

# “Side effects-part of the package” – A mixed methods approach to adverse events among patients with DR-TB under RNTCP Gujarat, India

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## Research article

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# Abstract

**Background:** Unsuccessful treatment outcomes among patients with drug resistant tuberculosis (DR-TB) are due to high rates of adverse events (AEs). However, information related to AEs is not systematically collected and managed under programmatic setting. The present study assessed the a) incidence and pattern of adverse events in first three months of DR-TB treatment initiation; b) treatment seeking behaviour for AE management; and c) explore the challenges in seeking treatment and reporting AEs. **Methods:** This mixed methods study included all patients diagnosed and initiated on treatment under RNTCP during July-September 2018 at Ahmedabad DR-TB centre. The patients were interviewed telephonically and assessed for all AEs experienced by them. In-depth interviews and key-informant interviews were conducted among patients, DOTS supervisors and programme staffs (treatment supervisors, medical officer and district program manager). **Results:** A total 207 AEs were reported by the 74 DR-TB patients. All patients experienced at least one AE during initial treatment period. Incidence rate of AEs (experienced) was 3.11 (1st month-4.6, 2nd month-2.7, 3rd month-2.02) per 100 person days. Of the 207 AEs, gastro-intestinal (59, 28.3%), ophthalmic (32, 15.4%) and otolaryngology (25, 11.9%) system related AEs were commonly experienced. Treatment was not sought in two-fifths of the AEs. Themes and subthemes related to challenges in treatment seeking or reporting of AEs were 1) Patient related- Misconceptions, accessibility and affordability of management, lack of counselling support, stigma and discrimination, and past treatment experience; 2) Health system related- lack of guideline and training for AE management, and poor coordination between hospital and tuberculosis centre. **Conclusion:** The incidence of AEs was high among patients with DR-TB in the first three months of treatment and treatment seeking/reporting was low. Adequate health education and counselling of the patient and orientation of the health systems are the need of the hour. An efficient real-time reporting and management of AE can be developed and tested for effective DR-TB control. **Keywords:** Adverse event, Drug resistant tuberculosis, Operational research, Incidence, India, Treatment seeking.

## Background

Tuberculosis (TB) is the leading infectious cause of death and still continues to be a major public health problem. The emerging issue of Drug-resistant Tuberculosis (DR-TB) due to inappropriate treatment regimens, poor quality drugs and inadequate intake of first-line Anti-TB drugs has worsened the situation; making its management quite a challenge (1). Globally, an estimated 558 000 people with TB were resistant to the most effective first-line drug i.e., rifampicin (RR-TB), and of these, 82% had multidrug-resistant TB (MDR-TB) in 2017. Similarly, an estimated 3.5% of new cases and 18% of previously treated cases had MDR/RR-TB globally and India shares nearly one fourth of the estimated cases (2).

India, a high burden DR-TB country has rolled out the programmatic management of drug resistant TB (PMDT) in 2007 and covered all parts of the country by 2013 (3). Over a period, the country implemented the World Health Organization's (WHO) ambulatory care model and changed from criteria-based drug sensitivity testing (DST) to universal DST to detect and treat the DR-TB to address the DR-TB burden. Now, patients with DR-TB are treated with various DR-TB regimens and shorter DR-TB regimen (based on

Bedaquiline and Delamanid) has also been introduced under expanded access in the country. This is due to low successful treatment outcomes (47%) with the conventional regime and vice versa with the shorter regime (4).

Higher proportion of patients with DR-TB are encountering adverse events (AEs) due to long duration of treatment, use of second line anti-tuberculosis drugs, multi-drug use, long duration of injections and other patient related characteristics (5). It was reported that 20-100% of patients with DR-TB had undergone at least one AE involving gastro-intestinal tract, hepato-biliary, neurological, oto-vestibular, eye, musculoskeletal and other systems; with symptoms ranging from mild to severe and some serious adverse reactions (6–9). However, anecdotal evidence has shown that the reporting of AEs by patients is low; which can end up in severe AEs and impact treatment outcome. Studies have reported the association of AEs with poor medication adherence and unsuccessful treatment outcomes like loss to follow up, treatment failure and death (10,11).

