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Early View

Original article

# Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report

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**Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report**

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**Key words:** Tuberculosis; MDR-TB; adverse events; aDSM, delamanid; bedaquiline, prevention of TB sequelae

**Running title:** Global monitoring of anti-TB treatment side effects (aDSM)

**Take-home message**: Previous evidence on adverse events is available from single studies. This global project (658 patients from 26 countries) demonstrates aDSM is feasible and serious adverse events of recommended drugs are reasonably low (overall, 57/504, 11.3%).

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**Abstract (247 words)**

WHO (World Health Organization) recommends countries to implement pharmacovigilance and to collect information on aDSM (active drug safety monitoring and management of adverse events-AEs).

Aim of this prospective study was to evaluate the frequency and severity of AEs to anti-tuberculosis (TB) drugs in a cohort of consecutive TB patients treated with new (i.e. bedaquiline, delamanid) and repurposed (i.e. clofazimine, linezolid) drugs, based on the WHO aDSM project.

AEs were collected prospectively after attribution to a specific drug together with demographic, bacteriological, radiological and clinical information at diagnosis and during therapy. This interim analysis included patients who completed or were still on treatment at time of data collection.

Globally, 45 centres from 26 countries/regions reported 658 patients (68.7% males, 4.4% HIV co-infected) treated as follows: 87.7% with bedaquiline, 18.4% with delamanid (6.1% with both), 81.5% with linezolid and 32.4% with clofazimine. Overall 504 AE episodes were reported: 447 (447/504, 88.7%) were classified as minor (grade 1-2) and 57 (57/504, 11.3%) as serious (grade 3-5).

The majority of the 57 serious AEs reported by 55 patients (51/57; 89.5%) ultimately resolved. Among patients reporting serious AEs some drugs held responsible were discontinued: bedaquiline in 0.35% (2/577), delamanid in 0.8% (1/121), linezolid in 1.9% (10/536) and clofazimine in 1.4% (3/213) of patients.

Serious AEs were reported in 6.9% (9/131) of patients treated with amikacin, 0.4% (1/221) with ethionamide/prothionamide, 2.8% (15/536) with linezolid and 1.8% (8/498) with cycloserine/terizidone.

The aDSM study provided valuable information but implementation needs scaling-up to support patient-centred care.

**Introduction**

With over 558,000 patients estimated by the World Health Organization (WHO) in 2017 (1) rifampicin- and multidrug-resistant tuberculosis (MDR-TB) are a clinical and public health priority (1,2). From the public health perspective, it is imperative to prevent the selection of drug-resistant strains of *Mycobacterium tuberculosis* by effective treatment of drug-susceptible TB patients and to

reduce the transmission of drug-resistant strains by diagnosing and treating them rapidly and effectively (3). The clinical management of MDR- and XDR (extensively drug-resistant)-TB is expensive and medically challenging: clinicians are left with fewer effective drugs (which in turn cause more frequent serious adverse events (AEs) than those used for the treatment of drug-susceptible TB (1,2,4,5). Since the implementation of a global approach to treat MDR-TB with second-line drugs (known as the 'DOTS Plus' strategy) (4) monitoring, recording and reporting of AEs have become more important.

In recent years, new (*i.e.*, delamanid and bedaquiline) and repurposed anti-TB drugs have been introduced in the treatment of MDR-TB (2). Bedaquiline was recently included in the new WHO MDR-TB classification (6,7) as a priority drug (Group A) following growing evidence of efficacy and tolerability (8-14). Delamanid is in the WHO Group C (add-on agents)(6), with a promising safety profile (15-18).

The repurposed anti-TB drugs (6,19) linezolid (20,21) and fluoroquinolones (19) have been included in Group A, clofazimine in group B (22) and imipenem/meropenem in group C (23-25), based mainly on effectiveness studies, toxicity and programmatic considerations.

Although more evidence is becoming available from trials and observational studies on anti-TB drug toxicity, global aDSM (active TB drug safety monitoring and management of AEs) information on the following drugs is still missing: a) new drugs; b) linezolid and clofazimine; c) drug combinations including drugs as bedaquiline, delamanid, clofazimine, fluoroquinolones which increase the QT interval in the electrocardiogram (with possible life-threatening arrhythmias) (26,27); d) amikacin (Group C, and other second-line-injectable drugs), cycloserine/terizidone (Group B), ethionamide/prothionamide, para-aminosalycilic acid (PAS), ethambutol, pyrazinamide (Group C) and high dose-isoniazid (6,19).

The WHO recommends pharmacovigilance and aDSM, inviting national TB programmes to implement 'active and systematic clinical and laboratory assessment of patients on treatment with new TB medicines, or novel MDR-TB regimens in order to detect and report potential or confirmed drug toxicities'(28-30).

As of today, no global study has reported AEs of anti-TB drugs based on a prospective aDSM approach including patients treated with the new drugs bedaquiline and delamanid and repurposed drugs such as linezolid and clofazimine.

This approach has been possible through the Global Tuberculosis Network (GTN) (31), which recently reported the study design of the first aDSM project originally involving 27 countries (30).

The aim of the present register-based study was to prospectively evaluate the frequency and severity of AEs due to anti-TB drugs in a cohort of consecutive TB patients treated with new and repurposed drugs in 26 countries following the principles and methods of the WHO aDSM project (28-30,32). We summarize the findings of an interim analysis of patients who completed or were still on treatment at the time of data collection.

## Methods

### *Study design*

A pilot study was implemented in 2015 to assess feasibility and utility of the project as well as to pre-test the data flow and analysis. The coordinating centre's Ethics Committee approved the study on July 11th, 2017. The study was proposed to the clinical centres or national TB programmes participating in the network. Each centre or country signed a confidentiality and data-sharing agreement with the coordinating centre and obtained local ethics committee clearance or had a waiver indicating no requirement for ethical approval due to the local regulations.

Starting from July 2017 and after the participating centre signed-up to the project, all consecutive patients (including children and adolescents) undergoing treatment with bedaquiline and/or delamanid were enrolled based on their drug exposure (30). No specific exclusion criteria were adopted for patient selection. Mexico, Paraguay, Spain, Slovakia and Sudan started reporting when the first case in the country initiated anti-TB treatment with bedaquiline and/or delamanid.

The AEs of any drug involved in the treatment regimen were prospectively collected, ensuring a probabilistic mechanism of causality assignment (e.g., attribution of the AE to a specific drug based on its evidence-based profile). Each clinical unit participating in the study had a Consilium-like mechanism for the management of the AEs (5). All AEs and the proposed attribution to one or more specific drugs were revised by the international coordination team and discussed with the reporting clinicians. The scientific evidence available during the study period drove the attribution of an AE to a specific drug based on a probability method. Any discrepancy was resolved by consensus. We contacted investigators to ensure accuracy after recoding and validation of the dataset before final analysis. The data sets reported by clinical centres and national TB programmes were updated twice a year. The present manuscript reports the results of the interim analysis conducted on the data reported up to the up to the 28th August 2019.

## Variables and definitions

The data were obtained via a collection form in an electronic format based on the WHO-recommended template, although additional clinical details were requested (30). Annual data collection occurs twice and is based on the information provided by the clinical files of the recruited clinical centres.

The information collected included anonymized patient's demographic data, bacteriological, radiological, and clinical status at diagnosis, and data on treatment safety during therapy. According to the WHO aDSM project, serious AEs include death or a life-threatening event, hospitalization or prolongation of hospitalization, persistent or significant disability, or congenital anomaly. Serious AEs included grade 3-5 AEs (grade 3: serious; grade 4: life threatening; grade 5: death) (13,28,32). Minor AEs included those of grade 1 (mild) and grade 2 (moderate) (13,28,32).

Whenever an AE occurred, the clinicians reported it using a form summarising the AE details, including the grade, the drug(s) responsible (with details on the dosage and the accompanying medications), the examinations performed, the actions taken, the duration and the outcome of the event (recovered/resolved; recovering/resolving; with sequelae; not recovered/resolved; died, unknown).

All case definitions (e.g. MDR-TB, new case, retreatment case, etc.) were derived from WHO documents (1,6,7).

The study coverage (Electronic Annex 1; number of patients treated with new drugs reported/number of patients estimated) was defined in any country in agreement with the investigators and the national TB programme authorities (10).

***Data analysis***

A descriptive analysis was performed on the patients evaluated in the cohort. The analysis was stratified by geographical area (e.g., Europe versus non-Europe, where Europe refers to WHO European Region and non-Europe to WHO Regions other than Europe), gender, risk factors (e.g. HIV sero-status, diabetes) and AE severity.

Qualitative and quantitative variables were summarised using absolute frequency, percentage median (interquartile ranges (IQR)), and mean (standard deviations, SD). Chi-squared or Fisher exact tests were used to compare qualitative variables, and the *t* or Mann–Whitney test was used to statistically compare quantitative variables.

AEs were analysed both 'per drug' (proportion of patients treated with a given drug who experienced an AE attributed to this drug) and by groups (organ/system) of AEs according to a format allowing international comparisons (13).

The map in Figure 1 was created using the ggplot2 and rworldmap packages in R version 3.5.1 (33) (10,33).

**Results**

Overall, 45 centres from 26 countries/regions in all continents reported 658 patients as of August 28th 2019 (Figure 1, Electronic Annexes 1-3).

Argentina, Australia (Victoria State), Brazil, Bulgaria, Chile, China (Zhejiang Province), Greece, Lithuania, Mexico, The Netherlands, Niger, Paraguay, Portugal, Russian Federation (Moscow and Arkhangelsk Oblasts), Slovakia, Spain, Sudan, Sweden and Switzerland (Vaud county) reported 100% of the patients treated with new drugs in the country/region, while Belarus, Belgium, India, Italy, Latvia, Peru and the United Kingdom reported a proportion of national patients ranging from 15% to 80% (Electronic Annex 1).

Demographic, epidemiological, and clinical characteristics of the patients are summarised in Table 1 (stratified by geographical area, Europe versus other than Europe). The AEs per drug in cases who completed or were still under treatment are summarised in Tables 2A-2B (for each drug: number of patients with AEs/number of patients treated with the drug) and in Electronic Annex 3. The serious cardiological AEs are summarised in Table 3 (serious QT prolongation and serious arrhythmia) and the minor ones in Electronic Annex 4. A summary of serious AEs per organ/system is summarised in Figure 2 and per drug in Electronic Annex 5. The interval between drug administration and AE occurrence, according to the treatment outcome at the study data collection, is summarized in Electronic Annex 6.

Out of 658 patients, 577 (87.7%) were treated with bedaquiline (of whom 40 with co-administered delamanid, in combination or sequentially) and 121 (18.4%) with delamanid: 161 (24.5%) had TB caused by MDR-TB or rifampicin-resistant (RR) strains of *Mycobacterium tuberculosis*, 224 (34%) pre-XDR strains (125 MDR-TB with additional resistance to a fluoroquinolone and 99 to an injectable drug), 245 (38.6%) XDR-TB strains, while 19 (2.9%) presented different other resistances explaining the prescription of new drugs (including 3 pan-susceptible TB patients: 2 with serious AEs to first-line drugs and 1 per clinical decision) (Electronic Annex 2).

Most patients were male (n= 452, 68.7%) and the median (IQR) age was 42 (33–53) years. There were 85 (13.0%) migrants. HIV co-infection was reported in 29 (4.4%) out of 653 patients (3 unknown status) with median (IQR) CD4 cell counts of 94 (30-212) cells/mm$^3$. The majority (n=

27/29, 93.1%) received antiretroviral therapy. A total of 47 (7.2%) individuals were lost to follow-up.

Pulmonary TB was diagnosed in 648 (98.5%) out of 658 patients, with 37 having involvement of both pulmonary and extrapulmonary sites and 10 with isolated extrapulmonary disease (4 lymph node, 3 gastrointestinal, 2 pleural, 1 testicular, and 1 psoas abscess).

The percentages of sputum smear- and culture-positive patients at diagnosis were 68.7% (451/657) and 89.8% (590/657) respectively; the remaining patients had a positive molecular test or were treated based on the resistance profile of the index case (5 patients), AEs (2 patients) and clinical decision (1 case) (Electronic Annex 2).

The mean (standard deviation, SD) number of drugs to which *Mycobacterium tuberculosis* was resistant was 6.2 (2.5). Overall, 439 (66.7%) out of 658 patients had been previously treated for TB.

The overall prevalence of drug resistance, related to the national drug resistance prevalence and-sample size, was as follows: streptomycin 415 (86.3%), pyrazinamide 368 (77.0%), ethambutol 476 (75.1%), fluoroquinolones 385 (61.9%), ethionamide/prothionamide 285 (60.8%), kanamycin 315 (52.9%), capreomycin 180 (31.0%), amikacin 171 (30.3%), PAS 86 (23.1%), cycloserine/terizidone 25 (7.9%) and linezolid 12 (4.7%).

Treatment regimens included, in addition to bedaquiline and/or delamanid, linezolid (81.5%), moxifloxacin (37.1%), levofloxacin (36.6%), clofazimine (32.4%), capreomycin (28.4%), amikacin (19.9%) and carbapenems (11.2%).

The median (IQR) range of the administrative delay in procuring bedaquiline was 0 (0–11) days. Patients were exposed to bedaquiline for a median (IQR) of 170 (99 -239) days, and to delamanid for 168 (145.5-182) days. Adjuvant surgical therapy and subsequent pulmonary rehabilitation were performed in 77 (11.9%) patients.

