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Research Article

Adverse Drug Reaction Monitoring In Patients Taking First Line Antitubercular Drugs Alone And In Combination With Antiretroviral Therapy In A Tertiary Care Centre Of Western India

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ABSTRACT

OBJECTIVES: Adverse Drug Reactions (ADRs) are common in patients taking Anti-Tubercular Treatment (ATT) alone or in combination with Highly Active Anti-Retroviral Therapy (HAART). Hence, this study was planned to evaluate the ADR profile and assess their causality, severity and preventability in patients receiving ATT alone and in combination with HAART.

MATERIALS AND METHODS: This was a 12-months prospective and observational study carried out in the department of TB & Chest and ART centre of a tertiary care hospital of western India. Total 300 patients were screened, which were divided into two groups: Group A included 240 patients on ATT alone and Group B included 60 patients who were taking ART+ATT. Demographic data as well as ADR profile was obtained using a data sheet and the suspected ADR reporting form. The obtained ADRs were assessed for causality, severity and preventability using various scales. The data was analysed using descriptive statistics and Chi-square test wherever applicable.

RESULTS: In Group A, 78 patients presented with a total of 123 ADRs and in the Group B 34 patients presented with 86 ADRs. Significantly higher number of ADRs in patients with ART+ATT regimen (57%) as compared to ATT alone (33%). Young adults (18-30 yrs) had more ADRs on ATT whereas middle aged group (30-50 yrs) had significantly more ADRs on ART+ATT regimen. Gastrointestinal ADRs were most common in both groups. ART+ATT regimen showed significantly more neurological & musculoskeletal ADRs as compared to ATT regimen. Loss of appetite was the most common ADR in TB patients, while headache & generalized weakness was the most common presentation in HIV with TB group. Out of 112 patients, 58 (52%) required a new drug for symptomatic treatment and 62 (55.35%) patients recovered from the ADR. In both the groups, majority of the ADRs were possible on causality assessment, mild on severity assessment and probably preventable on preventability assessment.

CONCLUSION: In conclusion, a combination of HAART and ATT resulted in increased number ADRs as compared to ATT alone. An effective integration of various national health programmes is needed for active management of ADRs in these patients.

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INTRODUCTION

World Health Organization (WHO) defines an Adverse Drug Reaction (ADR) 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 modifications of physiological function"*. Occurrence of ADR is an inevitable phenomenon. ADRs can occur even if all the steps of rational prescribing are followed accurately. So, no drug is completely safe. Pharmacovigilance deals with all the aspects of drug-related issues. It has gradually become a vital component in clinical practice, effective drug regulation systems and public health programs. Several studies have shown that 2 to 21% of patients need hospitalization due to various ADRs[1, 2], which are predictable in approximately 90% and preventable in at least 60% of cases[3]. Thus, ADRs are a major cause of morbidity and lead to a significant drain on the already limited healthcare resources[3]. ADR monitoring is the method of regularly monitoring unfavourable effects that may be due to the use of pharmacotherapy.

According to standard treatment guidelines by WHO, National AIDS Control Organization (NACO) and Revised National Tuberculosis Control Programme (RNTCP), combination of drugs is utilized for the treatment of both tuberculosis (TB) as well as acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV). But, unlike TB, AIDS is not completely curable but mostly its symptoms are manageable with medications. All the drugs used for the treatment of TB and HIV are associated with significant adverse effects of their own which eventually adds to the burden of disease and decreases patient compliance. Moreover, chronic nature of disease and use of multiple drugs for the treatment increases the chances of ADRs manifold. Usually most of the ADRs occur early in the course of treatment; though, some may develop after chronic treatment or even after stoppage of therapy. Thus, monitoring the adverse effects becomes an integral part of the treatment of these patients. TB is one of the most common co-morbid condition in HIV patients and is responsible for increased morbidity and mortality in People Living with HIV (PLHIV). The risk of developing TB is 21 times higher in PLHIV.[4] India has the 3rd highest–burden of HIV in the world, with an adult prevalence of 0.22%. Incidence rate of HIV-1 associated TB decreases by 80% when HAART was used in HIV infected patients[5]. Also, there was a significant reduction in mortality among patients with TB/HIV co-infection who were started on HAART[6]. But, combined administration of HAART and ATT increases the risk of cumulative ADRs and drug interactions which further complicates the treatment of TB/HIV co-infection[6]. Hence, co-administration of ATT along with HAART merits unique attention.