There is a large variation observed between studies reporting the number of events and proportions of DR-TB patients with AEs, as most of the studies relied on medical record data abstraction (8–10,12–15). This could be an underestimation; especially in the context of developing countries like India, where the primary importance is given on diagnosis and initiation of treatment rather than identification, management and reporting of all AEs by the health systems and poor treatment seeking behavior of patients. Such low reporting of AEs experienced by patients with the health systems further remains unmanaged.

As there is limited information available on the exact burden of AEs experienced by the patients with DR-TB in Indian context, we assessed the incidence and pattern of AEs experienced by patients with DR-TB, their health seeking behavior and factors associated with non-reporting of AEs under programmatic setting.

## Methods

### Study Design

A mixed methods study (sequential explanatory design) with quantitative-retrospective cohort study through record review and patient interviews and qualitative-descriptive design was used. The qualitative findings were used to supplement the quantitative data.

### Study setting

#### *General setting:*

The study was conducted in Ahmedabad district of Gujarat state, India. There are 34 DR district tuberculosis centers (DTC) in the state which have notified 2266 DR-TB cases in the year 2018 (16). Treatment success rate for patients with DR-TB was reported to be 43% and loss to follow up was 15% in the year 2017. The Ahmedabad district (including Ahmedabad municipal area and rural area) has a

population of 7,045,314 including 5,633,927 population of Ahmedabad city, which makes it the most populous city in Gujarat and the fifth most populous in India (16,17).

**Ahmedabad DR-TB center:** The DR-TB Centre in Ahmedabad is situated in State TB demonstration and training centre (STDC), Civil Hospital campus, Ahmedabad. The state nodal DR-TC and Intermediate state reference laboratory is also situated within the campus. It has facility for solid culture and drug susceptibility testing (DST), liquid culture and DST and Line probe Assay (LPA) and Cartridge Based Nucleic Acid Amplification Test (CBNAAT). Patients diagnosed with DR-TB are put on conventional treatment regimen, Universal drug sensitivity guided treatment regimen and Bedaquiline containing treatment regimen. There is a TB and Chest ward which is attached with the centre with advanced treatment facilities (16).

### **Study site:**

DR TB Centre attached to tertiary care hospital in Central Gujarat.

### **Study population:**

For quantitative study, all patients initiated on DR-TB treatment between 1<sup>st</sup> July to 30<sup>th</sup> September 2018 and having completed the first three months of treatment under the Revised National Tuberculosis Control Program (RNTCP) at the DR-TB Center, Ahmedabad, Gujarat were included in the study. Interviews were conducted in the fourth month of their treatment. Those patients who were 'loss to follow up' were also included irrespective of 'treatment taken' duration. Those patients a) who did not consent for the interviews; b) transferred out to other district DR-TB center and c) on Bedaquiline regimen were excluded.

For the qualitative component, in-depth interview (IDI) was conducted among conveniently selected patients and DOTS providers. Key-informant interview (KII) was conducted among medical officers, DR-TB supervisor and district programme managers.

### **Data collection and analysis**

A list of patients with DR-TB, who were diagnosed and/or initiated on treatment during 1<sup>st</sup> July 2018 to 30<sup>th</sup> September 2018 were obtained from DR-TB center. Further, relevant information like name, address, and contact number, date of initiation of treatment, drug resistance status, name of designated DOTS provider and Senior TB supervisor and data on AEs were abstracted from treatment cards. The patients

were telephonically interviewed once at end of third month of treatment initiation for AEs experienced by them month wise in the last three months using a semi-structured questionnaire. The details collected during the interview were noted down using electronic data collection tool (KoBo Collect v1.14) (19). If any AE was experienced by them in past three months, details like the month of AE occurrence, classification of system involved (including the symptoms) as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-ICH classification (20) with expert recommendation which has been used in various studies (5,21); and whether treatment was sought for the reported AE were noted. Socio-demographic characteristics like age, gender, residence (urban/rural), occupation, education and clinical characteristics like co-morbidities (HIV, Diabetes mellitus and other chronic conditions) and addiction (tobacco and alcohol), previous TB history were collected. The information related to healthcare provider from whom patient is taking daily injections (Auxiliary nurse midwife/qualified Private practitioner / unqualified private practitioner/ primary health centre-medical officer/other) was also obtained.