The median (IQR) treatment duration in the cohort was 385 (231-545) days, including 233 (35.9%) patients who completed treatment and 369 (56.7%) who were still on treatment (150/339, 44.2% having had 6 months of bedaquiline and 49/73, 67.1%, of delamanid) as of August 28$^{th}$ 2019.

**Adverse events**

Overall 504 AE episodes were reported by clinical centres of whom 447 (447/504, 88.7%) were classified as minor (grade 1-2) and 57 (57/504, 11.3%) were classified as serious (grade 3-5) (Electronic Annex 5).

*Serious AEs*

Overall, 57 serious AEs were reported by 55 patients for different organs/systems (57/504, 11.3%) (Table 2A-B, Electronic Annex 5), all resolved/resolving except 6 (6/57, 10.5%) as follows: 2 gastro/intestinal, 7 nervous system, 4 skin, 11 hearing, 5 psychiatric, 9 blood, 9 cardiac, 3 hepatic, and 7 renal (Electronic Annex 3).

The overall proportion of patients reporting serious AEs related to linezolid, clofazimine, bedaquiline and delamanid in patients treated with these medicines was 2.8% (15/536), 1.4% (3/213), 1.0% (6/577) and 0.8% (1/121), respectively (Table 2A). Among patients who completed treatment the proportion of serious AEs was (non significantly) higher (Table 2B).

Clinicians reported to have notified the AEs to the health authorities in their countries as follows: 30/57 (52.6%) serious and 19/447 (4.3%) minor AEs, respectively.

*Cardiological AEs*

Overall 17 out of 658 (2.6%) patients experienced a QTcF (Fridericia-corrected) prolongation ≥500 msec. Among them 16 received bedaquiline (6 with serious and 10 with minor AEs, 2 of them with co-administered delamanid). In a single case, treated with delamanid alone, a serious AE was reported and attributed to moxifloxacin (Table 3).

A QTcF interval prolongation causing serious cardiological AEs was reported by 8 patients only (Table 3); the drug responsible was bedaquiline in 4 patients, clofazimine in 2 patients, moxifloxacin and PAS in one patient, while in another patient it was due to a non-TB drug (amitriptyline, data not shown). No deaths were recorded. Out of those who received bedaquiline, the drug was withdrawn only in 2 patients reporting serious AEs (2/577, 0.35%), whilst in 2 patients the QT normalised after interrupting the concomitant administration of clofazimine. All serious QT-related AEs resolved/are resolving.

A single patient had one minor AE related to QTcF prolongation requiring withdrawal of the drug (moxifloxacin replaced by levofloxacin) (Electronic Annex 4).

Overall, 32 patients experienced minor AEs related to QT prolongation, the majority due to bedaquiline (28, 87.5%) and fluoroquinolones (3, 9.3%) (Electronic Annex 4).

A single patient discontinued delamanid after experiencing a serious AE (ventricular bigeminy arrhythmia appearing 4 days into treatment) (Table 3).

**Discussion**

The aim of the present study was to prospectively evaluate the frequency and severity of AEs due to anti-TB drugs in a cohort of consecutive patients following the principles and methods of the WHO aDSM project.

The project worked as a 'register' according to the WHO proposal to national programmes, aimed at promoting regular monitoring of AEs, as well as collecting and reporting information on bacteriological status at diagnosis, during and at the end of treatment with final outcomes (7,29,30). WHO recommends countries to use their existing surveillance methodology (electronic registers or existing electronic medical record systems) to extract the data and use them for clinical and public health purposes (29).

As of today, national TB programmes face difficulties in implementing aDSM and contributing to the global database. While the amount and type of information to collect is known and there is a sufficient burden of patients to satisfy the need to establish a routine AE recording and reporting system, the existing surveillance systems are currently not equipped to collect and analyse relevant variables.

The present project represents the first effort to document the feasibility of the aDSM approach and to collect quality scientific evidence on the AEs in patients treated with new and repurposed drugs in 'field conditions' in countries from all continents. The available scientific evidence on the safety and tolerability profile of anti-TB drugs can be retrieved from single observational and experimental studies. This project provides an international assessment following a register-based methodology.

A first important finding of the study is that when treatment regimens including bedaquiline and delamanid are used, the overall proportion of AEs is reasonably low (8.7% of patients with serious AEs (Grade 3 and 4, no Grade 5 AEs)).

Notably, the injectables (and ethionamide) are the drugs causing more AEs (Table 2A-B). With the new WHO all-oral approach (6,7) and the availability of new drugs, capreomycin will no longer be used, and amikacin as well as ethionamide/prothionamide (and PAS) will be used less. On the other hand, linezolid will increasingly be used, and being a drug with frequent and serious AE (20) there is a need to balance efficacy and toxicity (34). Therapeutic drug monitoring may help achieve a therapeutic target of AUC/MIC (area under the curve /minimal inhibitory concentration) >119 (35) while keeping trough concentrations low enough to prevent toxicity (36).

A second important outcome of this study is the possibility to carefully analyse the AEs caused by bedaquiline and delamanid and by repurposed drugs. While overall 11.1% of the patients had AEs to bedaquiline and 13.2% to delamanid (Table 2A), the serious AEs due to these drugs were few

with only 2 patients discontinuing bedaquiline (0.35%) and 1 discontinuing delamanid (0.8%) because of cardiological AEs (14,37).
The proportion of patients reporting serious AEs related to linezolid- and clofazimine-treated patients was 3% and 1.4%, respectively (Electronic Annex 3).

Overall, 5.8% of the patients experienced an AE with levofloxacin and 3.8% with moxifloxacin, while only 2 patients had serious AEs with normal dose moxifloxacin. None of the 12 patients treated with high-dose isoniazid and high-dose moxifloxacin reported AEs.
Worryingly, an important proportion of AEs identified by care providers were not reported to health authorities at the national level. We speculate that the explanations for the AE under-reporting include lack of awareness, the administrative burden (need to report to the country and to the aDSM system and to the drug manufacturer with different forms and multiple steps), confidentiality issues, the involvement of different sectors (public and private, prisons, etc.) and the fear to be blamed.
Furthermore, there were a few discrepancies on grading of the AE 'QTc prolongation'. In 4 patients the AEs were initially categorised as minor even though they had resulted in withdrawal of the offending drug. In agreement with the treating physician these AEs were re-classified as serious. Asymptomatic conditions like QTc prolongation need clear and well publicized criteria for accurate grading. QTc interval monitoring is usually performed in MDR-TB patients exposed to bedaquiline and delamanid in the WHO European Region; although rare fatal events have been recorded, the electrocardiogram is a cost-effective preventive intervention for those at risk of developing cardiologic AEs (38).
To avoid premature discontinuation of potent drugs, available national and or international expert panels could be consulted for guidance (5,31). Medical conditions which can significantly increase the probability of a cardiological AE in MDR-TB patients (*i.e.*, hypokalemia and AIDS) should be carefully monitored (39).
When compared with the recent individual data meta-analysis performed in 5 cohorts (Armenia, Georgia, South Africa, France and Janssen Therapeutic cohort) on 537 patients treated with bedaquiline under compassionate use (13), the proportion of AEs seems rather consistent with those found in our study. For example, 4.9% of patients suffered cardiac AEs in the 5-cohort study similar to the 5.5% in our study (denominator: patients treated with bedaquiline). Similarly, the proportion of interruptions of bedaquiline treatment in our study due to QTcF increase (0.35%) is consistent with that described in a recent systematic review of the literature (0.68%) (26).
The study has several strengths including the number of countries participating (26) and a large sample size (to our knowledge one of the largest multinational cohorts of MDR- TB patients treated

with bedaquiline- and/or delamanid-containing regimens based on WHO aDSM protocol), the prospective design, and the accuracy of the information collected in countries with different epidemiological and economic background. Last but not least, the majority of countries/states/regions (21/26) provided data on all the consecutive patients treated with bedaquiline and delamanid during the study period.

A limitation is represented by the use of a consensus-based process to attribute AEs to a specific drug, which included the local expert panel and the aDSM International Group panel. The scientific evidence on the safety and tolerability profile of a single drug or of a pharmacological combination was the driver adopted to identify the drug responsible of an AE; the probability of proving a causal relationship in specific patients, where the scientific evidence is poor, is very low. Further studies focused on the anti-TB drugs' safety, based on the re-challenge methodology (*i.e.*, drug administration after interruption following an AE's occurrence) could help elucidate the AEs' profile of the anti-TB drugs. Furthermore, only a few centres carried out therapeutic drug monitoring to assess the relationship between AEs and drug exposure (dosage and frequency of administration). Moreover, no variables related to concomitant medications, which could affect drug exposure, were recorded, with the only exception of HIV therapy in patients with HIV-infection. It was not possible to use approaches like the Naranjo score or the Yale algorithm (40,41). A second limitation is that few paediatric patients (four individuals aged less than 18 years) and people living with HIV (29; 4.4%) were included in the cohort to allow specific sub-analyses. The psychological role played by providing information on the treatment failure risk following drug withdrawal, as well as potential biased communication with migrants and the clinical setting (e.g., ambulatory care), could have affected the patients' tolerability profile and the AEs' reporting. Unfortunately, we did not collect any variables which could evaluate those important features. Furthermore, we evaluated the occurrence of AEs in both individuals completing their regimen and still on treatment, for whom the cumulative drug-toxicity (e.g., from linezolid) may be under-estimated. Among patients who completed treatment, where the cumulative toxicity can be adequately assessed, the proportion of AEs was (non significantly) higher.

We did not collect any genetic/pharmacogenomic data, which could increase the risk of some AEs. Future studies are needed to better clarify the role played by host and environmental characteristics in the occurrence of AEs.

Finally, as the majority of countries started their aDSM project with this study, pre-selection or under-notification of AEs (particularly minor ones and those not related to the new drugs) cannot be excluded. The under-reporting in a real-world setting can be a key issue in estimating the safety profile of a drug/pharmacologic regimen. Healthcare workers and patients should be aware of the

importance of reporting the AEs' occurrence to better understand the pharmacologic safety and the benefit/risk ratio of a prescription. A classification bias of some AEs should be considered: although all clinical centres enrolled in the project followed the WHO protocol on AEs' reporting, local audits aimed at assessing the implementation of the standard operating procedures (e.g., regular audiometry) were not carried out because of financial constraints.

Unfortunately, several countries (in America, Asia and Sub-Saharan Africa) when asked to participate, declined in view of the voluntary basis of the study perceived as 'difficult' 'or time-consuming' without provision for additional resources. For this reason, and because of the different entry time in the study (which works as a 'register'), the study does not allow us to evaluate the prevalence of drug-resistance in the different settings. There is an urgent need to overcome the administrative burden involved in reporting AE by easy-to-use e-forms that can be automatically-compiled from medical records.

The study will continue to evaluate early and final treatment outcomes as periodic updates occur and the 'cohort' is therefore a 'living' one. This cohort allows evaluation of novel treatments and combinations in a relatively short time-frame – particularly important given the substantial variation in international practice and guidelines recommending person-centered therapy for MDR-TB (42,43).

This approach will allow the participating countries to evaluate the 'quality' of their treatment services and minimise the risk of post-treatment sequelae responsible of functional damage and impaired quality of life (44-46).

In conclusion, the study results confirm that aDSM for patients undergoing anti-TB regimens with new drugs is feasible. Furthermore, the study reaffirms the relative safety of new drugs recommended by the new WHO guidelines, as the occurrence of serious AEs in this large cohort of patients from 26 countries was observed in less than 10% of patients. Greater adoption of the recommended aDSM at a local, national, and international level is possible by improving the quality of the process (*i.e.*, standardized, active, and regular recording and reporting based on shared standard operating procedures).

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**Authors'contribution:**
The manuscript was conceived, planned, written, edited and approved using a collaborative approach, following the internal GTN (Global Tuberculosis Network) and internationally acknowledged rules on Authorship, based on major intellectual contribution to the steps mentioned above. The study represents a global effort involving 26 countries in all continents.

Giovanni Sotgiu, Simon Tiberi, Rosella Centis, Lia D'Ambrosio and Giovanni Battista Migliori wrote the protocol. Giovanni Sotgiu, Laura Saderi and Raquel Duarte revised it for the methodological content.

Giovanni Sotgiu, Laura Saderi, Rosella Centis and Lia D'Ambrosio performed the analysis.

Simon Tiberi, Rosella Centis, Lia D'Ambrosio, Emanuele Pontali, Jan-Willem Alffenaar, Jose A. Caminero, Giovanni Sotgiu and Giovanni Battista Migliori wrote the first draft of the manuscript.

Sergey Borisov, Judith Bruchfeld, Alberto Piubello, Onno Akkermann, Justin Denholm, José-María García-García, Rafael Laniado-Laborín, Jesica Mazza-Stalder, Alberto Matteelli, Marcela Munoz-Torrico, Martin van den Boom, Dina Visca, Jose A. Caminero, Giovanni Sotgiu wrote the sections of the manuscript (second draft).

