World Health Organization

Information Note

WHO call for patient data on the treatment of multidrug- and rifampicin resistant tuberculosis

In order to ensure that the upcoming comprehensive revision of WHO policies on treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) is based on the most recent evidence and scientific analysis, the WHO Global TB Programme is issuing a call for individual patient data on MDR-TB treatment.

Please submit your notice of intent by 01 March 2018.

1. Minimum requirements for individual patient datasets (IPD)

Data that have already been reported to the existing individual patient dataset coordinated by McGill University should not be reported again.

Data from studies that have not yet been reported in peer-reviewed publications but otherwise fulfilling the below criteria will be considered for inclusion:

- Individual datasets of at least 25 patients;
- Patients with rifampicin-resistant TB confirmed using a WHO-recommended phenotypic or molecular test (including MDR-TB, MDR-TB with additional resistance to either a fluoroquinolone or injectable drug, or XDR-TB);
- Cases without confirmed rifampicin-resistant TB are not eligible. Baseline drug susceptibility results for fluoroquinolones, second-line injectable agents and for pyrazinamide would be highly desirable;
- Regimens may be a longer regimen lasting 18 months or more or the standardised shorter regimen.[1]
- Patients treated with MDR-TB regimens, with or without newer medicines – bedaquiline and delamanid – are eligible for inclusion;
- Regimens composed solely of first line agents (rifampicin, isoniazid, pyrazinamide, ethambutol, as well as streptomycin) or those with experimental drugs only will not be considered.

[1] The shorter regimen refers to standardized 9-12 month regimens with a typical composition of 4-6KmMfxPtoCfzZHhE/ 5-8MfxCfzZE.

- Patients started on MDR-TB regimens in 2010 or later and who have completed treatment and in whom an end-of-treatment outcome was assigned. Outcomes need to be as per WHO definitions[2] (outcomes as per 2005 definitions for earlier cohorts are also accepted).[3]
- For the individual patient data (IPD) analyses, records of patients who are still on treatment and whose outcome was not evaluated, CANNOT BE USED;
- Data should be organised in anonymised, individual records (i.e. one row per treatment episode) for the minimum set of variables, preferably coded in a standard way (see Annex 1). Datasets for which data for key variables is missing in 50% or more of records cannot be used.
- Background information on inclusion/exclusion criteria used for the shorter MDR-TB regimen will be important. Although not obligatory, other information which may be helpful includes: i) number of patients with confirmed MDR/RR-TB that were evaluated for treatment; ii) number that were considered ineligible; and iii) number of patients eligible who did or did not start treatment in the site and at the time of the study data provided.

If data relevant for the guidelines update are only available in aggregated format, please note also the following:

2. Minimum requirements for aggregated datasets

Data that have already been provided to WHO for policy development should not be reported again.

Data from studies that have not yet been reported in peer-reviewed publications but otherwise fulfilling the below criteria will be considered for inclusion:

- Individual datasets of at least 25 patients;
- Patients with rifampicin-resistant TB confirmed using a WHO-recommended phenotypic or molecular test (including MDR-TB, MDR-TB with additional resistance to either a fluoroquinolone or injectable drug, or XDR-TB);
- Cases without confirmed rifampicin-resistant TB are not eligible. A summary of baseline drug susceptibility results for fluoroquinolones, second-line injectable agents and for pyrazinamide would be highly desirable;
- Regimens may be a longer regimen lasting 18 months or more or the standardised shorter regimen.[1] Patients treated with MDR-TB regimens, with or without newer medicines – bedaquiline and delamanid – are eligible for inclusion;
- Regimens composed solely of first line agents (rifampicin, isoniazid, pyrazinamide, ethambutol, as well as streptomycin) or those with experimental drugs only will not be considered.

[2] Definitions and reporting framework for tuberculosis – 2013 revision (WHO/HTM/TB/2013.2). Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf Geneva, World Health Organization; 2013.
[3] Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005 Jun;9(6):640–5.