The data extracted through record review were entered in the excel. The data collected through the electronic data capture tool was downloaded, merged with extracted data in excel and exported to EpiData version 2.2.2.182 for analysis (EpiData Association, Odense, Denmark). Incidence of AEs has been reported as 100 person days month wise and for total duration of three months of initial treatment. Number and proportion were calculated for gender, occupation, residence, per capita income, characteristics of the patients like HIV status, DM status, addiction (tobacco, alcohol), past history of TB, patients with DR-TB on treatment experienced AE, pattern of AEs, AEs reported and its pattern, type of healthcare facility and healthcare providers contacted for management of AEs. Age was reported in mean (Standard deviation). A p-value of 0.05 was considered statistically significant. The findings have been reported using strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (22).

### ***For qualitative data***

The principal investigator, trained and experienced in qualitative research methods conducted IDIs among patients after consent during their quantitative interview, using an interview guide. The interview explored the views and experiences of the patients related to DR-TB treatment and AEs. Similarly, this also explored their treatment seeking behavior and “emic” view (patient perspective) on facilitators and barriers of seeking medical assistance from healthcare providers. IDIs and KII were also conducted among purposively selected health care providers using interview guide in local language and each interview lasted for nearly 15-20 minutes. Verbatim notes were taken during the interview. Transcripts were made on the same day of the IDI based on the verbatim notes by co-field investigator. The transcripts obtained were compiled and the PI read the transcripts to become familiar with the data. Manual descriptive content analysis was used to analyze the transcripts. It was reviewed by a second investigator (KS) to reduce bias and interpretive credibility. The decision on coding rules and theme

generation were done by using standard procedures and in consensus (23). Any difference between the two were resolved by discussion. The findings have been reported by using 'Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines (24).

**Ethical Issues:** Ethical approval was obtained from the Institutional Ethics Committee of the B. J. Medical College, Ahmedabad, India, and the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease, Paris, France. A verbal informed consent was obtained from the patients and the stakeholders for interviews and confidentiality has been maintained.

## Results

### Quantitative

During July-September 2018, a total of 74 eligible patients were interviewed among 128 patients registered and put on treatment at the study site (Figure 1). The mean (SD) age of participants was 32.4 ( $\pm$ 13.6) years. Of the 74 patients, 44 (59.5%) were male; 46 (62.2%) were educated up to secondary school; 54 (73%) belonged to below poverty line; 60 (81.1%) were residing in urban area; and 64 (86.5%) had tuberculosis in the past. The socio-demographic, behavioral and clinical characteristics of the participants are given in table 1. A total of 22 (29.7%) patients were tobacco users (either smokeless or smoking) and 24 (32.4%) reported presence of at least one comorbidity.

All 74 patients experienced at least one adverse event during the first three months of treatment and a total of 207 events were reported. The incidence rate of AEs (per 100 person days) during the study period was 3.11 (4.6, 2.7 and 2.02 for the first, second and third month from initiation of treatment respectively). System wise AEs have been described in figure 1. AEs related to gastro-intestinal, ophthalmic and otolaryngology were the commonly experienced among 59 (28.3%), 32 (15.4%) and 25 (11.9%) times respectively among patients. The pattern and month wise distribution of AEs is depicted in figure 2.

Of the 207 AEs experienced by patients, treatment was sought for 124 (61.7%) AEs (Figure 1). Patients were categorized as 'having sought treatment' if they reported more than 50% of experienced AEs, 'not having sought treatment' if they reported less than 50% of experienced AEs. None of the patient characteristics were significantly associated with the patient not seeking treatment (Table 2).

### Qualitative:-

To further explore the factors for low treatment seeking or reporting of AEs and to identify challenges from patient's and health care provider's perspective, exploratory qualitative interview was carried out with patients and health care providers. Twenty patients with DR-TB (14 male and six female) and eight DOTS providers (six Urban, two Rural), two medical officers and two DOTS plus supervisors and senior TB

treatment supervisors (one from rural and urban each) and two programme managers at district tuberculosis centre were interviewed.

The perceptions regarding adverse events in DR-TB treatment and treatment seeking behaviour for AE management from patients and health care provider perspective were coded under 12 codes organised into four categories. These four categories were grouped into two broad themes a) Health system related challenges and b) Patient-related challenges and listed in table 3.

