%)**
	Male	293	57.00
	Female	217	42.21
	Transgender	4	0.77
ADRs affecting human body system	**Organ system**	**Number of ADRs**	**Percentage (%)**
	Gastrointestinal	154	29.09
	Central Nervous	135	26.21
	Musculoskeletal	83	16.11
	Skin	45	8.73
	Hematologic and Hepatic	40	7.76
	Others	58	11.20

CLASSIFICATION OF ADRs ACCORDING TO BODY SYSTEMS AFFECTED

In the present study, gastrointestinal system related ADRs constitute the major part, 154 cases (29.09%) of total ADRs, followed by central nervous system related ADRs of 135 cases (26.21%), followed by Musculoskeletal system related ADRs of in 83 cases (16.11%). followed by 58 cases (11.2%) of Others related ADRs. 45 patients (8.73%) experienced Skin related ADRs. And Hematologic and Hepatic abnormalities related ADRs were found to be 40 cases (7.76%) respectively.

Table 3: ADRs affecting human body systems

Organ System	Number of ADRs	Percentage (%)
Gastrointestinal	154	29.09
Central Nervous	135	26.21
Musculoskeletal	83	16.11
Skin	45	8.73
Hematologic and Hepatic	40	7.76
Others	58	11.20

LIST OF ADVERSE DRUG REACTIONS

Vomiting constituted the most common GIT related ADRs which was noticed in 49 patients (32.23%), Neuropathy was the most common CNS related ADR which was noticed in 61 patients (45.18%),Major skin related ADRs were itching, noticed in 34 patients (75.55%),Generalized weakness was the most common Musculoskeletal system related ADRs which occurred in 38 patients (45.78%), Anemia is the major blood related ADR which occurred in 29 patients (72.05%) and jaundice in 11 patients (27.05%).Fever was seen in 25 patients (43.10%). dyspnea has occurred in 21 patients (36.20%) followed by cough, decreased vision, BP, chills and ototoxicity.

Table 4: ADRs with respect to different organ systems

Organ System	Adverse Drug Reaction	Number of Patients	Percentage (%)
Gastrointestinal	Vomiting	49	32.23
	Anorexia	36	23.37
	Diarrhea	31	20.12
	Nausea	22	14.19
	Abdominal pain	09	05.84
	Constipation	04	02.59
	Ingestion	01	00.64
	Ulcer	01	00.64
	Thirsty	01	00.64
Central Nervous System	Neuropathy	61	45.18
	Headache	24	17.77
	Insomnia	15	11.11
	Giddiness	14	10.37
	Drowsiness	05	03.70
	Depression	05	03.70
	Somnolence	02	01.48
	Confusion	02	01.48
	Agitation	02	01.48
	Anger	01	00.74
	Seizures	01	00.74
Skin	Itching	34	75.55
	Skin rashes	08	17.77
	Nail pigmentation	02	04.44
	Sweating	01	02.22
Musculoskeletal	Generalized weakness	38	45.78
	Myalgia	34	40.96
	Leg swelling	05	06.02
	Angioedema	04	04.81
	Arthralgia	01	01.20
Blood and Liver	Anemia	29	72.05
	Jaundice	11	27.05
Others	Fever	25	43.10
	Dyspnea	21	36.20
	Cough	05	08.62
	Reduced vision	02	03.44
	Blood pressure	02	03.44
	Chills	02	03.44
	Ototoxicity	01	01.72

Adverse Drug Reactions associated with different drug regimens:

In the present study Stavudine + Lamivudine + Efavirenz combination is responsible for major number of ADRs 142 (27.57%), followed by Stavudine+Lamivudine + Nevirapine which constitute nearly 138 (26.79%) of total occurrence. Zidovudine +Lamivudine + Nevirapine constituted 125 (24.27%) ADRs.Zidovudine+Lamivudine + Efavirenz combination is responsible for 110 (21.35%) ADRs.

Table 5: ADRs due to various regimens

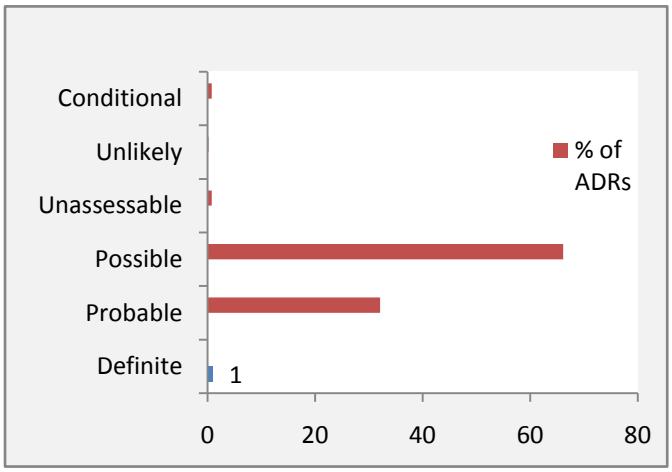
Regimen	Number of ADRs	Percentage
ZDV+LMV+ NVP	125	24.27%
ZDV+LMV+ EFV	110	21.35%
STV+LMV+ NVP	138	26.79%
STV+LMV+ EFV	142	27.57%