Even though there has been considerable development in the field of pharmacovigilance in our country, research and reporting outcomes are limited in this area. Pharmacovigilance as a science and specialty is slowly picking up in our country but research and reporting outcomes are limited. Hence, many ADRs tend to go unreported and a proportion of total burden of ADR cannot be recognized. 1st line antitubercular treatment (ATT) as well as 1st line antiretroviral treatment (ART) are prone to cause many ADRs but there is substantial lack of pharmacovigilance data on these drugs, hence they are considered to be a challenge to our national anti-TB and anti-HIV Programs[7]. These ADRs can influence patient compliance, which may lead to treatment failure and increase in the number of multidrug resistant cases. Various studies have been conducted in the past have documented ADR profile for various ATT[8, 9] and HAART[10, 11] regimens individually. But, there is limited data available on the ADR profiles of patients receiving both ATT and HAART. Thus, with the rising prevalence of TB/HIV co-infection, an analysis of ADR profile in such patients will allow us to reduce the morbidity by early detection and management of ADRs [7].

Therefore, in the present study the ADRs occurring in the patients on combination of ATT & HAART were also monitored along with patients on ATT alone and assessed for their causality, severity and preventability. This may help in recognizing and reducing preventable ADRs which will enhance the outcome of the treatment. Finally, it will guide the training and

education initiatives for improving the safe use of medicines.

MATERIALS & METHODS

This was a prospective, observational study carried out in the Tuberculosis & Chest OPD and ART Centre of a tertiary care teaching hospital for a duration of one year. The study was commenced after obtaining approval from the Human Research and Ethics Committee of the Institution. The following inclusion and exclusion criteria were set for the study:

Inclusion Criteria:

Following patients were included:

1. Adults over 18 years of age at the time of giving informed consent.
2. Patients diagnosed with TB and TB/HIV coinfection with or without other comorbid conditions having complaints of any Adverse Event.
3. Patients registered at TB/ART Center of the hospital.
4. Patients willing to give written informed consent.

Exclusion Criteria:

The following patients were excluded:

1. Patients below 18 years of age.
2. Patients with Psychiatric Illness (Neurosis/Psychosis/Coma) unable to give history.

Study procedure:

All the adult patients of either gender diagnosed with Tuberculosis infection by the TB and chest experts and receiving Anti-Tubercular Therapy were recruited for the study. Also, those patients diagnosed with an HIV infection and co-infection of Tuberculosis and receiving Highly Active Anti-Retroviral Therapy + Anti-Tubercular Therapy were also recruited for the study. Diagnosis of Tuberculosis and HIV were made either microbiologically or clinically or both (according to the standard treatment guidelines) by the treating physician at TB & ART Centre and these patients were taking regular treatment from the hospital or designated centres. The data was collected in a pre-designed, pre-approved patient data sheet either by directly interviewing the patient, or their attendants as well as from patients' case files maintained at the respective centres. A training session in Pharmacovigilance on how to fill the IPC Adverse Drug Reaction Reporting Form Version 1.3 was given to the attending doctors, nursing staff and technicians working at those areas to sensitize and motivate them for identification and reporting of ADRs.

The demographic details of the patient, relevant history and treatment details were duly recorded. ADRs were confirmed after consultation with the treating physician or after communication with the patient and were recorded in ADR Reporting Form. Relevant investigation details were also noted, if available. Patients were communicated for any newly developed ADR when they came for their regular follow up visits or by telecommunication. The documented ADRs were then assessed for causality, severity and preventability using following scales:

1. WHO-UMC Causality Assessment Scale
2. Naranjo's Algorithm for Causality Assessment
3. Modified Hartwig and Siegel Severity Assessment Scale
4. Modified Schumock and Thornton Preventability Assessment Scale

Data Analysis:

The data was entered and analysed using Microsoft Office Excel 2016. The results were expressed as numbers and percentages. $\chi 2$ value, degree of freedom d(f), Critical Value (CV) and P-value were calculated using Chi Square Test wherever applicable. P-value <0.05 was considered statistically significant.

