WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens

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THE END TB STRATEGY

World Health Organization

Objective of the presentation

- Outline the main components of the WHO framework for active TB drug-safety monitoring and management (aDSM)

WHO guidance on treatment & management of drug-resistant TB, 1996-2016

Choosing the treatment regimen in patients with confirmed MDR/RR-TB

- Confirmed susceptibility or presumed effectiveness to all medicines in the shorter MDR-TB regimen (isoniazid resistance excepted)
- No exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for ≥1 month
- No intolerance to any medicine in the shorter MDR-TB regimen and no risk of toxicity (e.g. drug-drug interactions)
- Pregnancy excluded
- Only pulmonary disease
- All medicines of the shorter MDR-TB regimen available to the programme

YES

Shorter MDR-TB regimen

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF AN EXCLUSION CRITERION

NO

Longer (individualized) MDR-TB regimens

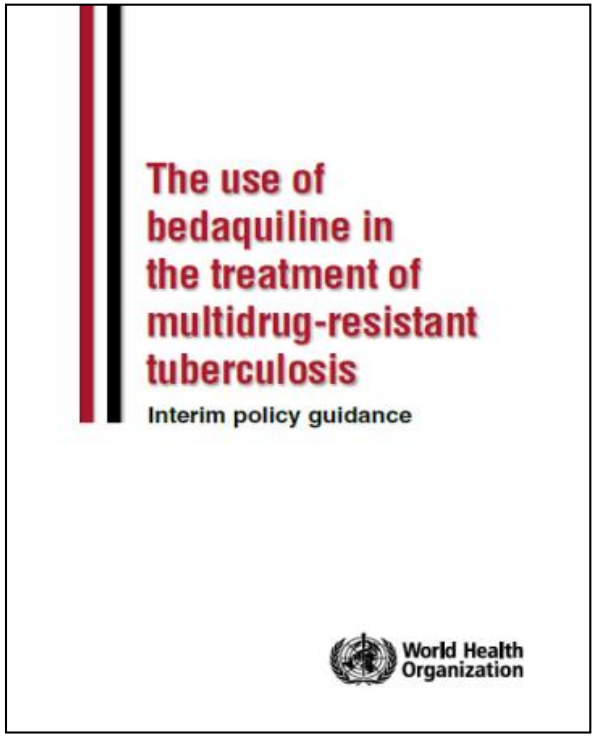
BEDAQUILINE : WHO interim policy guidance (June 2013)

"Bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB"

conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:

1. Treatment under close monitoring
2. Proper patient selection
3. Patient informed consent
4. Treatment as per WHO recommendations
5. Active pharmacovigilance in place



DELAMANID : WHO interim policy guidance (October 2014)

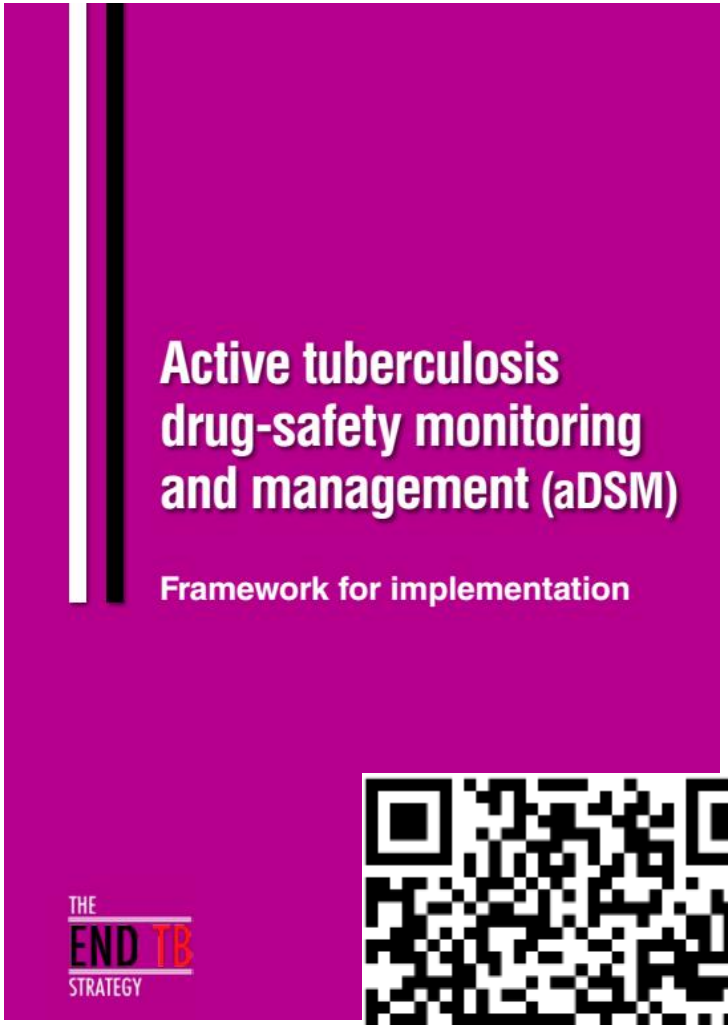
"Delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB"

