International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Study of Adverse Effects and Outcome of All Oral Longer Regimen for Drug - Resistant Tuberculosis at Nodal DRTB Center, S N M C, Agra

Manoj Kumar Pippal[1], Santosh Kumar[2], Gajendra Vikram Singh[3], Sachin Kumar Gupta[4]

[1]Junior Resident, Department of Tuberculosis and Respiratory Diseases, S N Medical College, Agra

[2]Professor, Department of Tuberculosis and Respiratory Diseases, S N Medical College, Agra

[3]Professor and Head, Department of Tuberculosis and Respiratory Diseases, S N Medical College, Agra

[4]Assistant professor, Department of Tuberculosis and Respiratory Diseases, S N Medical College, Agra
Corresponding Author Email: *guptasachin06[at]gmail.com*

Abstract: ***Introduction and Background: TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS until the coronavirus (COVID - 19) pandemic. In 2021, the estimated proportion of people with TB who had MDR/RR - TB was 3.6% among new cases and 18% among those previously treated. India is one of the nations in the world which has the highest burden of Multidrug - resistant tuberculosis (26%). The estimated number of MDR/RR - TB cases in India is 124000 (9.1/lakh population). A total of 109 countries were using all - oral longer regimens for the treatment of MDR/RR - TB. Material and Methods: The present study is a hospital - based observational prospective non - randomized without a control group, which was performed at a nodal DRTB center, Department of Tuberculosis & Respiratory Diseases, S. N. Medical College Agra. Results: 140 patients were enrolled on the All - Oral Longer regimen after obtaining informed consent. Among 140 patients 75.6%, 77.6%, 82.4%, 82.4%, and 80.2% were culture negative at the end of 3rd, 6th, 9th, 12th and 18th months respectively. The most common adverse event observed in this group of patients was Dermatological events which accounts for 29.2% followed by nervous system (17.8%) and gastrointestinal (15%) events. Among the study population 80.2% (112) were culture negative at the end of treatment, 5.6% died, 7.8% lost to follow up and 6.4% failed. Conclusions: Patients on the All Oral Longer regimen for DRTB have higher and more rapid sputum culture conversion rate, lower mortality, and fewer adverse events which are manageable, which indicates that the All Oral Longer regimen was well tolerated with better compliance in comparison to previous treatment regimens for DRTB.***

Keywords: drug - resistant tuberculosis; extensively drug - resistant tuberculosis; national tuberculosis elimination program; AOLR, PMDT

1. Introduction and Background

Globally in 2021, 71% of people (2.4/3.4 million) diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance. Among those tested, 141953 cases of MDR/RR - TB and 25038 cases of PRE - XDR - TB or XDR - TB were detected, giving a combined total of 16699. Worldwide, 161746 people with MDR/RR - TB were enrolled on treatment in 2021 (1).

There are five categories of drug - resistant TB used by the national health programs at present: isoniazid (INH) - resistant TB, RR - TB, and MDR - TB (RR and INH resistant), pre - extensively drug - resistant TB (pre - XDRTB) and XDR - TB. Pre - XDR - TB is TB that is resistant to rifampicin (MDR/RR - TB) and any fluoroquinolone (a class of second - line anti - TB drugs). XDR - TB is TB that is resistant to rifampicin (MDR/RR - TB), plus any fluoroquinolone, plus additional resistance of one of the drugs of Group A either Bedaquilline or Linezolid (2). Outcomes of treatment for drug - resistant tuberculosis are poor globally, with low cure rates and high mortality (4). The duration of treatment is long and many of the drugs are poorly tolerated (5), side effects and adverse events (AEs) are common, and the treatment and management of the cases are expensive and burdensome (6).