Causality Assessment

WHO-UMC scale

In the WHO-UMC scale most of the ADRs reported were possible 340(66.14%), followed by probable 165(32.10%).

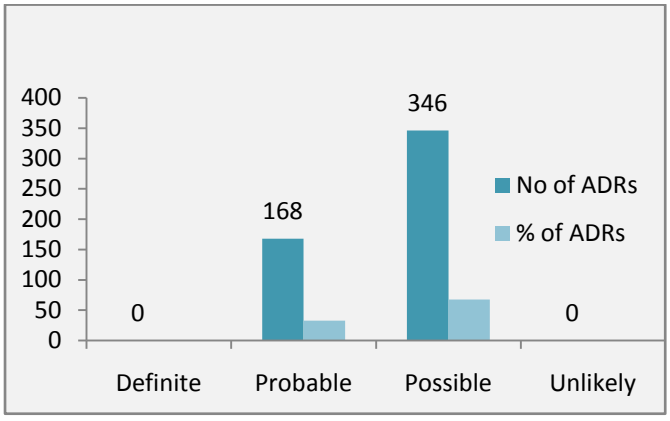
Figure-1: Causalty assessment of ADRs using WHO scale



Naranjo's Casualty Assessment

According to Naranjo's scale most of the ADRs reported were possible 346(67.31%) followed by probable 168(32.68%).

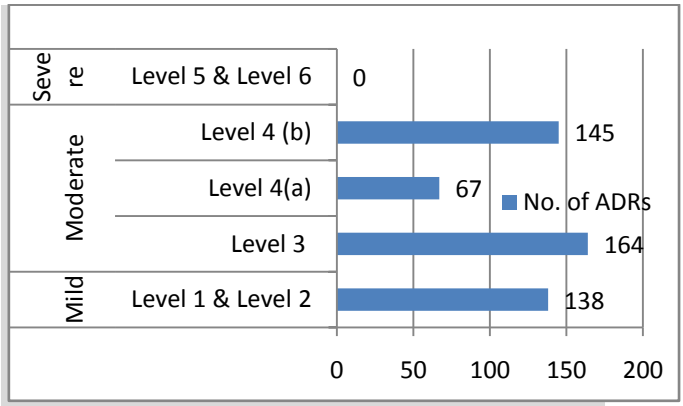
Figure-2: Causality assessment of ADRs using Naranjo's scale



Severity assessment based on Hartwig and Siegel's scale

Of the total of 514 ADRs 376(67.50%) were moderately severe followed by 138(26.84%) ADRs of mild severity.

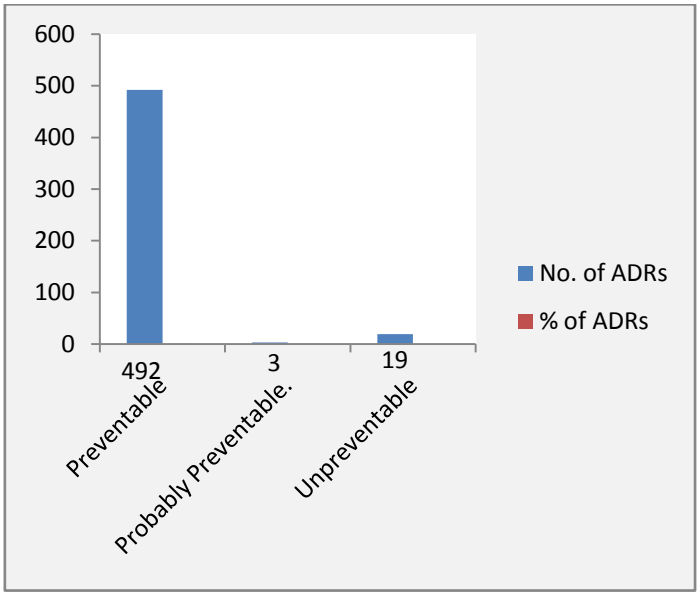
Fig 3: Sseverity assessment of ADRs based on Hartwig and Siegel's scale



Preventability assessment based on Schumock and Thornton's criteria

In our study the results showed that 492(95.72%) ADRs were definitely preventable followed by only 3(0.58%) were probably preventable and 19(3.69%) ADRs were unpreventable.