- Patients started on MDR-TB regimens in 2010 or later and who have completed treatment, with an end-of-treatment outcome assigned. Outcomes need to be as per WHO definitions[2] (outcomes as per 2005 definitions for earlier cohorts are also accepted).[3]
- Patients started on MDR-TB regimens with bedaquiline or delamanid in 2010 or later who have:
    - Completed treatment with an end-of-treatment outcome assigned. Outcomes need to be as per WHO definitions[2] (outcomes as per 2005 definitions for earlier cohorts are also accepted);[3] or
    - Completed at least six months of treatment with either or both drugs and for whom culture conversion data are available (Culture conversion need to be as per WHO definitions.[2]
- Background information on inclusion/exclusion criteria used for the shorter MDR-TB regimen will be important. Other information may be helpful - although not obligatory - on the number of patients with confirmed MDR/RR-TB that were evaluated for treatment, number that were considered ineligible, and the number eligible that did or did not start treatment in the site and at the time of the study data provided.
- At the time of submission (by 15 April) the data should be organised in summary tables to address priority questions about the effectiveness and safety of regimens (e.g. Ahuja et al;[4] Bastos et al;[5]) Further detail about the data aggregations will be provided to those who express an intent to report.

Correspondence

Please send all electronic correspondence, including enquiries to: **LDR.POLICIES@WHO.INT**

[4] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

[5] Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis. Eur Respir J. 2017 Mar;49(3):1600803.

Annex 1: List of minimum data elements for individual patient datasets (IPD)

(Highlighted under green area= essential data. Not highlighted = of interest, but not essential)

i) Baseline data at treatment initiation

Domain	Data element	Answer options and other remarks
Location	Geographic area	Country, region, district, city or ward in which the patient is started on treatment; use unique codes for place names.
	Facility name	Unique code of reference of the health centre
	Facility type	Public/private; specialized or general; primary, secondary, tertiary
Identification and demographic	Unique registration number	The code for the specific MDR-TB treatment episode being registered. The same patient may have >1 code assigned over time for different treatment episodes. Important for data linkages between different data sources, e.g. recovery of DST results from laboratory databases
	Date of birth	If full date (i.e. dd/mm/yyyy) is not known provide the year of birth or age in completed months or years
	Sex at birth	Male, female
	Origin	By country of birth or, if not available, citizenship. Race or ethnicity is used in some countries.
	Employment	Employed, retired, student, unemployed
	Imprisonment	If yes, to identify if current/previous and duration of imprisonment
	Current homelessness	Yes, No
Baseline clinical assessment	Date of diagnosis	The date (dd/mm/yyyy) when the patient was first diagnosed with the current episode of RR-/MDR-TB (based on clinical manifestations, or radiology plus bacteriology and DST
	Site of disease	Pulmonary, extrapulmonary (exact site)
	Previous TB	Yes, no, unknown If Yes, date of diagnosis of each episode, number of treatments, drug regimen composition and duration, and DST pattern Assign the standard WHO *patient registration group*[2]
	Previous treatment with first line TB medicines	Indicate medicines and durations in standard notation if known (e.g.2RHZE/4RH)
	Previous Treatment with second Line TB medicines	Indicate medicines and durations if known (e.g.6KmLfxEtoCsZ/18LfxEtoCsZ)

Domain	Data element	Answer options and other remarks
Baseline clinical assessment (*cont*)	Previous TB treatment outcome	If previously treated the outcome of the latest episode (cured, completed, failed, lost to follow up, unknown)
	Other medical history	Including diabetes mellitus, malnutrition, renal insufficiency, hepatic insufficiency/ cirrhosis, cardiac dysrhythmias, chronic obstructive pulmonary disease, convulsions, psychiatric conditions, drug use, alcohol use, smoking
	HIV	Known – positive or negative or unknown
	ARV	If HIV positive
	History of allergy or adverse drug reactions	Indicate the medicine and classify the type of reaction according to MedDRA and parameters of severity and seriousness[6]
	New events	Include all new events or changes in pre-existing conditions that began in the 30 days prior to the baseline interview. Include date of onset, and if applicable, date resolved (dd/mm/yyyy), outcome, severity and seriousness.
	Currently pregnant	Yes, no, uncertain (date of last menstruation may be recorded)
	Breastfeeding infant	Yes, no
	Patient symptoms	Fever, weight loss, cough, haemoptysis, dyspnoea, others (specify)
	Patient height	In centimetres
	Patient body weight	In kilogrammes and expressed as body mass index
	Abnormalities noted at examination	By functional system: head, ears, nose, and throat; vision; thyroid; lymphatic system nodes; cardiac; pulmonary; abdominal (including pancreas); skin; musculoskeletal; urogenital; neurological; extremities; other (specify)
	Functional status	Not ambulatory; ambulatory; able to work
Baseline bacteriology and drug susceptibility testing (DST) results	Date sample collected	Standard notation (dd/mm/yyyy) for the date when the specimen confirming MDR/RR-TB was collected (each test)
	Date result issued	Standard notation (dd/mm/yyyy) for the date when the result of the test confirming MDR/RR-TB was reported (each test)
	Microscopy	Use standard notation [see page 11 of reference at footnote 2]
	Xpert MTB/RIF test	Use standard notation [see page 12 of reference at footnote 2]