Our study with objectives is to determine the 1. Outcome among patients of RR/MDR/PRE - XDR/XDR tuberculosis in terms of culture conversion at the 3rd, 6th, 12th, and at 18th month.2. The adverse effects of all oral longer regimens among patients of R - R/MDR/PRE - XDR/XDR tuberculosis.3. The radiological patterns among patients of RR/MDR/PRE - XDR/XDR tuberculosis.4. The resistant patterns among patients of RR/M/PRE - XDR/XDR tuberculosis, is an attempt to study and understand the clinical, bacteriological, radiological, and social impact of the regimen and to study the adverse effects in detail so that conclusions of the study can be helpful for the policymakers at any level and thrust to the ongoing existing Tuberculosis eliminating strategies.

2. Material and Methods

It was hospital - based, non - randomized observational prospective study without control group conducted on a cohort of 140 Self - reporting and /or referred R - R/MDR/PRE - XDR/XDR - TB patients registered under the NTEP from January 21 to June 22 at nodal DR - TB centre and Department of Tuberculosis & Respiratory Diseases, S. N Medical College Agra.

Inclusion criteria:

- Persons who could provide written informed consent.
- Patients of age 18 years or older having confirmed pulmonary, R - R/ MDR/ PRE - XDR

/XDR pulmonary tuberculosis and not eligible for the Shorter regimen of DRTB.

- Females who were not pregnant or breast feeding & on non - hormonal - based birth control methods.

Exclusion criteria:

- MDR/XDR TB patient who is/are registered under DOTS outside, during the period of study.
- Extra pulmonary tuberculosis.
- Severe hepatic and renal disease.
- Patients with cardiac abnormalities like uncontrolled arrhythmias, marked prolongation of QT/QTc interval, e. g., repeated demonstration of QTcF (Fredericia correction) interval > 450ms, WPW syndrome, Bundle branch block, II/III heart block, Personal or family history of Long QT Syndrome.

All the study participants have been subjected to a detailed clinical history and examination and information obtained about Age, Sex, Height, Weight, Body Mass Index, Occupation, Income, and Previous history of TB or anti - TB Drug intake (prior exposure to 2nd line injectable drugs), or any preventive therapy and if present the drugs used, etc. The modified Kuppusamy scale of social classification (updated in 2021) has been used to classify the patients into their respective socioeconomic classes.

A detailed pre - treatment evaluation of enrolled included detailed history (including screening for mental illness, seizure disorder, drug/alcohol abuse, known adverse/serious adverse events etc.), Previous history of ATT taken especially SLI/FQ, thorough clinical examination, Weight & height, ECG, Complete blood count with hemoglobin & platelets count. Blood urea and S. Creatinine to assess renal function, Blood sugar to screen for Diabetes

	end of treatment specimen collection.
DST	FL & SL - LPA (Lfx, Mfx, Am, Eto) and LC&DST (Mfx, Lzd, Cfz*, Bdq*, Dlm*, Z) if culture +ve at the end of 6 months or any time beyond
UPT	As and when clinically indicated
CBC/platelets	Day 15, monthly in first 6 months, 6 or 7 or 8 if previous months +ve, then as and when clinically indicated
TSH & LFT	LFT quarterly, then as and when clinically indicated. TSH every 6 months
CXR	At the end of month 6, end of treatment and as and when clinically indicated
ECG	At 2 weeks, monthly in first 6 months and till Bdq/ Mfx/ Cfz/Dlm is extended, then as and when clinically indicated.
S. electrolytes (K, Mg, Ca)	As and when indicated and in case of any QTcF prolongation

Mellitus, UPT (for all women of childbearing age), Chest X - ray. HIV testing and counseling, Hearing evaluation/ Audiogram, Liver function tests, TSH levels to assess thyroid function, Routine Urine examination, Serum electrolytes – potassium, magnesium, calcium**,** Serum proteins, lipase, amylase**,** Ophthalmologist opinion to rule out chorioretinitis/uveitis. ECG and QTc interval were measured in lying down position preferably in the morning using a standardized BPL CARDIART 6208 VIEW machine and the QT interval was corrected with the Fridericia formula