## Discussion

The present study highlights adverse events (AEs) among patients with DR-TB, one of the most important factors associated with drug adherence in DR-TB (25–27). All 74 patients experienced at least one AE during the three months of treatment duration; GIT, ophthalmology and otolaryngology organ systems were most commonly involved. The incidence rate of AEs (per 100 person days) during the study period was 3.11 (4.6, 2.7 and 2.02 for the first, second and third month from initiation of treatment respectively).

Findings of our study are relevant and novel for a country like India where rate of MDR and LTFU is very high (2). Several studies have been conducted on AEs during DR-TB treatment till date which were mainly record-based, but discordance between AEs experienced by patients and reported in clinical records have been reported by various studies for TB as well as other diseases (28–32). To our best knowledge, the present study is the first to assess comprehensively the incidence and pattern of AEs experienced among patients with DR-TB using a patient centered approach, treatment seeking behavior for its management and factors associated with treatment seeking. Mixed methods design of the study is an additional strength of our study which explored the challenges in seeking treatment for AEs and reporting the same from both the patients and treatment providers perspective.

The findings related to pattern of AEs are consistent with previous studies (14,15,25,33). Our study reported higher incidence of AEs compared to other studies conducted in India. This could be due to direct reporting of AEs by the patients rather extraction from records which might have missed events (9,10,34). However, patients have tendency to overreport side effects on being interviewed and this may have contributed to higher incidence.

Higher proportion of AEs occurring in the first month of treatment in this study is in congruence with the pharmacological assumption of increased AEs in the first few months and days of treatment initiation (35). In studies done elsewhere in India and globally, higher proportion of AEs were reported in later months of treatment initiation. The likely reason could be a reporting bias as record based studies might miss the AEs in initial months either by the patients or by health systems.

In our study for two fifths of AEs, patients did not contact any health care providers (HCP) for treatment and thus remained unreported in program records. Missed and/or unreported AEs hamper the

pharmacovigilance system recommended by WHO (36), which focuses on management and prevention of AEs in tuberculosis. Delayed or nonreporting of AEs to health care facility can miss a serious AEs and this can further lead to LTFU or permanent disabilities or death (37). Regular follow up of patients and an enquiry into AEs, its reporting by HCPs and counsellors may improve reporting and management.

None of the demographic, clinical and behavioural characteristics were associated with treatment seeking behaviour. However, qualitative finding reflected various factors like misconceptions for AEs and its management, accessibility and affordability of management, lack of counselling support, past treatment experience being responsible for not seeking care. Furthermore knowledge regarding adverse events and importance of identification and early management was found to be low not only in patients but also in health care providers and these findings are consistent with other studies (38–40). Misconception regarding tuberculosis and adverse events were evident among health care providers similar to studies conducted in Gujarat and India (39,41,42). Affordability and accessibility of higher centre for diagnosis and treatment also plays an essential role in reporting and seeking care as most of the patients belong to lower socio-economic status or lose their job due to TB (43). Trainings and specific guidelines for identification, management and proper referral for further treatment was the felt need of the HCPs.

Our study is not without limitations. The information obtained regarding AE episodes were subjective and not cross-verified with any clinical evidence. However, it has been quoted that self-reported history by patients is the best source to capture any clinical event including AEs (44). We understand the possibility of recall bias in our study which could be low due to a) interview was done by an doctor; and b) systematic application of questionnaire and probing. Interpretation of the study findings needs caution as it studied small sample size and single DR TB centre. However, experience of AEs in all patients and low reporting reflects the ground situation which warrants further multicentric studies. In addition, the data is important in the local context in terms of identifying the training needs and counseling approach. Absence of visual clues and probing due to telephonic conversation could have compromised rapport and resulting under/over reporting of AEs is another limitation of our study. However, telephonic conversation provided a better platform to discuss sensitive topics and allowed the health care providers to respond to the programmatic challenges without hesitations.

Present study emphasizes on missed adverse events by the health systems. This may guide policy makers to sensitize and train all health care providers under RNTCP for AE and effective management. Counselling of patients at the time of initiation of treatment, and regular visit and systematic reporting of AE can be included in the treatment approach. Objective and real time assessment of AEs can be planned for further practice change. The pathway of care for AE can be studied to improve the understanding of treatment seeking behavior of the patients before establishing any independent AE management system in the program.