RESULTS

A total of 300 patients were screened during this duration of 12 months. They were divided into 2 groups:

Group A: Tuberculosis patients who attended TB & Chest OPD Centre and were given Anti-Tubercular treatment (ATT) during the study duration.

Group B: HIV positive patients with Tuberculosis, who attended ART Centre and were given ATT in addition to HAART during the study duration.

During the study duration, 240 patients were enrolled in Group A and 60 were enrolled in Group B. Out of total 240 patients in group A, 151 (63%) were males and 89 (37%) were females; and in group B 38 (63%) were males and 22 (37%) were females.

Overall prevalence of ADR

Group A: Out of total 240 patients, 78 patients (33%) who developed ADR were included in the final evaluation and remaining 162 were excluded either due to absence of any ADR or due to lost to follow up / not contactable. Among the 78 patients with ADR, 43 (55%) were males and 35 (45%) were females.

Group B: Out of total 60 patients, 34 patients (57%) developed ADR and were included remaining 26 (43%) were excluded due to reasons mentioned above. Among the 34 patients with ADR, 21 (62%) were males and 13 (38%) were females.

The difference between the prevalence of ADR in the genders was not statistically significant (P = 0.514)

Age distribution of study participants

Out of the total 240 patients in group A, 125 (52%) were between 18-30 years of age group, 72 (30%) were between 30-50 years of age group and rest 43 (18%) were more than 50 years of age. Whereas in the group B, out of total 60 patients, 20 (33%) were between 18-30 years of age group, 33 (55%) were between 30-50 years of age group and rest 7 (12%) were more than 50 years of age. Hence, overall more patients were of age 18-30 years in ATT group whereas more in 30-50 years' age group in case of ART+ATT, which was highly significant statistically (P = 0.001).

Correlation of ADRs with respect to age shows that in the ATT only group, 38 (49%) were between 18-30 years of age group, 23 (29%) were between 30-50 years of age group and rest 17 (22%) were more than 50 years of age. While among the patients receiving HAART + ATT, 11 (32%) were between 18-30 years of age group, 19 (56%) were between 30-50 years of age group and rest 4 (12%) were more than 50 years of age. Hence, more patients (49%) presented with ADR were of age 18-30 years in ATT group whereas more (56%) in 30-50 years' age group in case of ART+ATT, which was highly significant statistically (P = 0.016)

Anti-Tubercular Treatment Regimen Distribution

Out of total 78 patients with ADR in Group A, 72 (92%) received Drug Sensitive TB Regimen (DSTB) whereas 6 (8%) received Drug Resistant TB regimen (DRTB) of Mfx^{h} Km^{IM} Eto Cfz Z H^{h} E ($Moxifloxacin^{h}$ + $Kanamycin^{IM}$ + Ethonamide + Clofazimine + Pyrazinamide + $Isoniazid^{h}$ + Ethambutol). Out of total 34 patients with ADR in Group B, all patients received DSTB Regimen. Regarding the HAART regimen in group B, majority 23 (68%) were receiving ART Regimen of TDF+3TC+EFV (Tenofovir + Lamivudine + Efavirenz) followed by 5 (15%) receiving ZDV+3TC+EFV (Zidovudine + Lamivudine + Efavirenz), 4 (12%) receiving TDF+3TC+ATV/r and 2 (6%) patients receiving ABC+3TC+LPV/r

ADR Distribution

The highest number of ADRs in both groups were from Gastrointestinal System (62%, 41%) followed by Nervous System (15%, 22%). Table 1 gives the distribution of ADRs in both the groups.