QTcF interval = $QT/\sqrt[3]{RR}$

Follow - up evaluation of all the eligible study population has been carried out as per the Table 1:

- If Lzd is part of the regimen - rule out bone marrow suppression.
- HBsAG and other viral markers (Hepatitis A, C & E) to be done in case of jaundice.
- In case of baseline ECG abnormality or QTcF ≥450ms with longer oral M/XDR - TB regimen that contains Bdq, Mfx, Cfz or Dlm, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG.
- DST whenever available.
- Cohort event monitoring

Table 1: Follow - up evaluation schedule of longer oral M/XDR - TB regimen during treatment

Regimen Class	Longer Oral M/XDR - TB Regimen
Duration	18 - 20 months (no separate IP/CP)
Smear microscopy	With culture at the C&DST lab. Conduct SM within 7 days, if any smear at 6 month or later is positive to rapidly ascertain Bacteriological conversion / reversion. LC& DST lab to update the result on Nikshay and inform the concerned field staff of collection center on same day
Culture	Monthly from month 3 onwards to end of 6 months or 7 or 8 if the previous month's culture is +ve. Quarterly month 6 or 7 or 8 onwards based on previous month's culture results. If the culture results of month 6 or any of the quarterly culture is positive, collect one repeat specimen immediately and send it for culture to rapidly ascertain bacteriological conversion / reversion and if the repeat specimen is culture negative, then the subsequent quarterly or

Each patient was monitored for AEs, clinical and microbiological improvement, and outcomes during treatment.

Statistical analysis of data

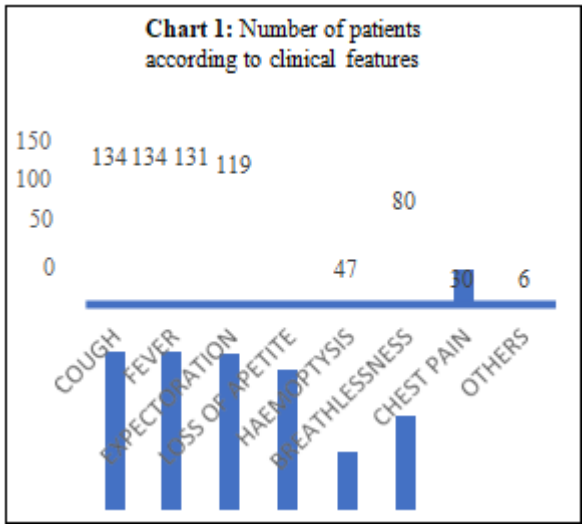
For the comparison of categorical variables, significance testing was done by $\chi 2$ and if needed then a 2 - sided Fisher exact test will be applied. Associations between selected risk factors with drug resistance will be estimated by computing odds ratios (ORs) and their 95% confidence intervals from an unconditional logistic regression model.

The criterion for significance will be set at $P<0.05$ based on a two - sided test. Analyses will be performed with suitable software.

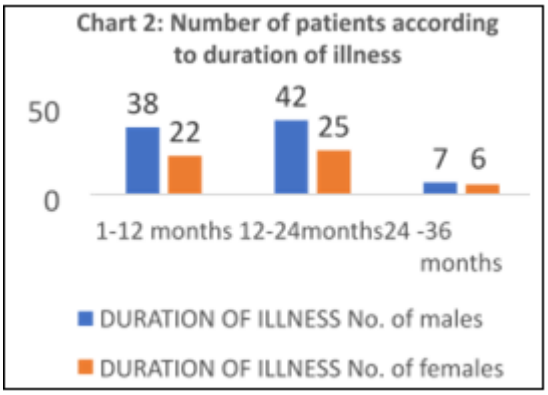
3. Results

Among the cohort of 140 eligible DRTB patients, approximately 62% were males and 38% were females. The mean age of study participants was 31.6 years with the majority of patients being the in the younger age group.58 patients (41.4%) were from rural areas and 82 patients (58.6%) were from urban areas. Among male patients, 50.8% were from urban areas and 49.2% were from rural areas. Whereas the proportion of female patients was more in an urban area (71.6%) as compared to rural areas (28.4%). The majority of the study population was in an upper lower class (IV) 43% and lower class (V) 25.6% as per the modified kuppuswamy classification. The majority were undernourished with BMI <18.5.