## Conclusions

The incidence of AEs was high among patients with DR-TB in the first three months of treatment and treatment seeking/reporting was low. Adequate health education and counselling of the patient and orientation of the health systems are need of the hour. An efficient real-time reporting and management of AE can be developed and tested for effective DR-TB control.

## **Declarations**

### **Ethics approval and consent to participate**

Ethics approval obtained from the Institutional Ethics Committee of the B. J. Medical College, Ahmedabad, India, and the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease, Paris, France and informed verbal consent was obtained from all participants.

### **Consent for publication**

Not applicable

### **Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

AJ, KSS, SK KM, AP, DK made substantial contributions to conception and design of the project. AJ, KSS, SK, KM, AP, DK, RS, made substantial contributions to the acquisition of data and analysis and interpretation of data. All authors were involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agrees to be accountable for all aspects of the work.

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## Tables

**Table:-1** Socio-demographic, behavioral and clinical characteristics of patients with DR-TB initiated on treatment under the RNTCP at DR-TB Center, Gujarat(July-September-2018)

Characteristics		N=74	(%)
Mean (SD) age in years		32.4 ( $\pm$ 13.6)	
Gender	Male	44	(59.5)
	Female	30	(40.5)
Education	Illiterate	13	(17.6)
	Up to secondary school	46	(62.2)
	Above secondary school	15	(20.2)
Occupation	Home-maker	05	(06.7)
	Unemployed	15	(20.0)
	Employed	54	(73.3)
Area of residence	Rural	14	(18.9)
	Urban	60	(81.1)
Socio-Economic Status	Above Poverty Line	17	(23.0)
	Below Poverty Line	54	(73.0)
	Not known	03	(04.0)
Addiction	No addiction	55	(74.3)
	Tobacco chewing	13	(17.6)
	Smoking	09	(12.2)
	Alcohol	05	(06.8)
	Refused	03	(04.1)
Co-morbidities	None	50	(67.6)
	Renal disease	12	(16.3)
	Cardiovascular system	10	(13.5)
	Diabetes	8	(10.8)
	HIV	6	(8.1)
	Liver disease	04	(05.4)
	Others <sup>a</sup>	04	(05.4)
Previous TB	Yes	64	(86.5)
	No	10	(13.5)
Drug resistant	Mono Isoniazid	24	(32.4)
	Multi Drug	50	(67.6)
Health care facility opted for injectables	Public healthcare	32	(43.2)
	Private health care	32	(43.2)
	Non-injectable regimen	10	(13.6)

<sup>a</sup> Hypothyroidism (2) and Paraplegia (2)

**Table:-2** Socio-demographic, behavioral and clinical characteristics associated with treatment seeking behavior for Adverse events by patients initiated on DR-TB treatment under the RNTCP at DR-TB Center, Gujarat(July-September-2018)

Characteristic	Treatment sought		Treatment not sought		Total n (%)	p value
	n	(%)	n	(%)		
Total	43		31		74	
<b>Sex</b>						
Male	26	(59.1)	18	(40.9)	44 (59.5)	0.83
Female	17	(56.7)	13	(43.3)	30 (40.5)	
<b>Education</b>						
Illiterate	12	(92.3)	1	(7.7)	13 (17.6)	0.06 <sup>a</sup>
Up to secondary	24	(52.2)	22	(47.8)	46 (62.2)	
> Secondary	7	(46.7)	8	(53.3)	15 (20.2)	
<b>Occupation</b>						
Home-maker	3	(60.0)	2	(40.0)	5 (6.7)	0.91 <sup>a</sup>
Unemployed	8	(53.3)	7	(46.7)	15 (20.0)	
Employed	32	(59.3)	22	(40.7)	54 (73.3)	
<b>Residence</b>						
Rural	9	(64.3)	5	(35.7)	14 (18.9)	0.82
Urban	34	(56.7)	26	(43.3)	60 (81.1)	
<b>Socio Economic Status</b>						
Above poverty line	9	(52.9)	8	(47.1)	17 (23.0)	0.94 <sup>a</sup>
Below poverty line	32	(59.3)	22	(40.7)	54 (73.0)	
Not known	2	(66.7)	1	(33.3)	3 (4.0)	
<b>Drug resistant</b>						
Mono Isoniazid	15	(62.5)	9	(37.5)	24 (32.4)	0.76
Multidrug resistant	28	(56.0)	22	(44.0)	50 (67.6)	
<b>Past history of TB</b>						
Yes	38	(59.4)	26	(40.6)	64 (86.5)	0.57
No	5	(50.0)	5	(50.0)	10 (13.5)	
<b>Co-morbidities</b>						
Present	11	(45.8)	13	(54.2)	24 (32.4)	0.40
Absent	32	(64.0)	18	(36.0)	50 (67.6)	
<b>Addiction</b>						
Yes	11	(57.9)	8	(42.1)	19 (25.7)	0.87
No	32	(58.2)	23	(41.8)	55 (74.3)	
<b>Healthcare facility opted for injectable treatment</b>						
Public healthcare	15	(46.9)	17	(53.1)	32 (43.2)	0.67
Private health care	23	(71.9)	9	(28.1)	32 (43.2)	
Not Applicable	5	(50.0)	5	(50.0)	10 (13.6)	