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**References**


1) World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Document WHO/CDS/TB/2018.20 Licence: CC BY-NC-SA 3.0 IGO.
2) Pontali E, Raviglione MC, Migliori GB and the writing group members of the Global TB Network Clinical Trials Committee. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev 2019 in press
3) Migliori GB, Nardell E, Yedilbayev A, D'Ambrosio L, Centis R, Tadolini M, van den Boom M, Ehsani S, Sotgiu G, Dara M. Reducing tuberculosis transmission: a consensus document from the World Health Organization Regional Office for Europe. Eur Respir J. 2019 5;53(6). pii: 1900391. doi: 10.1183/13993003.00391-2019
4) Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, Vink K, Jaramillo E, Espinal MA. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis. 2004 Nov;8(11):1382-4.
5) Tiberi S, Pontali E, Tadolini M, D'Ambrosio L, Migliori GB. Challenging MDR-TB clinical problems - The case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs. Int J Infect Dis. 2019 Mar;80S:S68-S72. doi: 10.1016/j.ijid.2019.01.040
6) World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. WHO/CDS/TB/2019.3 Licence: CC BY-NC-SA 3.0 IGO.
7) Migliori GB, Global Tuberculosis Network (GTN). Evolution of Programmatic Definitions Used in Tuberculosis Prevention and Care. Clin Infect Dis. 2018 Nov 20. doi: 10.1093/cid/ciy990.
8) Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, Leimane V, Andries K, Bakare N, De Marez T, Haxaire-Theeuwes M, Lounis N, Meyvisch P, De Paepe E, van Heeswijk RP, Dannemann B; TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014 Aug 21;371(8):723-32. doi: 10.1056/NEJMoa1313865.
9) Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, Vasilyeva I, Andries K, Bakare N, De Marez T, Haxaire-Theeuwes M, Lounis N, Meyvisch P, Van Baelen B, van Heeswijk RP, Dannemann B; TMC207-C209 Study Group. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2016; 47(2): 564–574.
10) Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, Sotgiu G, Tiberi S, Alffenaar JW, Maryandyshev A, Belilovski E, Ganatra S, Skrahina A, Akkerman O,

Aleksa A, Amale R, Artsukevich J, Bruchfeld J, Caminero JA, Carpena Martinez I, Codecasa L, Dalcolmo M, Denholm J, Douglas P, Duarte R, Esmail A, Fadul M, Filippov A, Davies Forsman L, Gaga M, Garcia-Fuertes JA, García-García JM, Gualano G, Jonsson J, Kunst H, Lau JS, Lazaro Mastrapa B, Teran Troya JL, Manga S, Manika K, González Montaner P, Mullerpattan J, Oelofse S, Ortelli M, Palmero DJ, Palmieri F, Papalia A, Papavasileiou A, Payen MC, Pontali E, Robalo Cordeiro C, Saderi L, Sadutshang TD, Sanukevich T, Solodovnikova V, Spanevello A, Topgyal S, Toscanini F, Tramontana AR, Udwadia ZF, Viggiani P, White V, Zumla A, Migliori GB. Effectiveness and safety of bedaquiline-containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis: a multicentre study. Eur Respir J 2017; 49(5). pii:1700387.

11) Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and MDR-TB: a systematic and critical analysis of the evidence. Eur Respir J 2016; 47: 394–402.
12) Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori G.B. Multidrug-resistance tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. Eur Respir J 2017; 49: pii: 1700146; doi.10.1183/13993003.00146-2017
13) Mbuagbaw L, Guglielmetti L, Hewison C, Bakare N, Bastard M, Caumes E, Fréchet-Jachym M, Robert J, Veziris N, Khachatryan N, Kotrikadze T, Hayrapetyan A, Avaliani Z, Schünemann HJ, Lienhardt C. Outcomes of Bedaquiline Treatment in Patients with Multidrug-Resistant Tuberculosis. Emerg Infect Dis. 2019 May;25(5):936-943. doi: 10.3201/eid2505.181823.
14) 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 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). pii: 1801528. doi: 10.1183/13993003.01528-2018.
15) Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, Gao M, Awad M, Park SK, Shim TS, Suh GY, Danilovits M, Ogata H, Kurve A, Chang J, Suzuki K, Tupasi T, Koh WJ, Seaworth B, Geiter LJ, Wells CD. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012;366(23):2151-60. doi: 10.1056/NEJMoa1112433.
16) Kim CT, Kim TO, Shin HJ, Ko YC, Hun Choe Y, Kim HR, Kwon YS. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis:a multi-center cohort study in Korea. Eur Respir J 2018;51(3). pii: 1702467. doi: 10.1183/13993003.02467-2017.

17) Kuksa L, Barkane L, Hittel N, Gupta R. Final treatment outcomes of multidrug and extensively drug-resistant tuberculosis patients in Latvia receiving delamanid-containing regimens. Eur Respir J 2017; 50(5). pii: 1701105.
18) Mohr E, Hughes J, Reuter A, Trivino Duran L, Ferlazzo G, Daniels J, De Azevedo V, Kock Y, Steele SJ, Shroufi A, Ade S, Alikhanova N, Benedetti G, Edwards J, Cox H, Furin J, Isaakidis P. Delamanid for rifampicin-resistant tuberculosis: a retrospective study from South Africa. Eur Respir J 2018; 51(6). pii:1800017. doi: 10.1183/13993003.00017-2018.
19) Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, Bang D, Barry PM, Bastos ML, Behera D, Benedetti A, Bisson GP, Boeree MJ, Bonnet M, Brode SK, Brust JCM, Cai Y, Caumes E, Cegielski JP, Centis R, Chan PC, Chan ED, Chang KC, Charles M, Cirule A, Dalcolmo MP, D'Ambrosio L, de Vries G, Dheda K, Esmail A, Flood J, Fox GJ, Fréchet-Jachym M, Fregona G, Gayoso R, Gegia M, Gler MT, Gu S, Guglielmetti L, Holtz TH, Hughes J, Isaakidis P, Jarlsberg L, Kempker RR, Keshavjee S, Khan FA, Kipiani M, Koenig SP, Koh WJ, Kritski A, Kuksa L, Kvasnovsky CL, Kwak N, Lan Z, Lange C, Laniado-Laborín R, Lee M, Leimane V, Leung CC, Leung EC, Li PZ, Lowenthal P, Maciel EL, Marks SM, Mase S, Mbuagbaw L, Migliori GB, Milanov V, Miller AC, Mitnick CD, Modongo C, Mohr E, Monedero I, Nahid P, Ndjeka N, O'Donnell MR, Padayatchi N, Palmero D, Pape JW, Podewils LJ, Reynolds I, Riekstina V, Robert J, Rodriguez M, Seaworth B, Seung KJ, Schnippel K, Shim TS, Singla R, Smith SE, Sotgiu G, Sukhbaatar G, Tabarsi P, Tiberi S, Trajman A, Trieu L, Udwadia ZF, van der Werf TS, Veziris N, Viiklepp P, Vilbrun SC, Walsh K, Westenhouse J, Yew WW, Yim JJ, Zetola NM, Zignol M, Menzies D. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821-834. doi: 10.1016/S0140-6736(18)31644-1.
20) Sotgiu G, Centis R, D'Ambrosio L, Alffenaar J, Anger H, Caminero J, Castiglia P, De Lorenzo S, Ferrara G, Koh W, Schecter G, Shim T, Singla R, Skrahina A, Spanevello A, Udwadia Z, Villar M, Zampogna E, Zellweger J, Zumla A, Migliori GB. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J. 2012;40(6):1430-42
21) Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 2015; 45: 161–170.
22) Dalcolmo M, Gayoso R, Sotgiu G, D'Ambrosio L, Rocha JL, Borga L,Fandinho F, Ueleres Braga J, Neder Galesi VM, Barreira D, Arakaki Sanchez D, Dockhorn F, Centis C, Caminero JA, Migliori GB.Effectiveness and safety of clofazimine within a standard multidrug-resistant

tuberculosis regimen in Brazil: first nation-wide report on over 2,500 cases. Eur Respir J 2017; Mar 22;49(3). pii: 1602445. doi: 10.1183/13993003.02445-2016

23) Tiberi S, Payen MC, Sotgiu G, D'Ambrosio L, Alarcon Guizado V, Alffenaar JW, Abdo Arbex M, Caminero J.A, Centis R, De Lorenzo S, Gaga M, Gualano G, Jazmín Roby Arias A, Scardigli A, Skrahina A, Solovic I, Sulis G, Tadolini M, W. Akkerman O, Alarcon Arrascue E, Aleska A, Avchinko V, Bonini E. H, Chong Marín F. A, Collahuazo López L, de Vries G, Dore S, Kunst H, Matteelli A, Moschos C, Palmieri F, Papavasileiou A, Spanevello A, Vargas Vasquez D, Viggiani P, White V, Zumla A and Migliori G.B. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis. Eur Respir J. 2016; 47: 1235-43.
24) Tiberi S, Sotgiu G, D'Ambrosio L, Centis R, Abdo Arbex M, Alarcon Arrascue E, Alffenaar JW, Caminero JA, Gaga M, Gualano G, Skrahina A, Solovic I, Sulis G, Tadolini M, Alarcon Guizado V, De Lorenzo S, Roby Arias AJ, Scardigli A, Akkerman OW, Aleksa A, Artsukevich J, Auchynka V, Bonini EH, Chong Marín FA, Collahuazo López L, de Vries G, Dore S, Kunst H, Matteelli A, Moschos C, Palmieri F, Papavasileiou A, Payen MC, Piana A, Spanevello A, Vargas Vasquez D, Viggiani P, White V, Zumla A, Migliori GB. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J. 2016 Jun;47(6):1758-66. doi: 10.1183/13993003.00214-2016.
25) Tiberi S; Sotgiu G; D'Ambrosio L; Centis R; Abdo Arbex M; Alarcon Arrascue E; Alffenaar JW; Caminero JA; Gaga M; Gualano G; Skrahina A; Solovic I; Sulis G; Tadolini M; Alarcon Guizado V; De Lorenzo S; Roby Arias AJ; Scardigli A; Akkerman OW; Aleksa A; Artsukevich J; Avchinko V; Bonini EH; Chong Marin FA; Collahuazo Lopez L; de Vries G; Dore S; Kunst H; Matteelli A; Moschos C; Palmieri F; Papavasileiou A; Payen MC; Piana A; Spanevello A; Vargas Vasquez D; Viggiani P; White V; Zumla A; Migliori GB. Effectiveness and Safety of Imipenem-Clavulanate Added to an Optimized Background Regimen (OBR) Versus OBR Control Regimens in the Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis. Clin Infect Dis. 2016 May 1;62(9):1188-90. doi: 10.1093/cid/ciw088
26) Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori G.B. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J 2017; 50(5). pii: 1701462.
27) Pontali E, Sotgiu G, Tiberi S, Tadolini M, Visca D, D'Ambrosio L, Centis R, Spanevello A, Migliori GB. Combined treatment of drug-resistant tuberculosis with bedaquiline and delamanid: a systematic review. Eur Respir J 2018; 52(1). pii: 1800934

28) World Health Organization. Active TB drug-safety monitoring and management (aDSM). WHO/HTM/TB/2015.28. Geneva, World Health Organization 2015.
29) Halleux CM, Falzon D, Merle C, Jaramillo E, Mirzayev F, Olliaro P, Weyer K. The World Health Organization global aDSM database: generating evidence on the safety of new treatment regimens for drug-resistant tuberculosis. Eur Respir J 2018; 51(3): pii:1701643 doi.org/10.1183/13993003.01643-2017.
30) Akkerman O, Aleksa A, Alffenaar JW, Al-Marzouqi NH, Arias-Guillén M, Belilovski E, Bernal E, Boeree MJ, Borisov SE, Bruchfeld J, Cadiñanos Loidi J, Cai Q, Caminero JA, Cebrian Gallardo JJ, Centis R, Codecasa LR, D'Ambrosio L, Dalcolmo M, Danila E, Dara M, Davidavičienė E, Davies Forsman L, De Los Rios Jefe J, Denholm J, Duarte R, Elamin SE, Ferrarese M, Filippov A, Ganatra S, Garcia A, García-García JM, Gayoso R, Giraldo Montoya AM, Gomez Rosso RG, Gualano G, Hoefsloot W, Ilievska-Poposka B, Jonsson J, Khimova E, Kuksa L, Kunst H, Laniado-Laborín R, Li Y, Magis-Escurra C, Manfrin V, Manga S, Marchese V, Martínez Robles E, Maryandyshev A, Matteelli A, Migliori GB, Mullerpattan JB, Munoz-Torrico M, Mustafa Hamdan H, Nieto Marcos M, Noordin NM, Palmero DJ, Palmieri F, Payen MC, Piubello A, Pontali E, Pontarelli A, Quirós S, Rendon A, Skrahina A, Šmite A, Solovic I, Sotgiu G, Souleymane MB, Spanevello A, Stošić M, Tadolini M, Tiberi S, Udwadia ZF, van den Boom M, Vescovo M, Viggiani P, Visca D, Zhurkin D, Zignol M, Members of the International Study Group on new anti-tuberculosis drugs and adverse events monitoring. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: A global feasibility study. Int J Infect Dis. 2019 ;83:72-76. doi: 10.1016/j.ijid.2019.03.036.
31) Rossato Silva D, Rendon A, Alffenaar JW, Chakaya JM, Sotgiu G, Esposito S, Migliori GB. Global TB Network: working together to eliminate tuberculosis. J Bras Pneumol. 2018; 44 (5):347-349. doi: 10.1590/S1806-37562018000000279.
32) U.S. Department of Health and Human Services, National Institutes of Health,National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Last access 28 July 2019.
33) R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org. Data last access 28 July 2019
34) Bolhuis MS, Akkerman OW, Sturkenboom MGG, Ghimire S, Srivastava S, Gumbo T, Alffenaar JC. Linezolid-based Regimens for Multidrug-resistant Tuberculosis (TB): A

Systematic Review to Establish or Revise the Current Recommended Dose for TB Treatment. Clin Infect Dis. 2018 Nov 28;67(suppl_3):S327-S335.