The most common presenting symptom among the study population was cough and fever found in 96.2% followed by expectoration in 93.75%. Anorexia was present in 85%.57.5% of had breathlessness on exertion.33.7% presented with hemoptysis and 21.2% with chest pain.



Most of the patients had a duration of illness between 12 - 24 months (47.5%) and 1 - 12 months (42.5%) and only 10% of patients had a duration of illness between 24 - 36 months.



In 40.8% study population personal habits such as tobacco consumption, alcohol consumption, and smoking were present while 59.2% had no habits.16 had co - morbidities (hypertension, diabetes, thyroid dysfunction) in which diabetes was most common at 6%.5% of patients had HIV co - infection.64% had RR/MDR - TB and 27% had PRE - XDR and 9%had XDR pulmonary TB. Baseline chest x - ray of 64.2% had cavitation and 40.4% had >50% lung involvement.93% had previous exposure to second - line anti - tubercular drugs either from government institutions or private organizations.

Out of 87 male and 53 female patients initiated on all oral longer regimens, a Baseline QTc interval of <450ms was in 89.2% of males and <470ms was in 91.2% of females.

Among the entire study population 75.6%, 77.6%, 82.4%, 82.4%, and 80.2% were culture negative at the end of 3rd, 6th, 9th, 12th and18th months respectively

Body System involved	Gr1 Mild	Gr2 Moderate	Gr3 Severe	Gr4 Life – threatening	Total
G I	25	8	5	0	38 (15%)
Liver	6	2	1	0	9 (3.6%)

Table 2: System wise adverse event noted in

V S	7	5	3	2	17 (6.8%)
Neural	25	12	8	0	45 (17.8%)
Psych iatric	6	2	1	0	9 (3.2%)
Eye	7	2	2	0	11 (4.4%)
Renal	1	1	0	0	2 (0.8%)
Hematology	24	9	3	0	36 (14.2%)
Skin	60	14	0	0	74 (29.2%)
muscle	6	0	0	0	6 (2.4%)
Other	5	2	0	0	7 (2.6%)
Total	172 (67.8%)	57 (22.4%)	23 (9.2%)	2 (0.6%)	254 (1 00%)

comorbidities had low sputum culture conversion rate when it compared to person without them. Out of 140 patients 80.2% (112) were culture negative at the end of treatment, 5.6% died, 7.8% lost to follow up, while 6.4% failed.

An attempt to correlate different factors with treatment outcome. It was observed that BMI (>18.5) (P value 0.0081) and having no personal habits (p - value 0.0001) were positive predictors of favorable treatment outcomes. While low BMI (p - value 0.0081) and >50% lung damage (P value 0.004), cavitary lesions (P value 0.034), HIV co - infection (p - value 0.025) and presence of comorbidities (p - value 0.025) were negative predictors of favorable treatment outcome all oral longer regimen and grading of severity (N=140).

	Outcome		
Factors	Favorable	Unfavorable	P value
Gender			
Male	66	21	0.958
Female	40	13	
Residence			
Urban	64	18	0.443
rural	42	16	
Age			
≤45	94	28	0.337
>45	12	6	
BMI (kg/m2)			

<18.5	56	26	0.0081
>18.5	50	7	
Personal habit			
Yes	32	26	1
No	74	8	
Resistance pattern			
RR/MDR	69	21	0.724
PRE - XDR/XDR	37	13	

In our study, we found that the most common adverse events were skin discoloration followed by peripheral neuropathy, and nausea/vomiting after Grouping of different adverse events based on body systems involved and their severity according to DAIDS criteria.