# derived by applying chi-square test with Yate's correction}

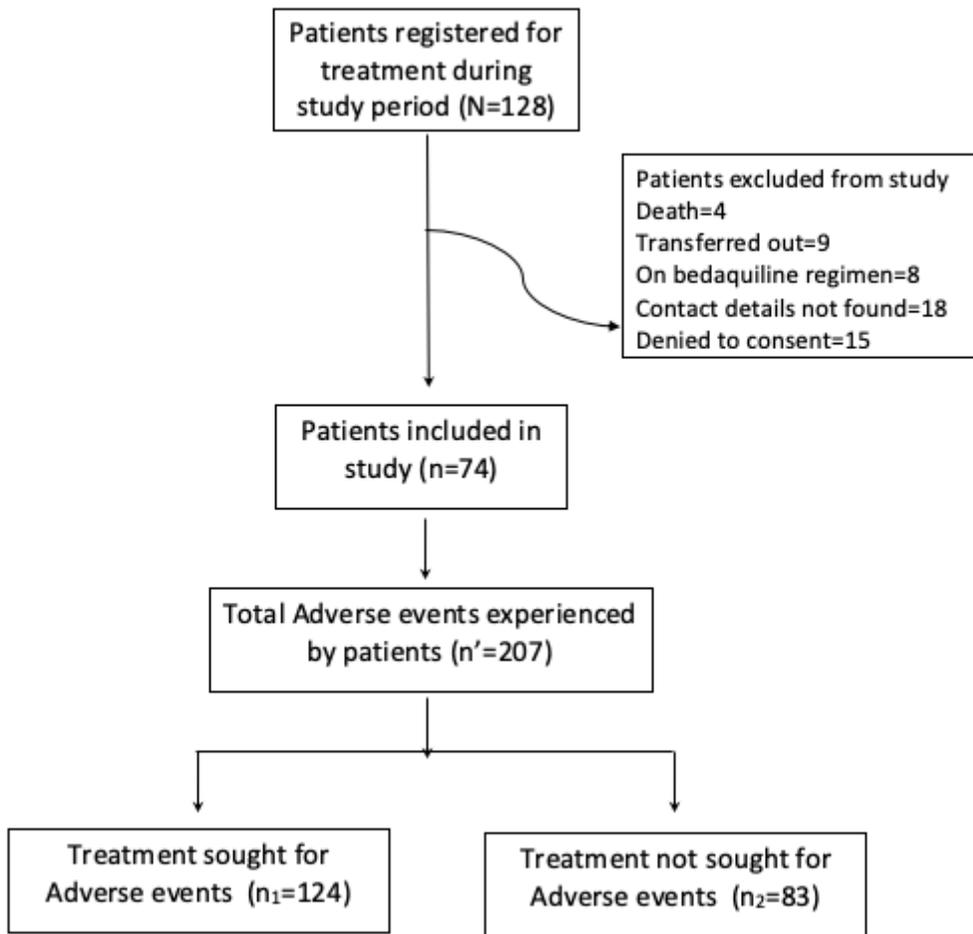
**Table 3. Perception and challenges regarding reporting of adverse events related to DR-TB treatment from the health providers' and patient's perspective.**