conditional recommendation, very low confidence in estimates of effect

Subject to the following 5 conditions:

1. Proper patient inclusion
2. Treatment as per WHO recommendations
3. Treatment is closely monitored
4. Active pharmacovigilance in place
5. Patient informed consent obtained

-> October 2016 : may be used in patients 6-17 years



aDSM

"active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities"

apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf

aDSM components

1. **Clinical monitoring**
   - active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs
2. **Management of AEs** in a timely manner
3. **Systematic and standardized recording and reporting of AEs**
   - Data collection to include safety data
   - At least all SAEs reported and assessed for causality
   - Close coordination between national TB and PV structures

aDSM "packages"

1. **Core:** requiring monitoring for and reporting of all serious adverse events (SAEs)

2. **Intermediate:** includes SAEs as well as AEs of special interest

3. **Advanced:** includes all AEs of clinical significance

aDSM eligibility

aDSM applies primarily to the following:

1. MDR-TB patients treated with bedaquiline, delamanid and other new medicines;

2. MDR-TB patients enrolled on treatment with novel regimens (including the shorter MDR-TB regimen);

3. All XDR-TB patients on second-line treatment, as these regimens usually include multiple repurposed drugs

Once coverage of these patient groups is reached, aDSM can extend to other MDR-TB patients on treatment