It was observed that patients having severe lung damage and cavitation had very low rate of sputum culture conversion. Patients having BMI>18.5 Kg/m2 had high culture conversion rate which was more than those patients who were having low BMI (<18.5 Kg/m2). The resistance pattern does not have any significance on sputum culture conversion. Patients having habit of smoking, tobacco chewing and alcohol intake had low conversion rate in comparison to person with no habit. Patients having HIV co - infection had low sputum culture conversion rate when it compared to person without HIV co - infection. Patients having HIV

Table 3: Correlation of various factors associated with treatment outcome in DR - TB patients at 3RD month (N=140).

Cavitary lung lesion			
Yes	63	27	0.034
No	43	7	
Lung involvement			
<50%	70	13	0.004
>50%	36	21	
HIV co infection			
Yes	103	27	0.025
No	3	4	
Comorbidities			
Yes	97	23	0.025
No	9	7	

4. Discussion

Our study showed that the majority of DR - TB patients were in the younger age group. About 46% (64) of the mass index were at significantly high risk of unfavorable outcomes.

40.8% (58) of patients were having personal habits such as smoking, tobacco consumption, and alcohol consumption and it has been noted that alcohol consumption, smoking, and tobacco consumption are associated with poor outcomes, which matches with the study of *Sandip V. Barvaliya et al*, Personal habits of smoking, tobacco chewing and alcohol consumption were found to be negative predictors of successful treatment outcome.

Among the study subjects only 7 patients were HIV positive, which was less as compared with a study conducted by *Borisov SE, Dheda K, Enwerem M, Romero Leyet R et al.* A study of *Molly F. Franke et al* demonstrated patients with HIV had a lower probability of conversion than patients without HIV similar to our study.16 patients (12.2%) were found to have co - morbidities in which diabetes was most common (6%). It was similar to the study patients were in the age group of 18 - 25 years while the mean age of the study population was 31.6 years; similar to other studies *Norbert Ndjeka et al (median age was 34 years), RohitSarin et al (median age was 29.77 years).* The high prevalence of DR - TB in the young population is alarming as this would result in considerable health and financial burden on individual families and the country.

Approximately 62% (87) of the patients were males and 48% (53) were females having an increasing male - to - female ratio with respect to age, similar to the study conducted in *NITRD, Delhi by RohitSarin et al* and *Norbert Ndjeka et al.* It suggests that females are more susceptible to the disease in younger age as compared to the males.

58.4% (82) of the patients were having BMI < 18.5 kg/m2. Low mean body weight and mean BMI indicate that majority of the patients were 'undernourished'. Studies of *MengqiuGao et al* and *V. S. Salhotra et a*l demonstrated that patients with low body one by ***Mengqiu Gao et al*** in China. In our study Presence of comorbidities was associated with poor treatment outcomes in terms of the slow rate of culture conversion. Out of the total no of male patients (87) initiated on all oral longer regimens, The study population was stratified according to the radiographic assessment of lung cavitation and the extent of the disease. Among 140 patients, 90 (64.2%) were having cavitary lung disease, and 57 (40.4%) patients were having >50% lung involvement. A study by *Molly F. Franke et al* Demonstrated that Patients with both cavitary disease and highly positive sputum smear had a lower probability of conversion relative to patients without either, similar to our study.

During our study out of 140 patients, most of the patients had a duration of illness between 12 - 24 months (47.5%) and 1 - 12 months (42.5%). only 10% of patients have duration of illness between 24 - 36 months. Almost all of the patients (93%, 130) previously had exposure of second - line anti - tubercular drugs which was more than the study conducted by *Alena Skrahina, HennadzHurevich et al.* This reflects the progressive acquisition of drug - resistance mutants during sequential exposure to inadequate treatment leads to RR/MDR, PRE - XDR, and XDR - TB; thereby increasing the risk of DR - TB in treatment - experienced patients.