35) Srivastava S, Magombedze G, Koeuth T, Sherman C, Pasipanodya JG, Raj P, Wakeland E, Deshpande D, Gumbo T. Linezolid Dose That Maximizes Sterilizing Effect While Minimizing Toxicity and Resistance Emergence for Tuberculosis. Antimicrob Agents Chemother. 2017;61(8). pii: e00751-17.
36) Song T, Lee M, Jeon HS, Park Y, Dodd LE, Dartois V, Follman D, Wang J, Cai Y, Goldfeder LC, Olivier KN, Xie Y, Via LE, Cho SN, Barry CE 3rd, Chen RY. Linezolid Trough Concentrations Correlate with Mitochondrial Toxicity-Related Adverse Events in the Treatment of Chronic Extensively Drug-Resistant Tuberculosis. EBioMedicine. 2015 Oct 9;2(11):1627-33.
37) von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V Jr, Ticona E, Segura P, Cadena E, Yu C, Cirule A, Lizarbe V, Davidaviciene E, Domente L, Variava E, Caoili J, Danilovits M, Bielskiene V, Staples S, Hittel N, Petersen C, Wells C, Hafkin J, Geiter LJ, Gupta R. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med. 2019;7(3):249-259.
38) Guglielmetti L, Tiberi S, Burman M, Kunst H, Wejse C, Togonidze T, Bothamley G, Lange C; TBnet; of the TBnet QTc survey. QT prolongation and cardiac toxicity of new tuberculosis drugs in Europe: a Tuberculosis Network European Trialsgroup (TBnet) study. Eur Respir J. 2018 Aug 16;52(2). pii: 1800537. doi: 10.1183/13993003.00537-2018
39) Monedero-Recuero I, Hernando-Marrupe L, Sánchez-Montalvá A, Cox V, Tommasi M, Furin J, Chiang CY, Quelapio M, Koura KG, Trébucq A, Padanilam X, Dravniece G, Piubello A. QTc and anti-tuberculosis drugs: a perfect storm or a tempest in a teacup? Review of evidence and a risk assessment. Int J Tuberc Lung Dis. 2018; 22(12): 1411-1421
40) Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. doi:10.1038/clpt.1981.154. PMID 7249508.
41) Kramer MS, Hutchinson TA. The Yale algorithm. Special workshop--clinical. Drug Inf J. 1984;18(3-4):283-91.
42) Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, van Deun A, Dat PT, Lan N, Master I, Mebrahtu T, Meressa D, Moodliar R, Ngubane N, Sanders K, Squire SB, Torrea G, Tsogt B, Rusen ID; STREAM Study Collaborators. A Trial of a Shorter Regimen for

Rifampin-Resistant Tuberculosis. N Engl J Med. 2019;380(13):1201-1213. doi: 10.1056/NEJMoa1811867.

43) Churchyard GJ. A Short Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2019;380(13):1279-1280. doi: 10.1056/NEJMe1902904.

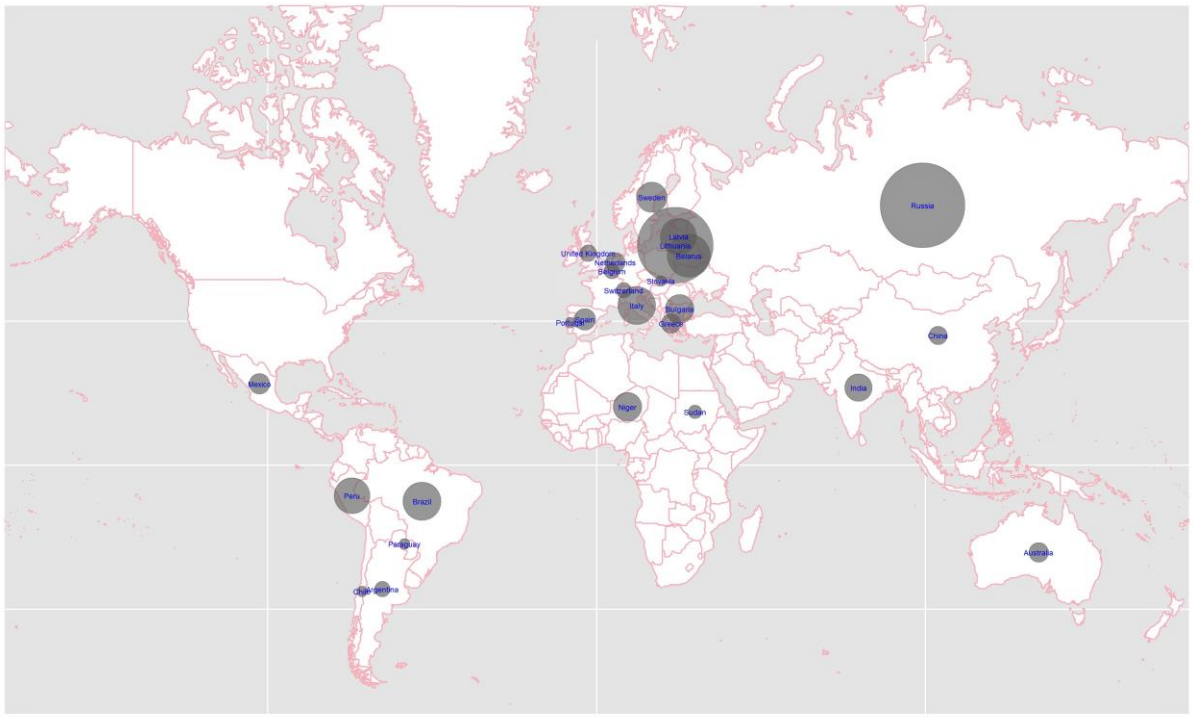
44) Muñoz-Torrico M, Rendon A, Centis R, D'Ambrosio L, Fuentes Z, Torres-Duque C, Mello F, Dalcolmo M, Pérez-Padilla R, Spanevello A, Migliori GB. Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis? J Bras Pneumol. 2016;42(5):374-385. doi: 10.1590/S1806-37562016000000226.

45) Tiberi S, Torrico MM, Rahman A, Krutikov M, Visca D, Silva DR, Kunst H, Migliori GB. Managing severe tuberculosis and its sequelae: from intensive care to surgery and rehabilitation. J Bras Pneumol. 2019;45(2):e20180324. doi: 10.1590/1806-3713/e20180324.

46) Visca D, Zampogna E, Sotgiu G, Centis R, Saderi L, D'Ambrosio L, Pegoraro V, Pignatti P, Muňoz-Torrico M, Migliori GB, Spanevello A. Pulmonary rehabilitation is effective in patients with tuberculosis pulmonary sequelae. Eur Respir J. 2019;53(3). pii: 1802184. doi: 10.1183/13993003.02184-2018.

**Figure 1:** Global distribution of the clinical centres participating in the study. The size of the grey dots reflects the number of patients reported.

**Figure 2:** Summary of the distribution of 57 serious adverse events by organ/system


Russia
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Latvia
Lithuania
Belarus
United Kingdom
Netherlands
Belgium
Slovakia
Switzerland
Italy
Bulgaria
Greece
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China
India
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Niger
Sudan
Peru
Brazil
Paraguay
Chile
Argentina
Australia

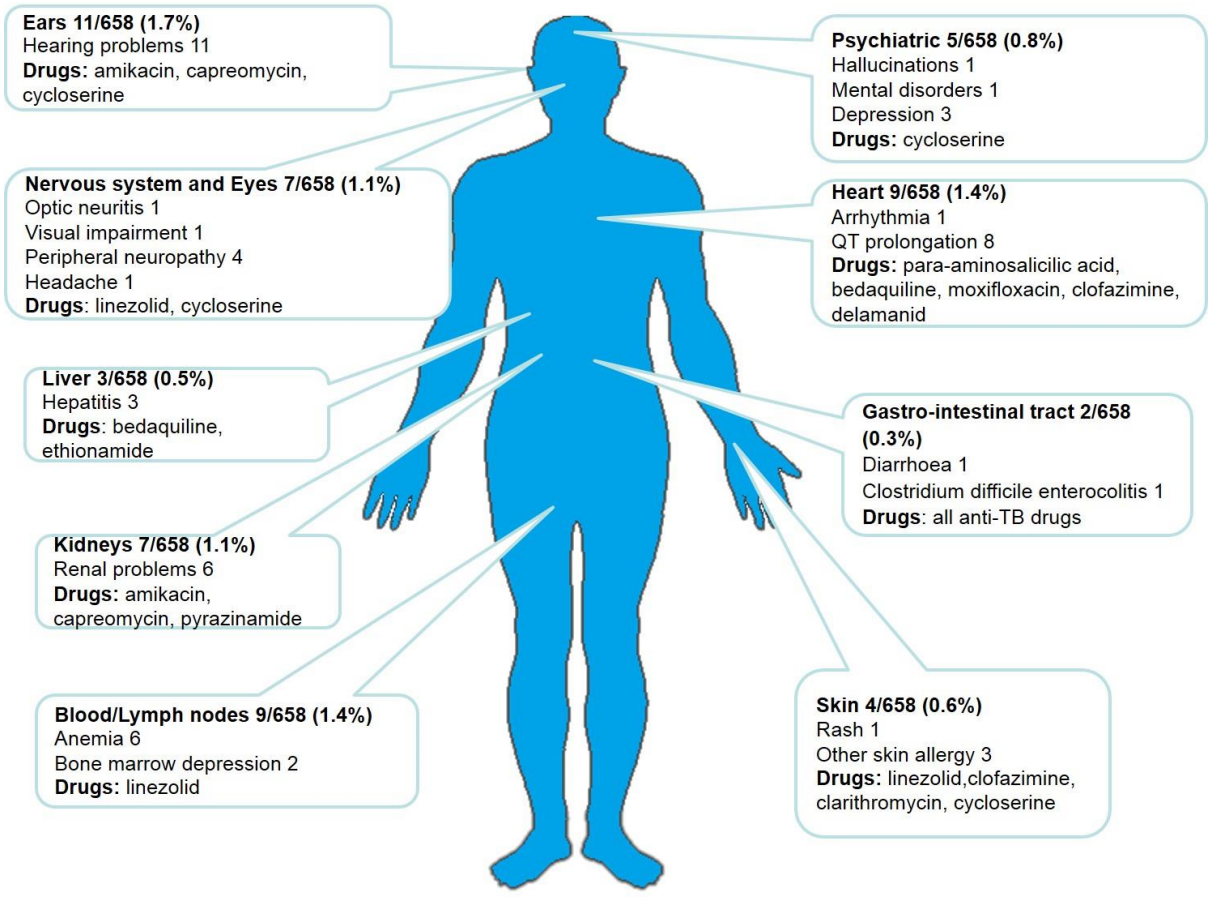
**Ears 11/658 (1.7%)**
Hearing problems 11
**Drugs:** amikacin, capreomycin, cycloserine
**Psychiatric 5/658 (0.8%)**
Hallucinations 1
Mental disorders 1
Depression 3
**Drugs:** cycloserine
**Nervous system and Eyes 7/658 (1.1%)**
Optic neuritis 1
Visual impairment 1
Peripheral neuropathy 4
Headache 1
**Drugs**: linezolid, cycloserine
**Heart 9/658 (1.4%)**
Arrhythmia 1
QT prolongation 8
**Drugs:** para-aminosalicilic acid, bedaquiline, moxifloxacin, clofazimine, delamanid
**Liver 3/658 (0.5%)**
Hepatitis 3
**Drugs**: bedaquiline, ethionamide
**Gastro-intestinal tract 2/658 (0.3%)**
Diarrhoea 1
Clostridium difficile enterocolitis 1
**Drugs**: all anti-TB drugs
**Kidneys 7/658 (1.1%)**
Renal problems 6
**Drugs:** amikacin, capreomycin, pyrazinamide
**Blood/Lymph nodes 9/658 (1.4%)**
Anemia 6
Bone marrow depression 2
**Drugs:** linezolid
**Skin 4/658 (0.6%)**
Rash 1
Other skin allergy 3
**Drugs:** linezolid,clofazimine, clarithromycin, cycloserine

**Table 1. Descriptive analysis of the characteristics of 658 TB patients by area of origin (Europe vs. other settings)**

| Variables | Total (n= 658) | Geographic area of origin | | |
|---|---|---|---|---|
| | | Non-European (n= 120) | European (n= 538) | p-value* |
| Male, n (%) | 452/658 (68.7) | 80/120 (66.7) | 372/538 (69.1) | 0.60 |
| Median (IQR) age, years | 42 (33-53) | 40.5 (30-54) | 42.5 (34-53) | 0.25 |
| Median (IQR) body weight, Kg | 60 (53-70) | 54.7 (49.0-61.5) | 62 (54-71) | <0.0001 |
| Median (IQR) height, cm | 173 (165-178) | 167 (160-174) | 174 (168-178) | <0.0001 |
| Migrant, n (%) | 85/656 (13.0) | 8/120 (6.79 | 77/536 (14.4) | 0.02 |
| Pregnant, n (%) | 5/347 (1.4) | 2/72 (2.8) | 3/275 (1.1) | 0.28 |
| Breastfeeding women, n (%) | 2/326 (0.6) | 2/66 (3.0) | 0/260 (0.0) | 0.04 |
| Thyroid disease, n (%) | 9/568 (1.6) | 4/120 (3.3) | 5/448 (1.1) | 0.10 |
| Patients with previous ECG abnormalities, n (%) | 68/545 (12.5) | 6/120 (5.0) | 62/425 (14.6) | 0.004 |
| Alcohol abuser, n (%) | 148/657 (22.5) | 11/119 (9.2) | 137/538 (25.5) | <0.0001 |
| Drug abuser, n (%) | 41/658 (6.2) | 6/120 (5.0) | 35/538 (6.5) | 0.54 |
| Methadone user, n (%) | 7/561 (1.3) | 0/120 (0.0) | 7/441 (1.6) | 0.36 |
| Patients with diabetes mellitus, n (%) | 63/651 (9.7) | 19/120 (15.8) | 44/531 (8.3) | 0.02 |
| People living with HIV, n (%) | 29/655 (4.4) | 0/120 (0.0) | 29/535 (5.4) | <0.0001 |
| Median (IQR) CD4 counts, cells\mmc | 94 (30-212) | - | 94 (30-212) | - |
| Patients on ART, n (%) | 27/29 (93.1) | 0/60 (0.0) | 27/145 (18.6) | <0.0001 |
| Previous anti-TB treatment, n (%) | 439/658 (66.7) | 109/120 (90.8) | 330/538 (61.3) | <0.0001 |
| Surgical therapy, n (%) | 77/647 (11.9) | 6/120 (5.0) | 71/527 (13.5) | 0.01 |
| Pulmonary TB, n (%) | 648/658 (7.1) | 119/120 (99.2) | 529/538 (98.3) | 0.50 |
| Extra-pulmonary TB, n (%) | 47/658 (7.1) | 2/120 (1.7) | 45/538 (8.4) | 0.006 |
| Sputum smear positives, n (%) | 451/657 (68.7) | 116/120 (96.7) | 335/537 (62.4) | <0.0001 |
| Culture positives, n (%) | 590/657 (89.8) | 118/120 (98.3) | 472/537 (87.9) | 0.001 |