Table 1. Distribution of ADRs in Group A (n = 78) and Group B (n = 34)

ADRs related to Organ System	Pt on ATT		Pt on ART+ATT	
	Number	Percentage	Number	Percentage
Gastrointestinal	**76**	**62%**	**35**	**41%**
Gastritis	7	6%	1	1%
Epigastric Pain	11	9%	5	6%
Loss of Appetite	12	10%	7	8%

Nausea	6	5%	8	9%
Vomiting	11	9%	8	9%
Glossitis	1	1%	2	2%
Diarrhoea	3	2%	2	2%
Constipation	1	1%	0	0%
Altered Taste Sens.	0	0%	1	1%
Oral Candidiasis	0	0%	1	1%
Dyspepsia	6	5%	0	0%
Epigast. Discomfort	8	7%	0	0%
Indigestion	7	6%	0	0%
Abdominal Pain	3	2%	0	0%
Neurological	**18**	**15%**	**19**	**22%**
Headache	5	4%	9	10%
Insomnia	2	2%	4	5%
Dizziness	5	4%	3	3%
Sedation	0	0%	1	1%
Tingling & Numbness	0	0%	1	1%
Mood Changes	0	0%	1	1%
Vertigo	4	3%	0	0%
Altered Behavior	1	1%	0	0%
Anxiety	1	1%	0	0%
Hematological	**4**	**3%**	**5**	**6%**
Anemia	4	3%	5	6%
Musculoskeletal	**8**	**7%**	**11**	**13%**
Gen. Weakness	2	2%	9	10%
Back Pain	2	2%	1	1%
Joint Pain	0	0%	1	1%
Myalgia	4	3%	0	0%
Cutaneous	**5**	**4%**	**7**	**8%**
Rash	4	3%	5	6%
Urticaria	1	1%	2	2%
Hepatotoxicity	**3**	**2%**	**6**	**7%**
Altered LFT	3	2%	2	2%
Jaundice	0	0%	1	1%
Dark Urine	0	0%	3	3%
Miscellaneous	**9**	**7%**	**3**	**3%**
Fever	5	4%	0	0%
Weight Loss	4	3%	2	2%
Menstrual Changes	0	0%	1	1%
Total	**123**	**100%**	**86**	**100%**
χ^2: 5.830; d(f): 6; CV: 12.592; p-Value: 0.016 (HS)				

A total of 123 ADRs were observed in group A, out of which 76 (62%) involved GIT, 18 (15%) involved CNS and 3 (2%) ADRs were of hepatotoxicity. In group B, 86 ADRs were observed, maximum ADRs were involving GIT 35 (41%) followed by 19 (22%) involving CNS. Hence, maximum number of ADRs involved GIT followed by CNS in both groups which was highly statistically significant (P = 0.016)

Management of ADRs

Out of 112 patients with ADRs, majority 58 (52%) required a new drug for symptomatic treatment followed by 31 (28%) in whom the drug had to be withdrawn. 23 (21%) patients needed no intervention to manage their ADRs. Figure 1 gives the management of ADRs in both the groups.