In the present study, 64% (90) of patients were RR/ MDR - TB 27% (38) were PRE - XDR and 9% (12) were XDR PTB. In this study population of XDR - TB patient were lower as compared to the study conducted by *Alena Skrahina, Hennadz Hurevich et al, V. S. Salhotra et al*, and *Norbert Ndjeka et al*. According to a study conducted by *MengqiuGao et al* there no significant difference in culture conversion rate among different phenotypes of DRTB patients, similar to our study.

In our study, the outcome of all oral longer regimen was observed in terms of sputum culture conversion rate at the 6th, 9th, 12th, and 18th months which were as follows: Our

results revealed that out of 140 patients, 106, 109, 115, 115, 112 patients got culture converted at the end of the 3rd, 6th, 9th, 12th, and 18th months respectively.

In our cohort, among the available culture results, the culture conversion rate in these difficult - to - treat DR - TB patients was found to be 75.6%, 77.8%, 82.4%, 82.4%, 80.2% at the end of 3rd, 6th, 9th, 12th and 18th months of treatment with all oral longer regimen respectively. In most of the studies, culture conversion was reported at the end of 3rd, and 6th month. In this study culture conversion was slightly lower than reported in clinical trials *Palwasha Y Khan et al, Molly F. Franke et al, Shao - Jun Zhang et al, V. S. Salhotra et al, MengqiuGao et al, Alena Skrahina, HennadzHurevich et al* but similar to study conducted by *Sandip V Barvaliya et al* treatment outcome was successful in 102 (80.3%) patients with sputum culture conversion. 70 patients (78.6%%) out of 90 RR/ MDR

TB patients, 30 patients (78.4%) out of 38 PRE - XDR TB patients and 9 patients (78.8%) out of 12 XDR TB got culture converted at the end of 6months of treatment. The results of this study are even more impressive in light of the fact that patients enrolled here included PRE - XDR and XDR - TB, which are often more difficult to treat than MDR - TB patients. Of note, it is reassuring that almost no difference in culture conversion rates after receiving all oral longer regimen.

Median time for sputum culture conversion was 90 days which was higher than other studies *V. S. Salhotra et al, Sandip V Barvaliya et al, MengqiuGao et al, Borisov SE, Dheda K, Enwerem M, Romero Leyet R et al* because we followed PMDT guidelines for sending the sputum culture in which first sample was sent at the end of 3rd month of treatment with all oral longer regimen.

High and faster culture conversion rate was observed in case of patients having BMI>18.5. which is in accordance with the study of V. S. Salhotraet al, *Sandip V Barvaliya et al , MengqiuGao et al*.

It is well known that second line anti - TB drugs are more toxic as compared to first line drugs. The number of AEs observed in our study was higher in comparison to existing studies *V. S. Salhotra et al, Sandip V Barvaliya et al.* This is probably because of long term follow up and high percentage of low BMI patients in our study which have been shown to have greater risk of drug toxicity and death, but adverse event was lower than the study conducted by *Alena Skrahina, HennadzHurevich et al.*

The number of adverse events reported among the study subjects was 254 episodes in 140 patients out of which 67.8% episodes were of Grade 1 (mild), 22.4% were Grade 2 (moderate), 9.2% were Grade 3 (severe) and 0.6% were Grade 4 (Life Threatening).71.6% of the adverse events were non - serious and among the serious adverse events (28.4%), 41 required hospitalizations, 30 had permanent disability and 2 were life - threatening.

The most common body systems showing Adverse Events were skin and appendages (29.2%) followed by the nervous system (17.8%), gastrointestinal (15%), and hematological manifestations (14.2%).