*Non-European VS. European

**Legend:** TB: tuberculosis; IQR: Interquartile Range; ECG: Electrocardiogram; ART: antiretroviral therapy

**Table 2A: Serious (grade 3-5) and minor (grade 1-2) adverse events per drug in the overall cohort (658 TB patients).**

| | Total adverse events[#] | | Patients with serious adverse events (n=52)^ | | Patients with minor adverse events (n=343) | |
|---|---|---|---|---|---|---|
| **Drugs** | **n* (%)** | **(95% CI)** | **n* (%)** | **(95% CI)** | **n* (%)** | **(95% CI)** |
| **Capreomycin** | 52/187 (27.8) | 21.4-34.2 | 5/187 (2.7) | 0.4-5.0 | 47/187 (25.1) | 18.9-31.3 |
| **Amikacin** | 30/131 (22.9) | 15.7-30.1 | 9/131 (6.9) | 2.6-11.2 | 21/131 (16.0) | 9.7-22.3 |
| **Ethionamide/ Prothionamide** | 39/221 (17.6) | 12.6-22.6 | 1/221 (0.4) | -0.4; 1.2 | 38/221 (17.2) | 12.2-22.2 |
| **Pyrazinamide** | 32/236 (13.6) | 9.2-18.0 | 1/236 (1.7) | 0.0-3.4 | 31/236 (13.1) | 8.8-17.4 |
| **Delamanid** | 16/121 (13.2) | 7.2-19.2 | 1/121 (0.8) | -0.8; 2.4 | 15/121 (12.4) | 6.5-18.3 |
| **Linezolid** | 69/536 (12.9) | 10.1-15.7 | 15/536 (2.8) | 1.4-4.2 | 54/536 (10.1) | 7.6-12.7 |
| **Bedaquiline** | 64/577 (11.1) | 8.5-13.7 | 6/577 (1.0) | 0.2-1.8 | 58/577 (10.1) | 7.6-12.6 |
| **PAS** | 24/215 (11.2) | 7.0-15.4 | 1/215 (0.5) | -0.4: 1.4 | 23/215 (10.7) | 6.6-14.8 |
| **Clofazimine** | 15/213 (7.0) | 3.6-10.4 | 3/213 (1.4) | -0.2; 3.0 | 12/213 (5.6) | 2.5-8.7 |
| **Cycloserine Terizidone** | 30/498 (6.0) | 3.9-8.1 | 8/498 (1.8) | 0.5-2.7 | 22/498 (4.4) | 2.6-6.2 |
| **Levofloxacin** | 14/241 (5.8) | 2.9-8.8 | 0/241 (0.0) | - | 14/241 (5.8) | 2.9-8.8 |
| **Clarithromycin** | 1/21 (4.8) | -4.3; 13.9 | 1/21 (4.8) | -4.3; 13.9 | 0/21 (0.0) | - |
| **Moxifloxacin** | 9/240 (3.8) | 1.4-6.2 | 1/240 (0.4) | -0.4; 1.2 | 8/240 (3.3) | 1.0-5.6 |

**Table 2B. Serious (grade 3-5) and minor (grade 1-2) adverse events per drug in 233 TB patients who completed treatment.**

| | Total adverse events | | Severe adverse events (n= 20) | | Minor adverse events (n= 176) | |
|---|---|---|---|---|---|---|
| **Drugs** | **n* (%)** | **(95% CI)** | **n (%)** | **(95% CI)** | **n (%)** | **(95% CI)** |
| **Capreomycin** | 27/80 (33.8) | 23.4-44.2 | 2/80 (2.5) | -0.9; 5.9 | 26/80 (32.5) | 22.2-42.8 |
| **Amikacin** | 12/42 (28.6) | 14.9-42.3 | 3/42 (7.1) | -0.7; 14.9 | 11/42 (26.2) | 19.9-39.5 |
| **Ethionamide/ prothionamide** | 20/71 (28.2) | 17.7-38.7 | 1/71 (1.4) | -1.3; 4.1 | 19/71 (26.8) | 16.5-37.1 |
| **Pyrazinamide** | 14/106 (13.2) | 6.8-19.6 | 1/106 (0.9) | -0.9; 2.7 | 12/106 (11.3) | 5.3-17.3 |
| **Delamanid** | 10/43 (23.3) | 10.7-35.9 | 1/43 (2.3) | -2.2; 6.8 | 9/43 (20.9) | 8.8-33.1 |
| **Linezolid** | 30/185 (16.2) | 10.8-21.5 | 5/185 (2.7) | 0.4-5.0 | 27/185 (14.6) | 9.5-19.7 |
| **Bedaquiline** | 34/205 (16.6) | 11.5-21.7 | 2/205 (1.0) | -0.4; 2.4 | 32/205 (15.6) | 10.6-20.6 |
| **PAS** | 11/102 (10.8) | 4.8-16.8 | 0/102 (0.0) | - | 11/102 (10.8) | 4.8-16.8 |
| **Clofazimine** | 9/71 (12.7) | 5.0-20.5 | 1/71 (1.4) | -1.3; 4.1 | 8/71 (11.3) | 3.9-18.7 |
| **Cycloserine Terizidone** | 14/178 (7.9) | 3.9-11.9 | 3/178 (1.7) | -0.2; 3.6 | 11/178 (6.2) | 2.7-9.7 |
| **Levofloxacin** | 6/88 (6.8) | 1.5-12.1 | 0/88 (0.0) | - | 6/88 (6.8) | 1.5-12.1 |
| **Clarithromycin** | 1/9 (11.1) | -9.4; 31.6 | 1/9 (11.1) | -9.4; 31.6 | 0/9 (0.0) | - |
| **Moxifloxacin** | 9/87 (10.3) | 3.9-16.7 | 0/87 (0.0) | - | 4/87 (4.6) | 0.2-9.0 |

**Legend Table 2A-2B**: CI: Confidence Interval; PAS: Para-aminosalicylic acid

# Cumulative frequency of adverse events occurred in patients treated with anti-TB drugs

* Numerator is the number of patients who had at least an AE with the drug and denominator is the total number of patients treated with the drug: patients with adverse event per drug/number of patients treated with the drug (some patients may have had more than 1 AE per drug, see Table 3)

^ in addition 3 patients with serious AEs due to all anti-TB drugs administered (2 gastrointestinal and 1 renal problem, see Table 3)

**Table 3: summary of 9 serious cardiological adverse events occurred in 9 patients out of 658 in the cohort.**

| Country | Age | Gender | Adverse event description | Drug considered responsible | Current_ prescribed regimen | Treatment outcome | Baseline QTc value (msec) | QTcF max. prolongation reached (msec) | Episode(s) occurred (n.) | Drug permanently interrupted | If yes after how many days | Total drug exposure (n. days) | Drug restarted | Outcome Adverse event resolved resolving |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **QT PROLONGATION** | | | | | | | | | | | | | | |
| Italy | 41 | Male | QT prolongation | Bdq, | Z,Cfz,Lzd,Trd, Merop,Clav,Bdq | Still on Treatment | 454 | 480 | 1 | Yes | 190 | 190 | No | Resolved |
| Italy | 32 | Female | QT prolongation | Cfz | Cfz,PAS,Tzn,Amk,Bdq,Lzd | Still on treatment | 454 | 500 | 1 | Yes | 23 | 23 | No | Resolved |
| Italy | 50 | Male | QT prolongation | Cfz | Mxf,Lzd,Tzn,Cfz,Amk,Bdq | Still on treatment | 465 | 566 | 1 | Yes | 204 | 204 | No | Resolved |
| Lithuania | 35 | Female | QT prolongation | Mfx^ | Dlm,Lfx,Mfx,Cm,Lnz | Still on Treatment | 352 | 618 | 1 | Yes | 11 | 11 | No | Resolved |
| Russia | 71 | Female | QT prolongation | Bdq | Bdq,Lzd,Lfx,Cs,Azitro,Cm | Cured | 354 | 556 | 1 | No | | 266 | Yes | Resolving |
| Russia | 55 | Female | QT prolongation | Bdq | Bdq,Lzd,Lfx,Cs,Azitro,Z | Cured | 341 | 527 | 1 | No | | 233 | Yes | Resolving |
| Russia | 73 | Female | QT prolongation | Bdq | Bdq,Lfx,Cs,Cm,PAS | Still on Treatment | 338 | 521 | 1 | Yes | 84 | 84 | No | Resolved Resolving |
| Sweden | 33 | Female | QT prolongation | PAS* | Bdq, Lfx, Cs, Z,E, Lzd, Cfz ** | Still on Treatment | 438 | 530 | 1 | Yes | 17 | 17 | No | Resolved |
| **ARRYTHMIA** | | | | | | | | | | | | | | |
| Sweden | 59 | Male | Ventricular extrasystoles (VES)-bigeminy arrhythmia | Dlm | Bdq, Cfz, Lfx, Lzd,Dlm | Cured | 393 | 420 | 1 | Yes | 4 | 4 | No | Resolved |

**Legend Table 3**: QT prolongation: an electrical disturbance visible on the electrocardiogram, measuring the delayed ventricular repolarisation, when the heart muscle takes longer than normal to recharge between beats QTc: corrected QT interval; QTcF= QT Fridericia-corrected; Z: pyrazinamide; Ofx: ofloxacin; Lfx: levofloxacin; Mfx: moxifloxacin; Pto: prothionamide; Cfz: clofazimine; Lzd: linezolid; Bdq: bedaquiline; Trd: terizidone; Merop: meropenem; Clav: clavulanic acid; Dlm: delamanid; Cm: capreomycin; Cs: cycloserine; Azitro: azitromycin; E: ethambutol; PAS: para-aminosalicylic acid; Amk: amikacin

*PAS was responsible for diarrhoea, increased magnesium level and QT prolongation (which normalized after stopping the drug)
**After 2 months of treatment during pregnancy, linezolid and clofazimine were added after delivery
^ Moxifloxacin was co-administered with delamanid; delamanid was well tolerated, with no adverse event reported
**Note**: moxifloxacin was withdrawn after 231 days in a patient with Wolf Parkinson White (WPW) syndrome: it was not considered as adverse event

**Electronic Annex 1: Participating countries and details on the cases reported**

| Countries | Estimated coverage[Ω] % | Cases enrolled N | Cases treated with Bdq only N (%) | Cases treated with Dlm only N (%) | Cases treated with Bdq and Dlm consecutively or in combination N (%) | Ethical committee clearance not necessary/waived yes/no |
|---|---|---|---|---|---|---|
| Argentina | 100 | 3 | 3 (100) | 0 (0) | 0 (0) | yes |
| Australia | 100[§] | 6 | 6 (100) | 0 (0) | 0 (0) | yes |
| Belarus[¶] | 80 | 45 | 31 (69) | 14 (31) | 0 (0) | yes |
| Belgium | 60 | 3 | 3 (100) | 0 (0) | 0 (0) | no (obtained) |
| Brazil | 100 | 34 | 34 (100) | 0 (0) | 0 (0) | yes |
| Bulgaria | 100 | 17 | 17 (100) | 0 (0) | 0 (0) | yes |
| Chile | 100 | 1 | 0 (0) | 0 (0) | 1 (100) | yes |
| China^ | 100[#] | 5 | 5 (100) | 0 (0) | 0 (0) | yes |
| Greece | 100 | 6 | 4 (67) | 0 (0) | 2 (33) | yes |
| India | 100[§] | 15 | 12 (80) | 1 (7) | 2 (13) | yes |
| Italy[$] | 80 | 33 | 26 (79) | 6 (18) | 1 (3) | no (obtained) |
| Latvia | 100 | 30 | 21 (70) | 3 (10) | 6 (20) | no (obtained) |
| Lithuania^^ | 100 | 160 | 100 (62) | 52 (33) | 8 (5) | yes |
| Mexico[¶¶] | 100 | 7 | 2 (29) | 2 (29) | 3 (42) | no (obtained) |
| Netherlands[¶] | 100 | 6 | 3 (50) | 0 (0) | 3 (50) | yes |
| Niger | 100 | 17 | 12 (71) | 0 (0) | 5 (29) | yes |
| Paraguay | 100 | 1 | 1 (100) | 0 (0) | 0 (0) | yes |
| Peru | 80 | 29 | 29 (100) | 0 (0) | 0 (0) | yes |
| Portugal | 100 | 1 | 0 (0) | 1 (100) | 0 (0) | no (obtained) |
| Russian Federation[¶] | 100* | 202 | 195 (97) | 2 (1) | 5 (2) | no (obtained) |
| Slovakia | 100 | 1 | 1 (100) | 0 (0) | 0 (0) | yes |
| Spain[$] | 100 | 8 | 7 (88) | 0 (0) | 1 (12) | yes |
| Sudan | 100 | 2 | 2 (100) | 0 (0) | 0 (0) | yes |
| Sweden | 100 | 19 | 18 (95) | 0 (0) | 1 (5) | no (obtained) |
| Switzerland | 100# | 3 | 2 (67) | 0 | 1 (33) | no (obtained) |
| United Kingdom | 20 | 4 | 4 (100) | 0 (0) | 0 (0) | yes |
| **TOTAL 26** | **Range 20%-100%** | **658** | **538 (82)** | **81 (12)** | **39 (6)** | |