[6] MedDRA. Available from: http://www.meddra.org/

Domain	Data element	Answer options and other remarks
Baseline bacteriology and drug susceptibility testing (DST) results (*cont*)	LPA or sequencing	Report mutation(s) tested for and detected in free text
	Culture	Use standard notation [see page 12 of reference at footnote 2]
	Phenotypic DST	To each first line and second line TB medicines tested. Use standard notation [see page 12 of reference at footnote 2] DST method used (solid/liquid media)
Results of other investigations at baseline	Date sample collected	Standard notation (dd/mm/yyyy) for each test
	HIV test	Positive, negative, indeterminate
	CD4 count	In cells/mm^3 (=cells/µL or cells/microliter)
	Glucose	In mmol/L or as mg/dL
	Electrolytes	Levels of potassium, magnesium, calcium
	Renal function	Urea, creatinine, creatinine clearance
	Liver function	ALT (SGPT), AST (SGOT), bilirubin, albumin
	Blood indices	Haemoglobin, haematocrit, leukocytes, platelets
	Electrocardiogram (ECG)	Rate; rhythm; trace; QTc interval
	Chest radiography	Cavitary; extent of parenchymal disease; uni- or bilateral (useful in grading extent and severity of disease)
	Other	Specify (e.g. thyroid stimulating hormone)
Treatment given	Date of registration for second-line treatment	Standard notation (dd/mm/yyyy) for date when the record was entered in the Second-line TB treatment register
	Date second-line treatment started	Standard notation (dd/mm/yyyy) for each TB medicine taken at any time in the previous 30 days
	Date second-line treatment stopped	Standard notation (dd/mm/yyyy) for each TB medicine taken at any time in the previous 30 days
	TB medicine	For each TB medicine give: name, dosage, frequency, route If date started and stopped is not available give duration in days or months
	Shorter regimen use	Yes / No. Refers to standardized shorter regimens lasting 9-12 months and based on the 2016 recommended regimen[Error! Bookmark not defined.]
	For shorter regimens: Switch from shorter regimen to a longer individualized regimen	Provide: indication for change from shorter to longer regimen (e.g. no conversion / treatment failure / acquired drug resistance / clinical deterioration not meeting criteria for bacteriologic failure / adverse reactions); date of change.
	Duration – Initial phase and total	Specify planned and actual duration of each phase of treatment

ii) Data collected at MDR-TB patient review

Domain	Data element	Answer options and other remarks
Outcome	Date of final outcome	Standard notation (dd/mm/yyyy) for date first outcome met
	Adverse events – during treatment	Indicate if any AE occurred during treatment – that caused any TB medicine to be permanently stopped – identify medicine stopped and type of AE
	Final treatment outcome	Cured, treatment completed, treatment failed, died, lost to follow up, not evaluated (as defined in page 7 of reference at footnote 2; for older datasets outcome coding as per the 2005 recommendations is also accepted. ICD code for cause of death is recommended.
	Relapse	Indicate if relapse is monitored, and if so for how long, and if occurred. Provide date of specimen collection for each post-treatment culture performed to assess for relapse (provide date irrespective of result). Indicate if reinfection excluded (by genotyping)
	Culture conversion	Indicate if this was measured, and if so the time of culture conversion (in months) and if conversion occurred by 6 months (if shorter regimen is used, then also report whether culture conversion occurred by 2 months)
Resource use	Hospitalization	Number of days hospitalized
	Surgery – (lung resection only)	If surgery – type of surgery, and what removed. Dates of surgery /s (variable highly desirable but not essential)