Themes	Sub-theme	Verbatim quotes
<b>Health system related</b>		
Provider related	Acceptance and neglect of the AEs	<p><i>"Side effects, which will be definitely there, as it is MDR TB, I counselled (my)best to the patients to continue the drug as they will be get used to side effects eventually"(36 male, STS, Rural)</i></p> <p><i>"There is no other treatment regimen available free of cost, patients have to complete course or have to die with TB." (28 Male, DOTS provider, Urban)</i></p>
	Stigma and discrimination towards patients	<p><i>"They are defaulters, they always complain more and adhere less to prescribed medicines" (39, Male DOTS provider, Urban)</i></p> <p><i>"When I visited the eye department in district hospital, the nurse asked me to maintain distance from other patients as she realized I am a TB patient." (44, male patient Urban)</i></p> <p><i>"I always ask them to contact medical facility, but defaulters have tendency to no believe in what we say..." (42, Male DOTS provider)</i></p>
Health care facility related	Poor capacity and no Standard Operating Procedures	<p><i>"Whenever, we asked for help regarding side effects, he (DOTS provider) directly refers me to district hospital which is far and not worth attending, they take lots of time and send me from one department to another department." (50, Female patient, Urban)</i></p> <p><i>"She (DOTS provider) sent me to ANM then to PHC and lastly to district hospital, why not (send me) directly there, it took me seven days to get proper care" (35, Male patient, Rural)</i></p> <p><i>"I rarely attend any MDR TB cases, they have such a complicated treatment regimen, I always refer them directly to higher centre or give them some antacids, nothing can be done at PHC."(41, female MO,PHC Rural)</i></p>
	Lack of coordination between DR-TB centre and hospital	<p><i>"We know, the patients have to suffer a lot in tertiary care centre for AE management, but we have to send them to concerned department for consultation." (36 Male, program manager, Urban)</i></p> <p><i>"With multiple referrals in government hospitals, patient have to come back without being attended many times due to high load of patients. It would be better to have special OPD for them" (44 Male, program manager, Urban)</i></p>
Program related	Lack of guideline and training for AE identification and management	<p><i>"I want to help patients, but I am not sure what I can do at my level for such a disease"(38,Female DOTS provider-Nurse Urban)</i></p> <p><i>"We could not decide based on symptoms and history alone whether it is really AE or complication of MDR TB."(41, female PHC-MO Rural)</i></p>
	Lack of proper counselling support	<p><i>"Medical Officer has scolded me for my repeated complaint of diarrhea and he has asked me to either continue or stop the medicines. Eventually I learned to stop</i></p>

	and empathy	<p><i>medicines temporarily whenever I do not feel good” (50, Male patient, Urban)</i></p> <p><i>“Doctor had advised me on the first day of treatment that, being defaulter of TB treatment, I have to bear all side effects of higher dose anti-TB drugs”. (50, Female patient, Rural)</i></p>
Patient level	Misconceptions	<p><i>“Side effects are good in a way which promises early cure.” (21, Female patient Urban)</i></p> <p><i>“Side effects are sign of effectiveness of drug which is killing power of Bacteria.” (62, Male patient Rural)</i></p> <p><i>“Medicines are free for us, why to complaint for that.” (64, Female patient Rural)</i></p>
	Previous treatment experience	<p><i>“I have visited district hospital twice and they took two days for referring me from one department to another for my abdominal pain and lastly, they have given me same tablet which was prescribed by ANM for acidity.” (32, Female patient Rural)</i></p> <p><i>“I have visited many times, various clinics, which resulted in no relief. In spite of that, now I stop taking drugs for few days whenever I do not feel good” (44, Male patient, Urban)</i></p>
	Accessibility and affordability	<p><i>“I am already not able to work and I could not further afford visiting (the) hospital (43, Male patient, Rural)”</i></p> <p><i>“I asked for help regarding skin rashes and ANM referred me to district hospital which is far and time consuming, I cannot afford to lose my day” (18, Male patient, Urban)</i></p> <p><i>“Why to report side effects, doctor will add some more vicious drugs...” (34, male patient Urban)</i></p>
	Nature of Adverse Event	<p><i>I was having tinnitus since so many days but I didn't bother for that, once I realized my hearing had reduced , I reported to ASHA the same. (42, Female patient, Rural)</i></p>