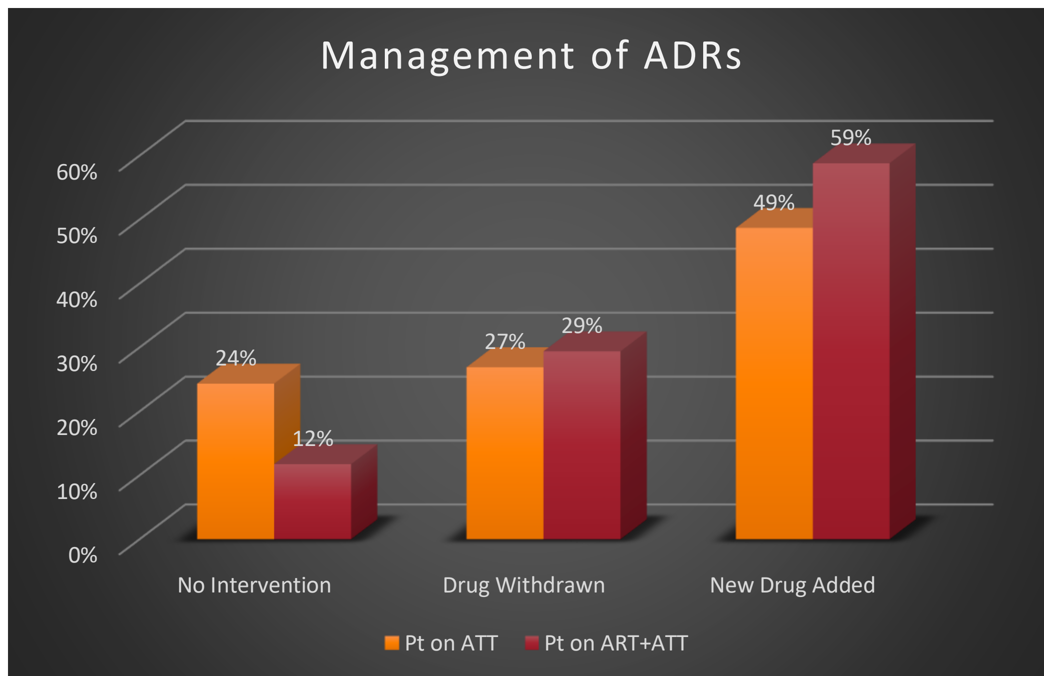

Figure 1. Management of ADRs (n = 112)

Outcome of ADRs

Majority 62 (55%) patients recovered fully from the ADR during our study period, while 50 (45%) were found to be recovering. There were no fatalities due to ADRs. Figure 2 gives the outcome of ADRs in individual groups.

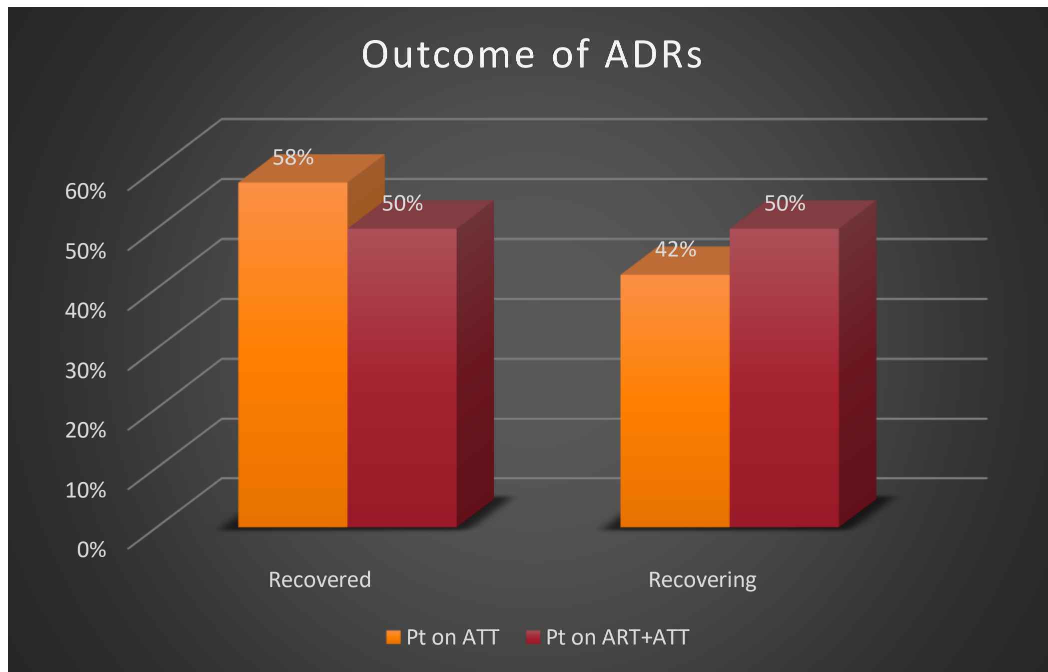

Figure 2. Outcome of ADRs (n = 112)

Causality assessment of ADR

According to WHO-UMC Causality Assessment Scale 31 (28%) out of the total 112 ADR were probable and 81 (72%) were possible. Also, causality assessment by Naranjo's Algorithm showed that 19 (17%) were probable whereas 93 (83%) were possible. Hence, both the scales consistently placed majority of ADRs under 'possible' category. Table 2 gives the causality assessment of ADRs using both the scales in the individual groups.