In our study most common adverse events were skin discoloration followed by peripheral neuropathy, and nausea/vomiting, which was different from a study conducted by *V. S. Salhotra et al* according to their study the most common AEs seen were peripheral neuropathy (21%), vomiting (18%), breathlessness (13%) and thrombocytopenia (11%), and differ from study conducted by *Sandip V Barvaliya et al* according to their study The most common were gastrointestinal (24, 19.4%) followed by skin and appendages (21, 16.9%) and body as a whole (17,%). Vomiting (11, 8.9%) was the most common clinical presentation and also differ from a study conducted by *Alena Skrahina, HennadzHurevich et al* according to their study top five body systems showing Adverse Events were metabolism and nutrition disorders (experienced by 135 patients, hepatobiliary disorders (experienced by 127 patients), cardiac disorders (experienced by 80 patients) and others including gastrointestinal system disorders, blood and the lymphatic system disorders, renal and urinary disorders, nervous system disorders, skin disorders and ear and labyrinth disorders.

As the occurrence of adverse events will prolong hospitalization and also affect treatment outcome, there is a need to regularly evaluate, monitor and emphasize prevention and management of them. Treatment was overall well tolerated in our cohort.

Out of 140 patient 80.2% (112) had favourable outcome in term of culture negative at the end of treatment, and 19.8% patient had unfavourable outcome in term of 5.6% died, 7.8% lost to follow up while 6.4% failed.

LTFU in present study was (7.8%, due to occurrence of pandemic COVID - 19 during the study period large number of patients were not accessible to health facility), but it was less as compared to study conducted by
Norbert Ndjeka et al.

The study supports that all oral longer regimen shortened the typical time for sputum culture conversion, increased the rate of conversion at follow up and has shown significant benefit in improving survival and treatment outcomes in DR TB patients under clinical and programmatic settings.

5. Conclusions

Despite limitations, we believe that the data generated in our study leads to certain important conclusions. We concluded that All Oral Longer regimen have high and rapid sputum culture conversion rate, low mortality and fewer adverse events which are manageable, which indicates that All Oral Longer regimen was well tolerated with better compliance in comparison to previous treatment regimen for RR/MDR/PRE - XDR/XDR tuberculosis. Further, the outcomes were encouraging in patients having high body mass index due to better nutritional status and immunity. Although All Oral Longer regimen containing Bedaquiline and Delamanid along with concomitant medications has the potential to prolong QTc interval, the benefit certainly

outweighs the risk. It strengthened the DR - TB treatment programme to new lengths. Since DR - TB (RR/MDR/PRE - XDR/XDR) is a major health problem in India and other developing countries, newer drugs like Bedaquiline, Delamanid, Pretomanid and other pipeline drugs under development have the potential of becoming cornerstone drugs for future DR - TB treatment and definitely a game changer.