Legend: Bdq= bedaquiline; Dlm= delamanid

Ω Countries' estimate of the national coverage of the aDSM project on new drugs;
¶ 2 centres;
^ 1 centre;
# in the Province/Canton reporting;
§ in the State reporting;
$ 6 centres;
^^ 5 centres;
¶¶ 3 centres;
*in the 2 Oblasts reporting;

**Electronic Annex 2: Details on the drug-resistance profile of 658 patients enrolled in the study**

| **Resistance pattern** | | **Pulmonary** | **Pulmonary + Extra-pulmonary** | **Extra-pulmonary** |
|---|---|---|---|---|
| **MDR/RR-TB 161/658 (24.5%)** | *MDR n=153** | 137 | 12 | 4 |
| | *Xpert R-resistant n=8*[§] | 7 | 1 | - |
| **Pre-XDR-TB 224/658 (34%)** | *MDR+FQ n=125* | 121 | 3 | 1 |
| | *MDR+Inj n=99* | 92 | 5 | 2 |
| **XDR-TB 254/658 (38.6%)**** | | 237 | 15 | 2 |
| **Other (DST) 19/658 (2.9%)** | *Susceptible n=3*[¶] | 3 | - | - |
| | *R-monoresistant n=4* | 3 | - | 1 |
| | *R+Other (not H) n=2* | 1 | 1 | - |
| | *H-monoresistant n=1* | 1 | - | - |
| | *H+Other (not R) n=8* | 8 | - | - |
| | *Polyresistant n=1* | 1 | - | - |
| **TOTAL** | **658 (100%)** | **611/658 (92.9%)** | **37/658 (5.6%)** | **10/658 (1.5%)** |

*3 MDR strain of the index case
[§]5 Xpert R-resistant+FQ
**2 XDR index case
[¶] 2 second-line regimen because of adverse events (AEs) of first-line drugs, 1 second-line regimen per clinical decision

Legend: TB: tuberculosis; MDR: multidrug-resistant; XDR: extensively drug-resistant; RR: rifampicin-resistant; Inj: injectables; H: isoniazid; R: rifampicin; DST: drug susceptibility testing; FQ: fluoroquinolone

**Electronic Annex 3. Severe Adverse Events of anti-tuberculosis drugs by organ/apparatus in 658 patients (of whom 55 reported 57 episodes)**

| **Severe Adverse Events** | | **Episodes n=57** | **Comments** | **Outcome** |
|---|---|---|---|---|
| **Gastrointestinal** | Diarrhoea/ enterocolitis *Clostridium difficile* | 1 | MDR-PULM Diarrhoea, grade 3 AE occurred 81 days after starting treatment with new drugs. Adverse event duration: 100 days (27th April – 5th August 2018) requiring prolonged hospitalization. AE attributed to all anti-TB drugs. Anti-TB drugs stopped and then re-challenged after recovery. Toxigenic *Clostridium difficile* was identified (laboratory test performed on 5 April 2018). | Resolved |
| | | 1 | XDR-PULM. *Clostridium difficile* infection required prolonged hospitalization. Grade 3 AE occurred 17 days before starting treatment with new drugs (25th April 2018). AE attributed to all anti-TB drugs. AE duration: 244 days (8th April – 8th December 2018). Anti-TB drugs stopped and re-challenged after recovery. | Resolved |
| **Nervous system** | Optic neuritis | 1 | XDR-PULM. Sudden appearance of visual blurring with associated retro-ocular pain, grade 3. AE occurred 643 days after starting treatment with new drugs. Adverse event duration: 20 days (30th June-20th July 2014).<br>AE attributed to linezolid (dosage 600 mg daily) administered for 643 days (25th Sept. 2012 – 30th June 2014) then stopped and not re-administered. | Resolved |
| | Visual impairment | 1 | XDR-PULM. Diplopia, visual acuity impaired, threat of losing visual function, grade 3 AE occurred 117 days after start of treatment with new drugs. Adverse event duration: 2 days (13th-15th Nov. 2017).<br>AE attributed to linezolid (dosage 600 mg daily) administered for 117 days (19th July – 13th November 2017) then stopped and not re-administered. | Resolved |
| | Peripheral neuropathy | Pt.1: 1<br>Pt.2: 1<br>Pt.3: 1<br>Pt.4: 1 | Pt 1 Pre-XDR-PULM: Tingling numbness with risk of crippling neuropathy, serious AE. AE occurred 93 days after starting treatment with new drugs and still ongoing (20th December 2018). AE attributed to linezolid (dosage 600 mg daily) administered for 104 days (19th July – 13th November 2017) then stopped and not re-administered.<br>Pt.2 MDR-PULM: Polyneuropathy, grade 3. Severity due to marked clinical signs, all drugs were withdrawn since 28th November 2016; after re-challenge linezolid dose was reduced from 1,200 mg daily to 600 mg daily. AE occurred 145 days after starting treatment with new drugs. Adverse event duration: 179 days (16th November 2016-22nd August2017). End of anti-TB treatment: 22nd August 2017 (total anti-TB treatment duration: 426 days, 22nd June 2016 – 22nd Aug 2017). Linezolid was administered for a total of 424 days (24th June 2016 | Pt1: Resolving<br>Pt2: Resolved with sequelae<br>Pt.3: Resolved with sequelae<br>Pt4: Not resolved |

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| | | | – 22nd August 2017) with dose reduction.<br>Pt.3 XDR-PULM: Polyneuropathy, grade 3 AE; episode occurred on 16th Nov 2017, 64 days after starting treatment with new drugs. AE attributed to linezolid (dosage 600 mg daily) administered for 64 days (13th September– 16th November 2017) then stopped and not re-administered. Recovery with persistent disability.<br>Pt4 MDR-PULM+EXTRAPULM: Severe peripheral neuropathy, grade 3 AE occurred on 18th September 2017, 255 days after start of treatment with new drugs and still ongoing.<br>AE attributed to linezolid (dosage 600 mg daily) administered for 257 days (13th January – 27th September 2017) then stopped and not re-administered. | |
| | Headache | 1 | Pre-XDR-PULM: Severe headache requiring hospitalization, grade 3 AE occurring 145 days after starting treatment with new drugs. Adverse event duration: 9 days (7 -16th February 2018). AE attributed to cycloserine (dosage 750 mg daily) administered for 146 days (15th Sept 2017- 08th Feb 2018); its dosage was not changed . | Resolved |
| **Skin / Subcutaneous** | Rash | 1 | Pre-XDR-PULM: Extensive papulo-vesicular lesions, grade 3. AE occurred 438 days after starting treatment with new drugs. Adverse event duration: 21 days (16th December 2014-06 January 2015). AE attributed to clofazimine (dosage 100 mg daily) administered for 439 days (4th October 2013-17th December 2014) then stopped and, after recovery, drug re-challenge causing a new AE and drug finally discontinued. | Resolved |
| | Other skin allergy | Pt1: 1<br>Pt.2: 1<br>Pt.3: 1 | Pt.1 Pre-XDR-PULM: Severe urticaria requiring hospitalization, grade 3 AE occurred 1 day after starting treatment with new drugs. AE duration: 6 days (4-10th April 2018). AE due to clarithromycin (dosage 500 mg daily), administered for 1 day (4th Apr 2018) as AE occurred immediately after first drug dose. Drug not re-administered after recovery.<br>Pt.2 XDR-PULM: Severe urticaria grade 3 with important hyperaemia and oedema of the face, but not Quincke oedema. AE occurred 21 days after starting treatment with new drugs. AE duration: 8 days (7-15th February 2018). All drugs (bedaquiline, linezolid, moxifloxacin, terizidone, prothionamide, PAS, amikacin) withdrawn on 7th February 2018.<br>On February 22nd, linezolid was re-challenged but immediately after its first infusion severe face hyperaemia occurred, grade 3, occurred again due to linezolid (dosage 600 mg daily). AE duration 4 days (22-26 Feb 2018). Linezolid was withdrawn on the same day (administered for 1 day only on 22nd February 2018). Drug not re-challenged after recovery. From 27th February | Pt.1: Resolved<br>Pt.2: Resolved<br>Pt.3: Resolving |

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| | | | 2018 anti-TB treatment re-started (bedaquiline, moxifloxacin, terizidone, pyrazinamide, ethambutol, azithromycin).<br>Pt.3 MDR-PULM: Toxic allergic dermatitis, grade 3 AE occurred at start of treatment with new drugs (19th March 2019) and still ongoing. AE attributed to terizidone* (dosage 600 mg daily), administered for 6 days (13-19th March 2019). Drug not re-challenged | |
| **Hearing** | Hearing problems | Pt.1: 1<br>Pt.2: 1<br>Pt.3: 1<br>Pt.4: 1<br>Pt.5: 1<br>Pt.6: 1<br>Pt.7: 1<br>Pt.8: 1<br>Pt.9: 1<br>Pt.10: 1<br>Pt.11: 1 | Pt.1 Pre-XDR-PULM: Tinnitus potentially leading to hearing loss, serious AE. AE occurred on 20th Feb 2018, 32 days after start of treatment with new drugs and still ongoing. AE attributed to amikacin** (dosage 750 mg, 5 days/week) administered for 156 days (18th September 2017 – 21th February 2018) then stopped and not re-challenged.<br>Pt.2 Pre-XDR-PULM: severe hearing problems leading to hospitalization, serious AE. AE occurred 145 days after start of treatment with new drugs. Adverse event duration: 9 days (7th -16th February 2018). AE attributed to cycloserine (dosage 750 mg daily) administered for 146 days (15th September 2017- 8th February 2018), not re-challenged after de-challenge.<br>Pt.3 MDR-PULM+EXTRAPULM: severe hearing problems, serious AE. AE occurred 80 days after starting treatment with new drugs. Adverse event duration: 1 day (7 -8th December 2018) attributed to amikacin. Drug withdrawn.<br>Pt.4 Pre-XDR-PULM: Important hearing loss, serious AE. AE occurred on 20th March 2013, 89 days after starting treatment with new drugs and not resolved. AE attributed to amikacin (dosage 1 g daily) administered for 182 days (21st December 2012-21st June 2013), drug not withdrawn but dosage reduced.<br>Pt.5 Pre-XDR-PULM: Severe hearing loss, serious AE. AE occurred on 8th Sept. 2015, 214 days after starting treatment with new drugs and recovered with sequelae. AE attributed to amikacin (dosage 1 g daily) administered for 214 days (6th February 2015- 8th September 2015), drug not withdrawn but dosage reduced.<br>Pt.6 RR+FQ-PULM: Serious vertigo. Patient unable to stand up, serious AE. AE occurred 103 days after starting treatment with new drugs. AE duration 6 days (30th March-05th April 2018). AE attributed to amikacin (dosage 1 g daily) administered for 109 days (17th December 2017- 5th April 2018), drug withdrawn and not re-challenged.<br>Pt.7 Pre-XDR-PULM: Severe hearing loss, serious AE. AE occurred on 23rd May 2018, 61 days after starting treatment with new drugs and recovered with sequelae. AE attributed to amikacin (dosage 1 g daily) administered for 66 | Pt.1: Resolving<br>Pt. 2: Resolved<br>Pt.3: Resolved with sequelae<br>Pt.4: Not resolved<br>Pt.5: Resolved with sequelae<br>Pt. 6: Resolved<br>Pt. 7: Resolved with sequelae<br>Pt. 8: Resolved<br>Pt. 9: Resolved<br>Pt. 10: Resolved<br>Pt. 11: Resolved |