Table 2. Causality Assessment of ADRs

	Patients on ATT		Patients on ART+ATT	
	Number	Percentage	Number	Percentage
WHO-UMC				
Certain	0	0%	0	0%
Probable	21	27%	10	29%
Possible	57	73%	24	71%
Unlikely	0	0%	0	0%
Total	78	100%	34	100%
Naranjo				
Definite	0	0%	0	0%
Probable	14	18%	5	15%
Possible	64	82%	29	85%
Doubtful	0	0%	0	0%
Total	78	100%	34	100%

Severity assessment scale

Severity Assessment by Modified Hartwig and Seigel Scale showed that out of 112, 43 (38%) ADRs were mild, 69 (62%) were moderate and none were severe. Table 3 gives the severity assessment in individual groups.

Table 3. Modified Hartwig and Seigel Severity Assessment Scale

Severity	Patients on ATT		Patients on ART+ATT	
	Number	Percentage	Number	Percentage
Mild	32	41%	11	32%
Moderate	46	59%	23	68%
Severe	0	0%	0	0%
Total	78	100%	34	100%

Preventability Assessment

Preventability Assessment by Modified Schumock & Thornton Scale showed that out of the total 112 ADRs, 55 (49%) ADRs were probably preventable followed by 33 (29%) definitely preventable and 24 (22%) not preventable ADRs. Table 5 gives the severity assessment in individual groups.

Table 4. Modified Schumock & Thornton Preventability Assessment Scale

Preventability	Patients on ATT		Patients on ART+ATT	
	Number	Percentage	Number	Percentage
Definitely Preventable	26	33%	7	21%
Probably Preventable	38	49%	17	50%
Not Preventable	14	18%	10	29%
Total	78	100%	34	100%

DISCUSSION

A 12 months' prospective, observational study was conducted in patients taking ATT alone or a combination of ART+ATT and being registered at either TB or ART Centre of a tertiary care teaching hospital for a duration of one year for monitoring the occurrence of ADRs. Total 300 patients were screened from which 112 (37%) patients developed ADRs and were included in the ADR analysis whereas remaining 188 either didn't develop any ADRs or were lost to follow up. This high incidence of ADRs was comparable to various other studies[7, 12-14].

It was observed that in both the regimen, the chances of developing an ADR was highest in the initial one month of starting the therapy. This is usually due to an intrinsic intolerance to the drug rather than chronic accumulation leading to the toxicity of the drug.[15] Thus, it is essential to closely monitor the patients during this period to prevent severe ADRs and increase patient compliance. Also, it will help in guiding the choice for medications to be included in the ATT and HAART regimens.

ADRs & DEMOGRAPHY:

It was found that, among the patients receiving ATT, ADRs were maximum in the age group of 18-30 years which was similar to the findings of Chhetri et al.[16] and dissimilar to the findings of studies by Shamiya Sadiq et al.[7] which reported highest incidence of ADRs in the age group of 30-50 years. Among the ATT + HAART, most of the patients belonged to >30-50 years (55%) age group. This was similar to the study by Bahl et al. which reported 75% of the patients in 21-40 years age group[17]. The prevalence of ADRs was more in males in the present study which was in accordance to previous studies[7, 18]. This could be due to altered drug metabolism due to differences in body mass index and hormonal patterns between male and female. Also, it was found in this study that ADRs were more prevalent in the weight range of 35-50 kgs. for both groups, which is comparable to results seen with Shamiya Sadiq et al.[7].