Fig 4: Preventability assessment of ADRs



DISCUSSION

This study observed the significance of ADRs associated with ART and ART+ATT in the local population of Visakhapatnam, Andhra Pradesh, India. Strength of the study include the recruitment of 144(HIV, HIV+TB) patients for a study period of 6 months. In this study the prevalence of ADRs was higher in males (56%) compared to females (43.20%) and this difference was significant ($p<0.05$). This findings were similar to the results observed from the study of Radhkrishnan et al [24]. The possible causes might be the differences in men and women's BMI, fat composition, hormonal effects on drug metabolism.

In the present study TB was the most frequently found opportunistic infection in 63(43.75%) patients, this is similar to studies conducted by Fithamlak et al and Debasu et al[25, 26]. In some studies Oral Candidiasis was the most common opportunistic infection, the difference in occurrence of OIs is due to prevalence of different organisms in different areas.

In our study, the overall incidence of ADR to highly active antiretroviral therapy was found to be 86.08%. Incidence is found to be greater than earlier study conducted by Akshay et al[27]where it was 64.78%. This may be because of the poor adherence, illiteracy, economic background and concurrent medications were not properly used for treating Opportunistic infections. Vomiting constituted the most common GIT related ADRs which was noticed in 49 patients (32.23%) followed by anorexia in 36 patients (23.37%), this is comparable to previous studies by Menezes et al[28]. This was followed by CNS with incidence rate of 26.21%. Musculoskeletal, skin, hematologic and hepatic incidence rates were 16.11%, 8.73% and 7.76% respectively. These results were comparable to previous studies [27]. In our study most common ADR reported was peripheral neuropathy found in 61 cases (11.86%) of total ADRs that is comparable to previous study by RA Breen et al [29] which followed by vomiting(09.53%), generalized weakness(07.39%), anorexia(7.00%) and 6.65% of itching and myalgia.

Most frequently used regimen was STV+LMV+NVP (31.25%) followed by STV+LMV+EFV (27.08%) ZDV+LMV+NVP (24.30%) and the least used regimen was ZDV+LMV+EFV (18.05%). While analyzing the ADR data of various regimens with respect to number of patients receiving it, the most toxic regimen found was STV+LMV+EFV (incidence rate of ADR's was 100%), followed by STV+LMV+NVP (86.67%) while these findings differ significantly from the previous study by Akshay et al[27] where most toxic regimen was ZDV+LMV+NVP incidence rate of 53.52%.

Causality assessment using WHO scale showed a total number of 340 (66.14%) reactions as "Possible" followed by 165 (32.10%) as "Probable". Causality assessment using Naranjo scale showed a total number of 346 (67.31%) as "Possible" with causality score 1-4, followed by 168 (32.68%) as "Probable". These results are not matching with previous studies done by Radhkrishnan et al[24] where majority of reactions 47(63.5%) were Probable and 26 (35.2%) were Possible.

Assessment of severity using Hartwig scale clearly gave a picture that 138(26.84%) of total ADRs mildly affected the patients while majority 378 (73.14%) of toxic reactions were mild which was supported by already existing studies by Menezes et al [28]. This may be due to the shorter exposure time of the patient to the offending drug. Preventability assessment by using Schumock and Thornton ADR Preventability scale revealed that out of 514 ADRs, 492 were preventable if adequate care might have taken. Preventability was very high (95.72%). Predictability assessment showed a total number of 466(90.66%) of reactions were predictable only 48 (9.33%) reactions were unpredictable which is supported by previous study done by Radhkrishnan et al [24].

CONCLUSION

This study reflects a fair picture of the most commonly experienced ADRs with the use of ART and ATT in HIV/AIDS and HIV/AIDS with TB patients. Incidence of ADRs was significantly high in males. Among the ADR's encountered above, the most common ADR's are associated with gastrointestinal system. STAVUDINE+LAMIVUDINE+EFAVIRENZ (SLE) regimen was responsible for majority of ADRs which were possible, moderate, preventable and predictable. The major opportunistic infection was Tuberculosis and diarrhea. The finding of this study showed that there is a need for intensive monitoring for ADRs in Indian HIV positive patients who are illiterate, of male gender, with CD4 count <200cells/µl, with tuberculosis. However, a prospective study taking a larger sample is necessary to arrive at a definite conclusion.

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CONFLICTS OF INTEREST

We the authors of this study declare that this manuscript has not been submitted to another journal or publishing venue. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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