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| | | | days (23rd March -28rd May 2018). Drug withdrawn and not re-challenged.<br>Pt.8 XDR-PULM: Tinnitus, threat of function loss, grade 3 AE occurred 6 days after starting treatment with new drugs. AE duration 2 days (23rd-25th January 2018) attributed to amikacin (dosage 1 g daily) administered for 26 days (29th December 2017-24th January 2018). Drug not re-challenged after withdrawn.<br>Pt.9 MDR-PULM: Bilateral hearing loss, tinnitus, threat of function loss, grade 3. AE occurred 2 days after starting treatment with new drugs. AE duration 14 days (6th-20th April 2018) attributed to capreomycin (dosage 1 g daily) administered for 5 days (4th-9th April 2018). Drug not re-challenged after withdrawn.<br>Pt.10 MDR-PULM: Tinnitus, threat of function loss, grade 3 AE occurred on 22nd March 2018, 93 days after starting treatment with new drugs and resolved. AE attributed to amikacin (dosage 1 g daily) administered for 93 days (19th December 2017 – 22nd March 2018). Drug not re-challenged after withdrawn.<br>Pt.11 MDR-PULM: Hearing problems, dizziness, grade 3 AE occurred 9 days after starting treatment with new drugs and resolved. AE duration: 2 days (24th-25th August 2018) attributed to cycloserine (dosage 750 mg daily) administered for 9 days (16th-25th August 2018). Drug not re-challenged after withdrawn. | |
| **Psychiatric** | Hallucinations | 1 | XDR-PULM Nightmares, fear, auditory hallucination with significant disability, grade 3 AE occurring 179 days after starting treatment with new drugs and resolved. AE duration: 2 days (14th-16th Jan 2018) attributed to cycloserine (dosage 750 mg daily) administered for 179 days (19th July 2017-14th January 2018). Drug not re-challenged after withdrawn. | Resolved |
| | Mental disorders | 1 | Pre-XDR-PULM: Permanent intense anxiety, fear, inner tremor, grade 3 AE occurred on 26th March 2018, 10 days after starting treatment with new drugs. AE not resolved but stable. AE attributed to cycloserine§ (dosage 500 mg daily) administered for 193 (14th September 2017-26th March 18). Drug re-challenged after being withdrawn. | Not resolved |
| | Depression | Pt.1: 1<br>Pt.2: 1<br>Pt.3: 1 | Pt.1 XDR-PULM: depression and suicidal thoughts, grade 4 AE occurred on 1st September 2017, 14 days after starting treatment with new drugs. AE resolving. AE attributed to cycloserine¶ (dosage 750 mg daily) administered for 183 days (2nd March-1st September 2017). Drug not re-challenged but dose reduced.<br>Pt.2 Pre-XDR-PULM: patient already on treatment for depression prescribed by a psychiatrist. Patient admitted to undergo new psychiatric evaluation, after reporting symptoms worsening and suicide thoughts. Grade 3 AE occurring 20 days after starting treatment with new drugs. AE duration: 9 days (1st-10th | Pt.1: Resolving<br>Pt.2: Resolving<br>Pt.3: Unknown (lost to follow-up). |

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| | | | December 2018) attributed to cycloserine# (dosage 1000 mg daily) administered for 56 days (10th October – 5th December 2018). Drug stopped and then re-challenged after recovery.<br>Pt.3 Pre-XDR-PULM: The patient had taken tranquilizers in potentially lethal dose, grade 4.AE occurring on 4th November 2017, 43 days after starting treatment with new drugs. AE duration: unknown as the patient was lost to follow-up. AE attributed to cycloserine¶¶ (dosage 750 mg daily) administered for 56 days (9th September-4th November 2017). Drug stopped and not re-challenged (patient lost to follow-up at 43 days after starting treatment with new drugs. | |
| **Blood / Lymph nodes** | Anaemia | Pt.1: 1<br>Pt.2: 1<br>Pt.3: 1<br>Pt.4: 1<br>Pt.5: 1<br>Pt.6: 1<br>Pt.7: 1 | Pt.1 XDR-PULM: Hb level 48 g/l, patient received urgent haematology consultation and blood transfusion of packed red blood cells. Grade 3. AE occurred 69 days after starting treatment with new drugs. AE duration: 133 days (19th September 2015-30th January 2016). AE attributed to linezolid (dosage 1,200 mg daily) administered for 115 days (12th July-4th November 2015). On 4th November 2015 all anti-TB drugs were stopped and then re-challenged after recovery.<br>Pt.2 Pre-XDR-PULM: Hb level 65 g/l, grade 3 AE occurring 145 days after starting treatment with new drugs. AE duration: 62 days (16th November 2016-17th January 2017). AE attributed to linezolid (dosage 1,200 mg daily) administered for 424 days (24th June -22nd August 2017). Drug stopped and then re-challenged after recovery.<br>Pt.3 Pre-XDR-PULM: Hb 69 g/l, serious AE. AE occurring on 10th December 2018, 85 days after starting treatment with new drugs, resolving. AE attributed to linezolid (dosage 600 mg daily) administered from 16th September 2018. Drug stopped and re-challenged.<br>Pt.4 MDR-PULM+EXTRAPULM: Hb decrease, prolongation of hospitalization and erythropoietin administered for 2 months, grade 3 AE occurring 188 days after starting treatment with new drugs. AE duration: 68 days (6th December 2017-12th February 2018). AE attributed to linezolid (dosage 600 mg daily) administered for 188 days (1st June-6th December 2017). Drug stopped and not re-challenged.<br>Pt.5 XDR-PULM: Anaemia till Hb 48 g/l, erythrocytes 1.2 10^12/l, serious AE, grade 3. AE occurred 41 days after starting treatment with new drugs. AE duration: 90 days (20th September – 19th December 2017). AE attributed to linezolid (dosage 600 mg daily) administered for 104 days (10th August-22nd November 2017). Drug stopped and not re-challenged. | Pt.1: Resolved<br>Pt.2: Resolved<br>Pt.3: Resolving<br>Pt.4: Resolved<br>Pt.5: Resolving<br>Pt.6: Resolving<br>Pt.7: Resolving |

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| | | | Pt.6 Pre-XDR-PULM: Hb decrease (Hb 35 g/l); serious AE grade 4. AE occurred 297 days after starting treatment with new drugs. AE duration 19 days (24th April-13th May 2019). AE attributed to linezolid (dosage 600 mg daily) administered for 311 days (1st July 2018 - 8th May 2019). Drug stopped and not re-challenged.<br>Pt.7 MDR-PULM: Hb decrease (Hb 69 g/l, Er 2,1 10^12/l), serious AE grade 3. AE occurred 100 days after start of treatment with new drugs. AE resolving. AE attributed to linezolid (dosage 600 mg daily) administered for 40 days (28th November 2018- 7th January 2019). Drug finally withdrawn. | |
| | Bone marrow depression | Pt.1: 1<br>Pt.2: 1 | Pt.1 RR+FQ-PULM: Severe sudden anaemia; grade 3 AE occurring 31 days after starting treatment with new drugs. AE duration: 30 days (17th January-16th February 2018). AE attributed to linezolid (dosage 600 mg daily) administered for 61 days (17th December 2017-16th February 2018). Drug stopped and then re-challenged.<br>Pt.2 Pre-XDR-PULM: Severe sudden anaemia; grade 3.AE occurring 61 days after starting treatment with new drugs. AE duration: 30 days (23rd May -22nd June 2018). AE attributed to linezolid (dosage 600 mg daily) administered from the start of treatment with new drugs (23rd March 2018), stopped and, after recovery, re-challenged. | Pt.1: Resolved<br>Pt.2: Resolved |
| **Cardiac** | Arrhythmia | 1 | See Table 4 for details | See Table 4 for details |
| | QT prolongation | 8 | See Table 4 for details | See Table 4 for details |
| **Hepatic** | Hepatitis | Pt.1: 1<br>Pt.2: 1<br>Pt.3: 1 | Pt.1 XDR-PULM: transaminases increased 10 times, severe AE with progressive increase of transaminases after bedaquiline introduction. AE occurred on 22nd August 2018, 20 days after starting treatment with new drugs. On 24th September 2018 all drugs were stopped. On 5th October 2018 anti-TB drugs were reintroduced except bedaquiline and the transaminases level continued to slowly go down (not yet normal on 18th January 2019, probably because of the long bedaquiline half-life). AE attributed to bedaquiline (dosage 200 mg 3 days/week) administered for 53 days (2nd August -24th September 2018).<br>Pt.2 XDR-PULM: hepatitis, serious AE. AE occurred 9 days after starting treatment with new drugs. AE duration: 20 days (20th September-10th October 2017). AE attributed to ethionamide (dosage 750 mg daily) administered for 9 days (11th-20th September 2017), stopped and not re-challenged after recovery.<br>Pt.3 XDR-PULM: Severe hepatotoxic reaction, due to concomitant Hepatitis C | Pt.1: Resolving<br>Pt.2: Resolved<br>Pt.3: Unknown (lost to follow-up) |

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| | | | and anti-TB treatment, grade 3 AE occurring 15 days after starting treatment with new drugs. AE duration: 197 days (21st December 2016-6th July 2017). AE attributed to bedaquiline (dosage 200 mg 3 days/week) stopped on 6th July 2017 and then re-challenged when stable but severe hepatotoxic reaction grade 3 occurred again on 25th July 2017. All TB drugs were stopped on 25th July and not re-challenged as the patient was lost to follow-up. Bedaquiline administered for 227 days (6th December 2016-25th July 2017). | |
| **Renal** | Renal problems | Pt.1: 1<br>Pt.2: 1<br>Pt.3: 1<br>Pt.4: 1<br>Pt.5: 1<br>Pt.6: 1<br>Pt.7: 1 | Pt. 1 MDR-PULM: low glomerular filtration rate, severe AE. AE occurring on 25th August 2017, 60 days after starting treatment with new drugs. AE duration 94 days (25th August -27th November 2017). AE attributed to capreomycin (dosage: 1 g 6 days/week) administered for 78 days (26th June – 12th September 2017) not stopped but dose reduced.<br>Pt.2 MDR-PULM: Renal problems, severe AE. AE occurred on 10th July 2017, 18 days after starting treatment with new drugs. AE attributed to amikacin administered for 35 days (5th June-10th July 2017) and then stopped..<br>Pt.3 Pre-XDR-PULM: Loss of renal function requiring prolongation of hospital admission, severe AE. AE occurred 138 days before starting treatment with new drugs (22nd November 2017). AE duration: 249 days (7th July 2017-13 March 2018). AE attributed to capreomycin (dose 1000 mg lowered from 7 to 3 times/ week) administered for 276 days (10th May 2017-10th February 2018), drug not stopped but dose reduced.<br>Pt.4 MDR-PULM: Renal biopsy showed tubulo-interstitial nephritis, severe AE requiring prolonged hospitalisation and prednisone at high dosage. AE occurred 2 days before starting treatment with new drugs. AE duration: 68 days (25th June- 1st September 2016). AE attributed to capreomycin (dose 1000 mg 5 times/week) administered for 94 days (15th April-18th July 2016), drug stopped and not re-challenged.<br>Pt.5 XDR-PULM+EXTRAPULM: low glomerular filtration rate and concomitant kidney tuberculosis; grade 3 AE occurred 30 days after starting treatment with new drugs. AE duration: 99 days (26th October 2015-2nd February 2016). AE attributed to capreomycin (dose 1000 mg 7 times/ week) administered for 192 days (26th September 2015-5th April 2016). Capreomycin stopped with all TB drugs from 6th November to 30th December 2015 and then re-challenged.<br>Pt. 6 XDR-PULM: acute renal failure occurred on the second day after right lower lobectomy in a patient with diabetic nephropathy of the single kidney (for previous nephrectomy due to the cancer, 1995). Grade 4 AE occurring 47 | Pt.1 : Resolved<br>Pt.2: Unknown<br>Pt.3: Resolved<br>Pt.4: Resolved with sequelae<br>Pt.5: Resolving<br>Pt.6: Resolving<br>Pt.7 : Resolved |

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| | | | days after start of treatment with new drugs. AE duration: 2 days (19th-20th July 2017). Anti-TB drugs' doses were not reduced.<br>Pt. 7 XDR-PULM: Nephropathy, glomerulonephritis, Grade 3<br>AE occurring 57 days after starting treatment with new drugs. AE duration: 21 days (15th September – 6th October 2017). The AE was attributed to pyrazinamide (dose 1.5g 7 times/ week) which was stopped and after recovery, re-challenged. The AE occurred again and pyrazinamide was finally withdrawn. Pyrazinamide was administered for 58 days. | |

* Terizidone started 5 days before anti-TB treatment with new drugs.
** Amikacin started 123 days before anti-TB treatment with new drugs.
§ Cycloserine started 183 days before anti-TB treatment with new drugs.
¶ Cycloserine started 169 days before anti-TB treatment with new drugs
# Cycloserine started 32 days before anti-TB treatment with new drugs
¶¶ Cycloserine started 13 days before anti-TB treatment with new drugs

Legend: TB: tuberculosis; MDR: multidrug-resistant; XDR: extensively drug-resistant; TB: tuberculosis; PULM: pulmonary; EXTRAPULM: extra- pulmonary; AE: adverse event; Pt: patient; PAS: para-aminosalicylic acid; Hb: haemoglobin.