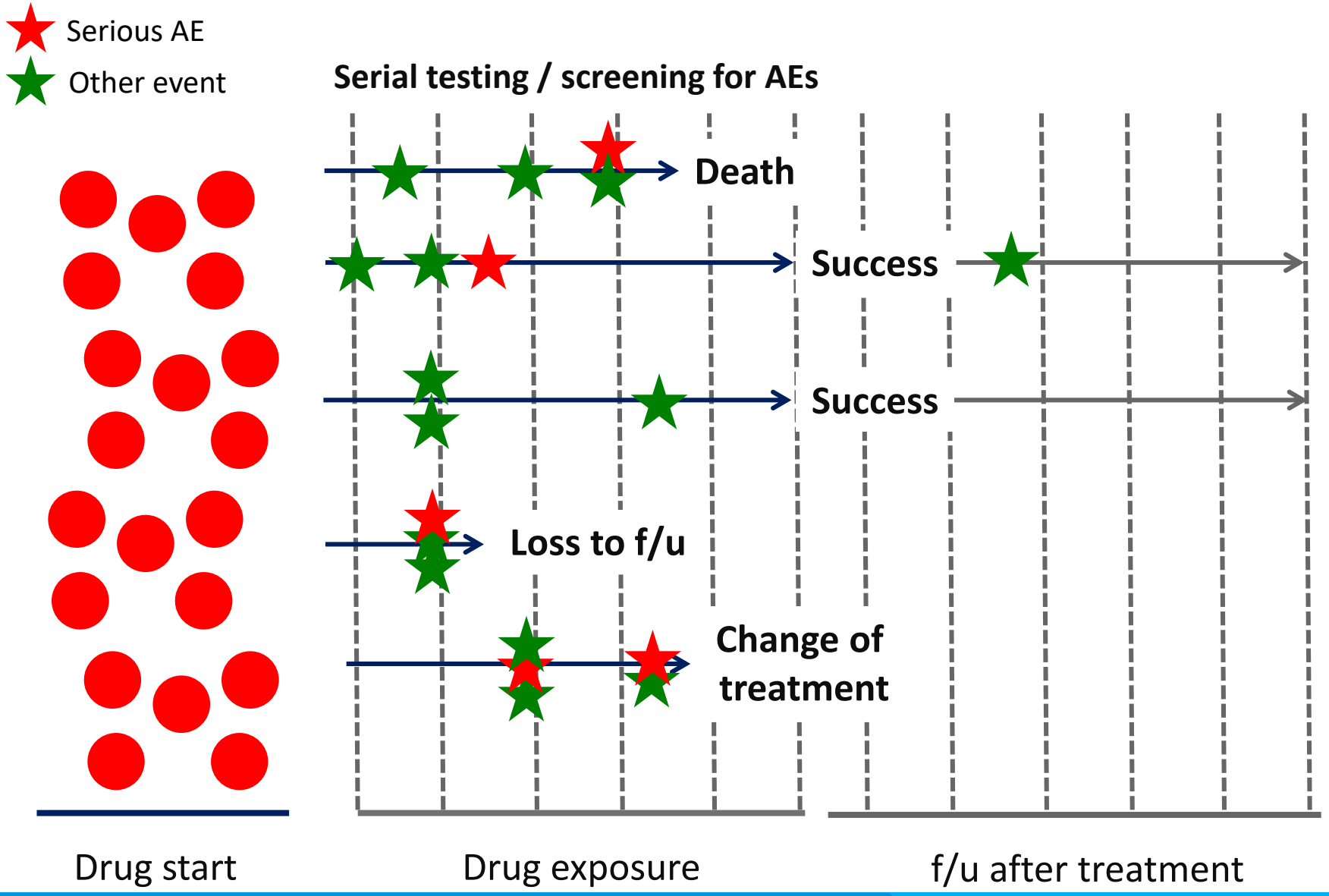
Seriousness

Seriousness involves any of the following:

- death or a life-threatening experience;
- hospitalization or prolongation of hospitalization;
- persistent or significant disability;
- congenital anomaly.

Events which do not result immediately in one of these outcomes but which might require an intervention to prevent it from happening may also be considered serious

aDSM : cohort-based approach



Clinical and laboratory testing schedule for aDSM

To be adapted to the treatment regimen and national policy[1]

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
Date																									
Clinical screen																									
Visual acuity																									
Simple hearing test																									
Audiogram																									
Neuro & psychiatric investigations																									
Serum creatinine																									
ALT (SGPT)																									
AST (SGOT)																									
Bilirubin																									
Alkaline phospatase																									
γGT																									
ECG																									
Lipase																									
Amylase																									
Potassium																									
Magnesium																									
Calcium																									
Albumin																									
CBC																									
Blood glucose																									
Thyroid tests: TSH																									

[1] *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (WHO/HTM/TB/2014.11). Geneva, World Health Organization. 2014

Shade cells for the months when the test will not be done.

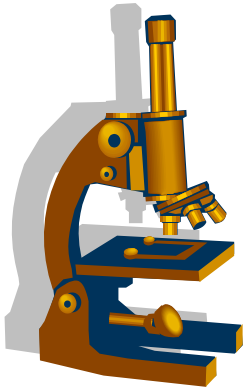
Notation for marking the cells: 0= screen/test not done 1=screen/test done; result pending 2=screen/test done; no SAE 3=screen/test done; SAE detected

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase);

CBC=complete blood count; ECG=electrocardiogram; γGT=gamma glutamyl transferase; TSH=thyroid stimulating hormone.