References

[1] Global Tuberculosis Report 2022 - who. int https: //www.who. int/. . . /tb - reports/global - tuberculosis - report - 2022.
[2] India TB Report 2022:: Central TB Division https: // tbcindia. Gov. in/index1. php?lang=1&level=1&sublinkid=5613&lid=3658.
[3] WHO. Global tuberculosis report 2015. World Health Organization. http: //www.who. int/tb/publications/global_report/en/World Health Organisation. Global tuberculosis report 2018. License: CC BY - NC - SA 3.0 IGO. Geneva, Switzerland; 2018.
[4] Wu S, Zhang Y, Sun F, et al. Adverse events associated with the treatment of multidrug - resistant tuberculosis: a systematic review and meta - analysis. Am J Ther.2016 Mar - Apr; 23 (2): e521–30. PubMed PMID: 24284652; eng.
[5] Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science.2005; 307 (5707): 223–227.
[6] Tuberculosis data [website]. Geneva: World Health Organization; 2022 (https: //www.who. int/tb/data/en/).
[7] WHO. Global tuberculosis report 2015. World Health Organization. http: //www.who. int/tb/publications/global_report/en/ World Health Organisation. Global tuberculosis report 2018. Licence: CC BY - NC - SA 3.0 IGO. Geneva, Switzerland; 2018.
[8] Harmanjit S, Navreet Kaur N, Nipunjot G, et al. Bedaquiline: a new weapon against MDR and XDR - TB. Int J Basic ClinPharmacol.2013; 2 (2): 96–102.
[9] Matteelli A, Carvalho ACC, Dooley KE, et al. TMC207: the first compound of a new class of potent anti - tuberculosis drugs. Future Microbiol.2010; 5 (6): 849–858.
[10] Koul A, Vranckx L, Dendouga N, et al. Diarylquinolines are bactericidal for dormant Mycobacteria as a result of disturbed ATP homeostasis. J Biol Chem.2008; 283 (37): 25273–25280.
[11] Huitric E, Verhasselt P, Andries K, et al. In vitro antimycobacterial spectrum of a diarylquinoline ATP synthase inhibitor. Antimicrob Agents Chemother.2007; 51 (11): 4202–4204.
[12] World (multidrug - resistant tuberculosis: Interim policy guidance [Internet].2016. (https: //www.who. int/tb/ publications/delamanid - in - mdr - tb - treatment/en/. Accessed on 16 March 2021).
[13] WHO Consolidated Guidelines on Tuberculosis: Module 4 - Treatment [Internet].2020. (https: //www.who. int/publications/i/item/9789240007048. Accessed on 16 March 2021).
[14] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta - analysis of 9, 153 patients. PLoS Med.2012; 9: e1001300. doi: https: //doi. org/10.1371/journal. pmed.1001300.
[15] Harausz EP, Garcia - Prats AJ, Law S, Schaaf HS, Kredo T, Seddon JA et al. Treatment and outcomes in children with multidrug - resistant tuberculosis: a systematic review and individual patient data meta - analysis. PLoS Med.2018; 15: e1002591. doi: https: //doi. org/10.1371/journal. pmed.1002591.
[16] Ahmad N, Ahuja SD, Akkerman OW, Alffenaar J - WC, Anderson LF, Baghaei P et al. Treatment correlates of successful outcomes in pulmonary multidrug - resistant tuberculosis: an individual patient data meta - analysis. Lancet.2018; 392: 821–34. doi: https: //doi. org/10.1016/S0140 - 6736 (18) 31644 - 1.
[17] Seddon JA, Hesseling AC, Godfrey - Faussett P, Schaaf HS. High treatment success in children treated for multidrug - resistant tuberculosis: an observational cohort study. Thorax.2014; 69: 458–64. doi: https: //doi. org/10.1136/thoraxjnl - 2013 - 203900.
[18] Khan PY, Franke MF, Hewison C, Seung KJ, Huerga H, Atwood S, Ahmed S, Khan M, Sultana T, ManzurUl - Alam M, Vo LNQ, Lecca L, Yae K, Kozhabekov S, Tamirat M, Gelin A, Vilbrun SC, Kikvidze M, Faqirzai J, Kadyrov A, Skrahina A, Mesic A, Avagyan N, Bastard M, Rich ML, Khan U, Mitnick CD. All - oral longer regimens are effective for the management of multidrug - resistant tuberculosis in high - burden settings. Eur Respir J.2022 Jan 20; 59 (1): 2004345. doi: 10.1183/13993003.04345 - 2020. PMID: 34140298.
[19] Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R, Padanilam X, Enwerem M, Chotoo S, Singh N, Hughes J, Variava E, Ferreira H, Te Riele J, Ismail N, Mohr E, Bantubani N, Conradie
[20] F. High treatment success rate for multidrug - resistant and extensively drug - resistant tuberculosis using a bedaquiline - containing treatment regimen. Eur Respir J.2018 Dec 20; 52 (6): 1801528. doi: 10.1183/13993003.01528 - 2018. PMID: 30361246.
[21] Hatami H, Sotgiu G, Bostanghadiri N, Abadi SSD, Mesgarpour B, Goudarzi H, Migliori GB, Nasiri MJ. Bedaquiline - containing regimens and multidrug - resistant tuberculosis: a systematic review and metaanalysis. J Bras Pneumol.2022 May 30; 48 (2): e20210384. doi: 10.36416/1806 - 3756/e20210384. PMID: 35649043; PMCID: PMC8836629.