**Electronic Annex 4. Summary of QT Prolongation episodes determining 35 minor adverse events in 32 patients out of the 658 treated with new and repurposed drugs in the cohort**

| Setting | Gender (n.%) | Age (mean ±SD) | Max. QT value (mean (±SD) | QT prolongation episode(s) occurred (n.%) | QTcF prolongation ≥ 450 msec (n.%) | QTcF prolongation ≥500 msec (n.%) | Drugs containing-regimens (total n.%) | Drugs considered responsible of AE (total n.%) | Action taken Drug temporarily withdrawn Dose not changed Drug permanently interrupted (total n.%) | Outcome Resolved Not resolved Resolving Unknown (total n.%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Europe (n=26)** | Females 10/26 (38,4%) | 41,0 (±13,1) | 476,4 (±39,6) | 1 episode 10/10 (100%) | 8/10 (80%) | 5/10 (50%) | FQ 16/26 (61,5%)<br><br>Cfz 9/26 (34,6%)<br><br>Bdq 26/26 (100%)<br><br>Dlm^^ 4/26 (15,3%) | FQ (Mfx) 3/26 (11,5%)<br><br>Bdq* 22/26 (84,6%)<br><br>Cfz 1/26 (3,8%) | Drug temporarily withdrawn 5/26 (19,2%)<br><br>Dose not changed 20/26 (76,9%)<br><br>Drug permanently interrupted 1/26^ (3,8%) | Resolved 17/26 (65,3%)<br><br>Not resolved 5/26 (19,2%)<br><br>Resolving 3/26 (11,5%)<br><br>Unknown 1/26 (3,8%) |
| | Males 16/26 (61,6%) | 49,0 (±14,72) | 474,0 (±41,7) | 1 episode 14/16 (87,5%)<br><br>> 1 episode 2/16°° (12,5%) | 13/16 (81,2%) | 4/16 (25%) | | | | |
| **Other than Europe (n=6)** | Female 1/6 (16,6%) | 63,0 (±0 ) | 466,0 (±25,6) | 1 episode 1/1 (100%) | 1/1 (100%) | 0/1 (0%) | FQ 1/6 (16,6%)<br><br>Cfz 6/6 (100%)<br><br>Bdq 6/6 (100%)<br><br>Dlm 0/6 (0%) | Bdq 6/6 (100%) | Dose not changed 6/6 (100%) | Resolved 6/6 (100% ) |
| | Males 5/6 ( 83,4%) | 38,0 (±8) | 463,2 (±14,8) | 1 episode 5/5 (100%) | 4/5 (80 %) | 1/5 (20%) | | | | |

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| **Total (n=32)** | Females 11/32 (34,4 %) | 43,0 (±14,1) | 476,7 (± 37,6) | 1 episode 11/11 (100%) | 9/11 (81,8%) | 5/11 (45,4%) | FQ 17/32 (53,1%)<br><br>Cfz 15/32 ( 46,8%)<br><br>Bdq (32/32,100%)<br><br>4/32 Dlm^^ (12,5%) | FQ (Mfx) 3/32 (9,3%)<br><br>Bdq* 28/32 (87,5%)<br><br>Cfz 1/32 (3,1%) | Drug temporarily withdrawn 5/32 (15,6%)<br><br>Dose not changed 26/32 (81,2%)<br><br>Drug permanently interrupted 1/32^ (3%) | Resolved 23/32 (71,8%)<br><br>Not resolved 5/32 (15,6%)<br><br>Resolving 3/32 (9,3%)<br><br>Unknown 1/32 (3%) |
| | Males 21/32 (65,6 %) | 46,3 (±14,0) | 471,4 (± 38,5) | 1 episode 19/21 (90,5%)<br><br>> 1 episode 2/21°° (9,5%) | 17/21 (81%) | 5/21 (23,8%) | | | | |

* in 1 case clofazimine was drug responsible in combination with bedaquiline;

**in 8 cases 1 fluoroquinolone (moxifloxacin) was drug responsible in combination with bedaquiline;

°° 1 case with 2 episodes, 1 case with 3 episodes of QT prolongation

^Moxifloxacin replaced by levofloxacin after QT prolongation (QTcF 497 mc- baseline 360 msec)

^^ in 2 cases delamanid was administered in combination with bedaquiline, in other 2 cases consecutively

Legend (acronyms): QT prolongation: an electrical disturbance visible on the electrocardiogram, measuring the delayed ventricular repolarisation, when the heart muscle takes longer than normal to recharge between beats.; SD=Standard deviation; QTcF = Fridericia-corrected QT interval ; AE= adverse event; FQ= fluoroquinolones; Cfz= clofazimine; Bdq= bedaquiline; Dlm=delamanid; Mfx=moxifloxacin

**Electronic Annex 5: Summary of adverse events reported per drug in the cohort of 658 cases of tuberculosis (TB) (adverse events are numerator and denominator)**

Panel A: Overall summary of adverse events (n= 501^) reported by clinical centres per drug on 658 TB cases

| | n* (%) | (95% Confidence Intervals) |
|---|---|---|
| Linezolid | 92 (18.4) | 15.0-21.8 |
| Bedaquiline | 79 (15.8) | 12.6-19.0 |
| Capreomycin | 73 (14.6) | 11.5-17.7 |
| Pyrazinamide | 57 (11.4) | 8.6-14.2 |
| Ethionamide/prothionamide | 46 (9.2) | 6.7-11.7 |
| Amikacin | 32 (6.4) | 4.3-8.5 |
| Cycloserine/terizidone | 32 (6.4) | 4.3-8.5 |
| Para-aminosalicilic acid | 29 (5.8) | 3.8-7.9 |
| Delamanid | 18 (3.6) | 2.0-5.2 |
| Levofloxacin | 16 (3.2) | 1.7-4.7 |
| Clofazimine | 16 (3.2) | 1.7-4.7 |
| Moxifloxacin | 10 (2.0) | 0.8-3.2 |
| Claritromycin | 1 (0.2) | -0.2; 0.6 |

* adverse events per drug/total number of adverse events

^ in addition 3 patients with serious AEs attributed to all anti-TB drugs administered (2 gastrointestinal and 1 renal problem)

Panel B: Grade 1-2 (minor) adverse events (n=447) reported by clinical centres per drug on 658 TB cases

| Grade 1-2 adverse events | n* (%) | (95% Confidence Intervals) |
|---|---|---|
| Linezolid | 76 (17.0) | 13.5-20.5 |
| Capreomycin | 68 (15.2) | 11.9-18.5 |
| Bedaquiline | 73 (16.3) | 12.9-19.7 |
| Pyrazinamide | 56 (12.5) | 9.4-15.6 |
| Ethionamide/prothionamide | 45 (10.1) | 7.3-12.9 |
| Para-aminosalicilic acid | 28 (6.3) | 4.1-8.6 |
| Amikacin | 23 (5.1) | 3.1-7.1 |
| Cycloserine/terizidone | 23 (5.1) | 3.1-7.1 |
| Delamanid | 17 (3.8) | 2.0-5.6 |
| Levofloxacin | 16 (3.6) | 1.9-5.3 |
| Clofazimine | 13 (2.9) | 1.3-4.5 |
| Moxifloxacin | 9 (2.0) | 0.7-3.3 |
| Claritromycin | 0 (0.0) | - |

* adverse events per drug/total number of adverse events

Panel C: Grade 3-5 (serious) adverse events **(**n=54^) reported by clinical centres per drug on 658 TB cases

| Grade 3-5 adverse events | n* (%) | (95% Confidence Intervals) |
|---|---|---|
| Linezolid | 16 (29.6) | 17.4-41.8 |
| Amikacin | 9 (16.7) | 6.8-26.6 |
| Cycloserine/terizidone | 9 (16.7) | 6.8-26.6 |
| Bedaquiline | 6 (11.1) | 2.7-19.5 |
| Capreomycin | 5 (9.3) | 1.6-17.0 |
| Clofazimine | 3 (5.6) | -0.5; 11.7 |
| Delamanid | 1 (1.9) | -1.7; 5.5 |
| Ethionamide/prothionamide | 1 (1.9) | -1.7; 5.5 |

| | | |
|---|---|---|
| Moxifloxacin | 1 (1.9) | -1.7; 5.5 |
| Pyrazinamide | 1 (1.9) | -1.7; 5.5 |
| Claritromycin | 1 (1.9) | -1.7; 5.5 |
| Para-aminosalicilic acid | 1 (1.9) | -1.7; 5.5 |
| Levofloxacin | 0 (0.0) | - |

* adverse events per drug/total number of adverse events

^ in addition 3 AEs (2 gastrointestinal and 1 renal problem) attributed to all anti-TB drugs administered

Panel D: Overall summary of bedaquiline-related adverse events (n=79) reported by clinical centres on 658 TB cases

| **Bedaquiline, n* (%)** | **n= 79** |
|---|---|
| Arrythmia | 27 (34.2) |
| Pancreatitis | 11 (13.9) |
| Hepatoxicity | 9 (11.4) |
| Hypertransaminasemia | 7 (8.9) |
| Renal failure | 5 (6.3) |
| Nausea/vomiting | 5 (6.3) |
| Arthromialgia | 3 (3.8) |
| Peripheral neuropathy | 3 (3.8) |
| Rash | 3 (3.8) |
| Diarrhoea | 2 (2.5) |
| Allergy | 1 (1.3) |
| Anaemia | 1 (1.3) |
| Gastritis | 1 (1.3) |
| Other | 1 (1.3) |

* adverse event due to bedaquiline/total number of adverse events due to bedaquiline

Panel E: Overall summary of delamanid-related adverse events **(**n=18) reported by clinical centres on 658 TB cases

| **Delamanid, n* (%)** | **n= 18** |
|---|---|
| Hypokalaemia | 3 (16.7) |
| Arrythmia | 2 (11.1) |
| Arthromyalgia | 2 (11.1) |
| Rash | 2 (11.1) |
| Hepatotoxicity | 2 (11.1) |
| Anaemia | 1 (5.6) |
| Nausea/vomiting | 1 (5.6) |
| Candidosis | 1 (5.6) |
| Depression | 1 (5.6) |
| Eosinophilia | 1 (5.6) |
| Gastritis | 1 (5.6) |
| Headache | 1 (5.6) |

*adverse event due to delamanid/total number of adverse events due to delamanid

Panel F: Overall summary of linezolid-related adverse events (n=92) reported by clinical centres on 658 TB cases

| **Linezolid, n* (%)** | **n= 92** |
|---|---|
| Peripheral neuropathy | 37 (40.2) |
| Anaemia | 24 (26.1) |
| Optic neuritis | 5 (5.4) |
| Renal failure | 5 (5.4) |
| Bone marrow suppression | 3 (3.3) |
| Thrombocytopenia | 3 (3.3) |
| Pancreatitis | 2 (2.2) |
| Diarrhoea | 2 (2.2) |
| Hypokalaemia | 2 (2.2) |
| Nausea/vomiting | 2 (2.2) |
| Candidiasis | 1 (1.1) |
| Epistaxis | 1 (1.1) |
| Hearing problems | 1 (1.1) |
| Hepatotoxicity | 1 (1.1) |
| Increased foetal movement | 1 (1.1) |
| Increased lactate levels | 1 (1.1) |
| Rash | 1 (1.1) |

* adverse event due to linezolid/total number of adverse events due to linezolid

Panel G: Overall summary of capreomycin-related adverse events (n=73) reported by clinical centres on 658 TB cases

| **Capreomycin, n* (%)** | **n= 73** |
|---|---|
| Renal failure | 20 (27.4) |
| Eosinophilia | 16 (21.9) |
| Hearing problems | 12 (16.4) |
| Hypokalaemia | 10 (13.7) |
| Allergy | 10 (13.7) |
| Increased blood creatinine | 2 (2.7) |
| Diarrhoea | 1 (1.4) |
| Headache | 1 (1.4) |
| Peripheral neuropathy | 1 (1.4) |

* adverse event due to capreomycin/total number of adverse events due to capreomycin

Panel H: Overall summary of pyrazinamide-related adverse events (n=57) reported by clinical centres on 658 TB cases

| **Pyrazinamide, n* (%)** | **n= 57** |
|---|---|
| Hyperuricemia | 12 (21.1) |
| Arthromyalgia | 11 (19.3) |
| Renal failure | 7 (12.3) |
| Allergy | 6 (10.5) |
| Eosinophilia | 5 (8.8) |
| Hypertransaminasemia | 4 (7.0) |
| Nausea/vomiting | 3 (5.3) |
| Hepatotoxicity | 3 (5.3) |
| Itching | 2 (3.5) |
| Diarrhoea | 2 (3.5) |
| Gastritis | 2 (3.5) |

* adverse event due to pyrazinamide/total number of adverse events due to pyrazinamide

**Electronic Annex 6: Interval between drug administration and adverse event occurrence, according to the treatment outcome at the study data collection.**

| | **Still on treatment** | **Other outcomes** | **Total** |
|---|---|---|---|
| | **Median (IQR) interval between first drug administration and AEs, days** | | |
| **Linezolid** | 71 (32-139) | 115 (52-191) | 93.5 (40-169) |
| **Bedaquiline** | 71 (28-160) | 94 (30-184) | 90 (30-177) |
| **Capreomycin** | 57 (32-62) | 75 (34-176) | 62 (32.5-150.0) |
| **Pyrazinamide** | 61 (30-105) | 69 (33-178) | 62 (31-116) |
| **Ethionamide/prothionamide** | 162.5 (48.5-235.5) | 159.5 (25-305) | 159.5 (30.5-281.5) |
| **Amikacin** | 81.5 (46.5-94.5) | 61 (45-109) | 80 (45-106) |
| **Cycloserine/terizidone** | 105 (55-291) | 93.5 (43-153) | 105 (44-215) |
| **Para-aminosalicilic acid** | 114 (32.5-206.0) | 258 (70-629) | 216 (93-603) |
| **Delamanid** | 121.5 (59-181) | 76 (22.5-100.5) | 77 (24-179) |
| **Levofloxacin** | 57 (53-103) | 17 (7-160) | 57 (12-160) |
| **Clofazimine** | 132 (130-132) | 97 (83-161) | 131 (83-161) |
| **Moxifloxacin** | 70.5 (22.5-118.5) | 119.5 (52-254) | 88 (34-170) |
| **Claritromycin** | - | - | - |
| **Mean (SD) total duration, days** | **92 (34.3)** | **102.9 (60.1)** | **79.5 (42.4)** |

Legend: IQR: interquartile range; AE: adverse event; PAS: Para-aminosalicylic acid; SD: standard deviation