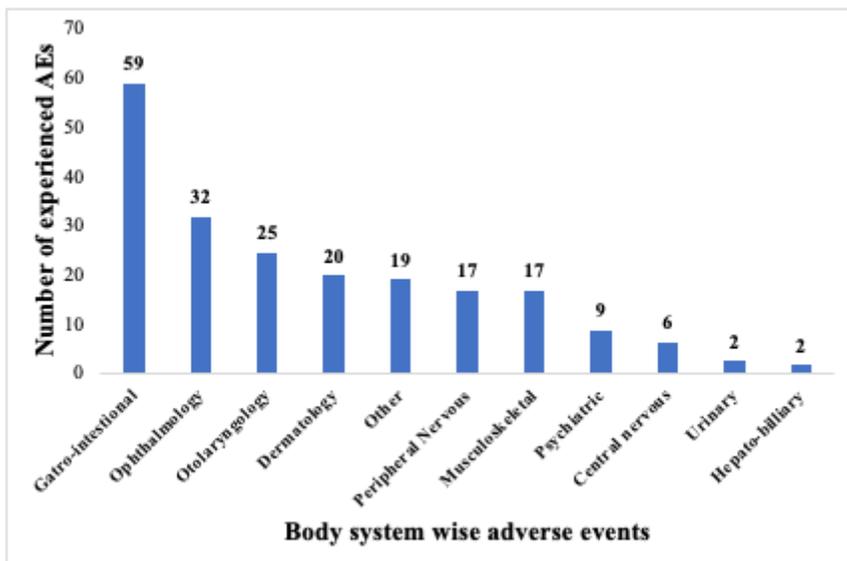
DOTS- Directly Observed Treatment Short course, ASHA- Accredited Social Health Activist, STS- Senior treatment supervisor, MO-PHC Medical officer, Primary Health Centre, ANM- Auxiliary Nursing Midwives

## Figures



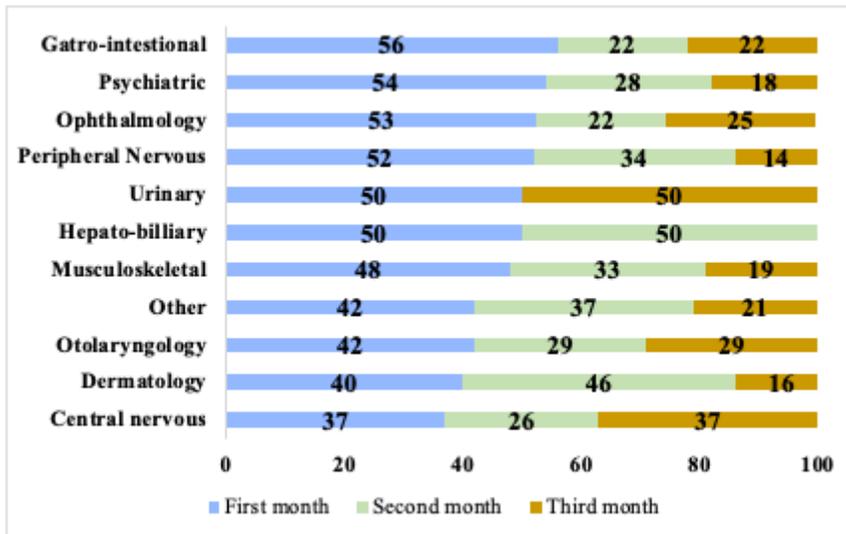
**Figure 1**

Flow of recruitment, AE experience and treatment seeking for management among patients initiated on DR-TB treatment under the RNTCP at DR-TB Center, Gujarat(July-September-2018)



**Figure 2**

System wise distribution of adverse events (n=207) experienced by patients during first three months of DR-TB treatment under the RNTCP at DR-TB Center, Gujarat(July-September-2018) {Other includes:- Weight loss, Weight gain, Body weakness, Hair loss, Bitterness and dryness of mouth, Menstruation irregularity, Restlessness, Dehydration, Oral cavity rash, Flu, Neck swelling, Headache, Palpitation, Pale look}



**Figure 3**

Pattern and month wise distribution of adverse events experienced by patients during first three months of DR-TB treatment under the RNTCP at DR-TB Center, Gujarat(July-September-2018) {Other includes:- Weight loss, Weight gain, Body weakness, Hair loss, Bitterness and dryness of mouth, Menstruation irregularity, Restlessness, Dehydration, Oral cavity rash, Flu, Neck swelling, Headache, Palpitation, Pale look}

## Supplementary Files

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