In the study, higher percentage (57%) of ADRs were reported in TB/HIV co-infected patients as compared to ATT alone (33%). This was comparable to the study by Dean et al. which

reported ADRs in 54%[19]. Among the HAART, more ADRs were observed in lamivudine, tenofovir and efavirenz containing regimen (68%) as compared to lamivudine, zidovudine and efavirenz containing regimen as reported by Sharma et al.[20] and Shamiya Sadiq et al.[7]

ADRs & ORGAN SYSTEM INVOLVEMENT:

In the present study, the most common organ system involved in the ATT treatment group was reported to be GIT (62%) with loss of appetite as the most common ADR reported. This was similar to the findings of Tak et al.[21] and Shamiya Sadiq et al.[7] GIT was followed by the involvement of central nervous system in 15% of patients with dizziness (4%) as the most common adverse effect. Similar findings were reported by Chhetri et al.[16], who also reported 14.28% CNS ADR, of which dizziness comprised of 4.76% events. All the first line ATT drugs except Streptomycin were most likely cause of dizziness similar to observations of Ramanath et al.(103) Hematological system comprised 3% ADRs of anemia. This was in accordance with the observations made by Shamia Sadiq et al.[7] 2% ADRs of altered LFTs were reported in our study which is comparable to 2.70% reported by Shamia Sadiq et al.[7] In the group B with patients on both ATT + ART also, GIT was the most frequently involved system comprising mainly of nausea, vomiting followed by loss of appetite and epigastric pain similar to the findings of Cesar et al.[22] and Shamiya Sadiq et al.[7] The second most commonly involved system was CNS involving headache and insomnia, followed by dizziness. Efavirenz was suspected to cause CNS toxicity. This is consistent with the findings reported by Berenguer et al.(118) In the ART regimen containing Zidovudine, anemia was the most common ADR reported in accordance with findings reported by Sharma et al.[20]

ADR MANAGEMENT AND OUTCOME

In the group A, majority of the reported ADRs were of moderate severity (59%). It was observed that majority patients recovered (58%) from ADR. Also, majority of ADRs did not require discontinuation of ATT regimen. In about 49% cases, symptomatic therapy was advocated for the ADR which is similar to findings of Shamiya Sadiq et al.[7] Similarly, a study conducted by Chhetri et al., reported majority of the ADRs (93.33%) to be mild which did not need any treatment changes[16]. Also, Tak et. al. reported full recovery in the majority of patients without any complications and mortality.[21]

In the group B, majority (68%) of the ADRs were of moderate severity. Recovery was reported in 50% of all the patients with ADRs. About 59% of the ADRs required symptomatic treatment. Withdrawal of the suspected drug was reported in 40% cases similar to study findings of Issakidis et al.[23]

ADR & CAUSALITY ASSESSMENT:

In our study, majority of ADE were assessed to be ‘possible’ (71%, 85%) and ‘probable’ (29%, 15%) by the WHO-UMC and Naranjo Probability Scale respectively. In accordance to our reports, Chhetri et al. also reported majority of the ADRs as ‘possible’ as per Naranjo’s algorithm[16]. A study by Anwikar et al. also reported that majority of the ADRs (96.49%) were possible and 3.50% were probable as assessed by WHO-UMC scale.[24]

Overall, a comparative analysis of two groups revealed that prevalence of ADE was more in TB/HIV co-infection as compared to TB alone. This can be due to multiple drug regimens leading to more ADRs, drug interactions, high tablet load etc. which needs to be assessed by further studies.

The study had a few potential limitations. The most important being, no regular follow up of patients was done. They were interviewed when they spontaneously came to the OPD for their next visit. Moreover, due to the COVID-19 pandemic and nationwide lockdown, there were decreased number of patients for a duration of 2 to 3 months in the study period. Hence, the sample size was not large enough to reach adequate statistical significance for the general population. Also, due to the spontaneous reporting of ADR, the true magnitude of the problem is difficult to gauge.

CONCLUSION

In conclusion, it can be said that the number of ADRs increase with the concomitant administration of both ART and ATT regimens, as compared to ATT alone. Though the ADR are

mostly preventable and mild in nature, they can still affect the patient compliance. A careful monitoring of ADRs in patients on multidrug therapy is an effective way to prevent the development of ADRs and their early management. On the basis of the study results, it is evident that there is a need for integration and collaboration of Revised National Tuberculosis Control Programme, National AIDS Control Programme, and Pharmacovigilance program of India to enhance drug safety in the patients taking ATT alone or in combination with ART.

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