PATIENT HISTORY

CLINICAL TESTS



SAE

notification

DATA ENTRY

GLOBAL aDSM DATABASE

Data elements list – DRAFT sample

Data	Category labelling	Remarks
Facility information		
Country	string to be coded	Can use the country code or Iso code
Facility name or site identifier	string to be coded	Need to check in the agreement of sharing data which level of confidentiality is required.
Nature of the AEs reported	AE, SAE	Depending on what "package" is implemented at the site or country level
Coding use for AE/SAE terminology	WHOART, MedDRA, None	To be discussed if we agree that None is acceptable as well (in this case the coding need to be done by a service provider), I think we can cover that cost for the initial phase, piloting, but in the future, to be considered in term of sustainability
Scale used for grading of severity of AEs/AEs	string to be coded	(WHO scale; CTCAE grading system; DAIDS AE Grading Table; Other; None)
scale used to describe the degree of causality between drug and AE/SAE	string to be coded	Depending on what is chosen by the site, the option for reporting on causal relationship will be displayed differently (2

Global aDSM database

- A global aDSM database was created in 2016
- Coordinated by the Special Programme for Research and Training in Tropical Diseases at WHO Headquarters (TDR) and the WHO/GTB
- The Luxembourg Institute of Health (LIH) is responsible for its day-to-day management
- National programmes and other bodies can report AEs to the database for patients treated with medicines which are new or repurposed for an indication other than TB
- Belarus has started to report

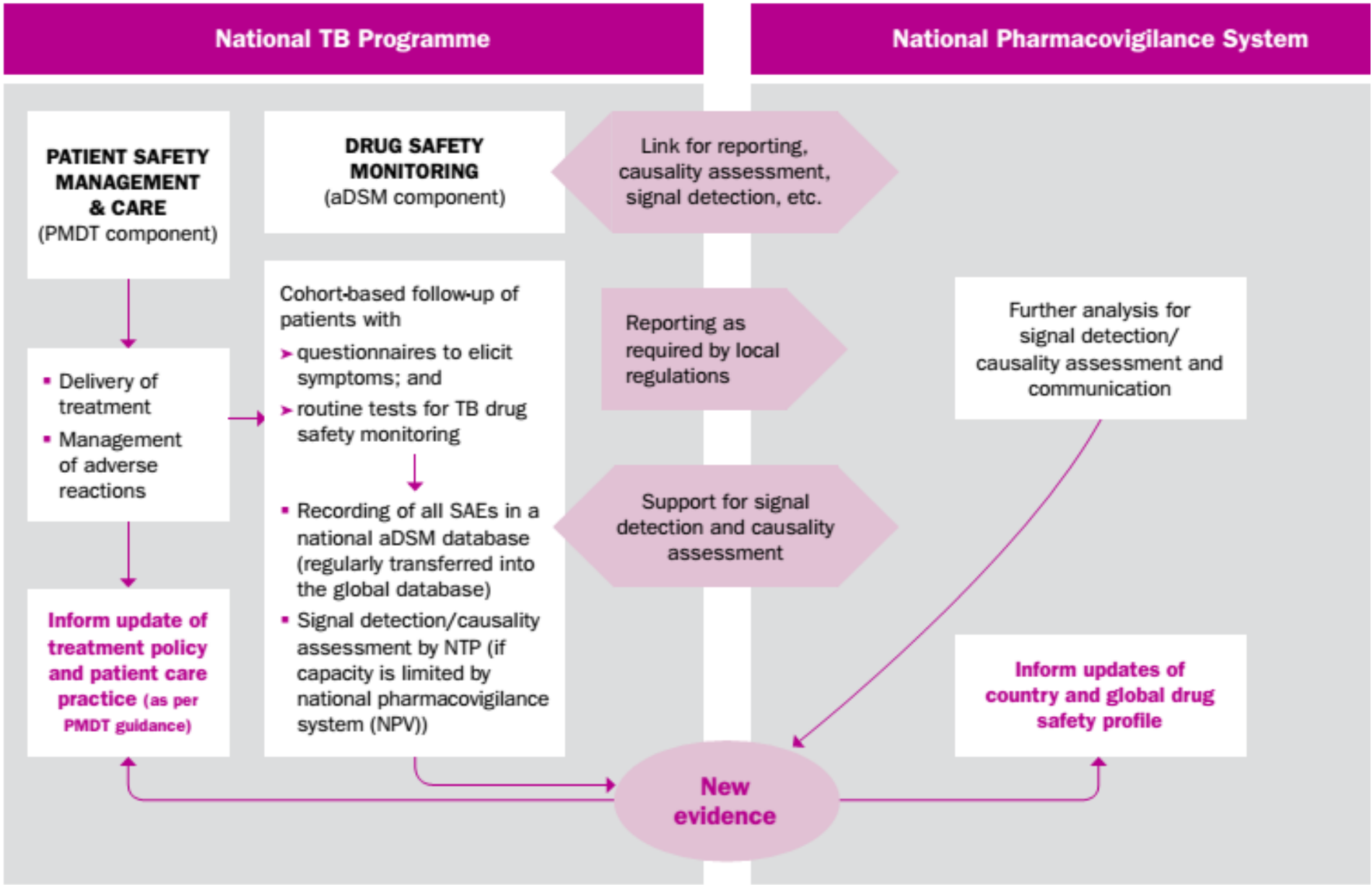
www.who.int/tdr/research/tb_hiv/adsm/en/

What happens to the data ?

- Programme indicators
- Causality assessment
- Signal detection
- Drug-safety profiles

Key steps in aDSM implementation

- Create a national coordinating mechanism for aDSM
- Develop a plan for aDSM
- Define management and supervision roles and responsibilities
- Create standard data collection materials
- Train staff on the collection of data
- Define schedules and routes for data collection and reporting
- Consolidate aDSM data electronically
- Develop capacity for signal detection and causality assessment


National TB Programme
National Pharmacovigilance System
PATIENT SAFETY MANAGEMENT & CARE
(PMDT component)
DRUG SAFETY MONITORING
(aDSM component)
Link for reporting, causality assessment, signal detection, etc.
Delivery of treatment
Management of adverse reactions
Cohort-based follow-up of patients with
questionnaires to elicit symptoms; and
routine tests for TB drug safety monitoring
Reporting as required by local regulations
Further analysis for signal detection/ causality assessment and communication
Recording of all SAEs in a national aDSM database (regularly transferred into the global database)
Signal detection/causality assessment by NTP (if capacity is limited by national pharmacovigilance system (NPV))
Support for signal detection and causality assessment
Inform update of treatment policy and patient care practice (as per PMDT guidance)
Inform updates of country and global drug safety profile
New evidence

www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/

www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/en/

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Tuberculosis (TB)

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  - Treatment and care
  - Preventive care
  - Drug-resistant TB
    - MDR-TB surveillance
    - Treatment of drug-resistant TB
    - Public-private mix for drug-resistant TB
  - TB and HIV
  - TB and children
  - Addressing needs of vulnerable populations
  - Technical support to countries
  - Community engagement:

Treatment of drug-resistant TB

Resistance to TB drugs is a formidable obstacle to effective TB care and prevention globally. Multidrug-resistant TB (MDR-TB) is multifactorial and fuelled by improper treatment of patients, poor management of supply and quality of drugs, and airborne transmission of bacteria in public places. Case management becomes difficult and the challenge is compounded by catastrophic economic and social costs that patients incur while seeking help and on treatment.

Key topics

Active drug-safety monitoring and management | Short regimens | Treatment guidance for DR-TB

Active TB drug-safety monitoring and management (aDSM)

The term active TB drug-safety monitoring and management (abbreviated as aDSM) describes a new TB programme component to provide for the active and systematic clinical and laboratory assessment of patients on treatment for XDR-TB, or with new TB drugs or novel MDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.

In conclusion

- The WHO DR-TB treatment policy updates aim to improve the assignment of patients to treatment regimens which can increase the likelihood of cure
- Important uncertainties remain on the effectiveness and safety of the treatment options, both regarding older and newer medications
- More evidence will be needed and new studies to ensure that treatment is better targeted according to the patient profile
- aDSM and the global aDSM database aim to document signals of previously unknown or poorly documented adverse events in patients on new drugs or novel MDR/XDR-TB regimens

Question to countries

How far are you from having aDSM up and running?

What main barriers have you encountered (if any)?

Would you consider reporting to the global aDSM database?