

Active tuberculosis drug-safety monitoring and management (aDSM)

Framework for implementation



World Health
Organization

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Abbreviations

| | |
|---------------|--|
| ADR | adverse drug reaction |
| aDSM | active tuberculosis drug-safety monitoring and management |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| GDF | Global Drug Facility |
| GTB | Global TB Programme |
| EMP | WHO Essential Medicines and Health Products Department |
| KNCV | KNCV Tuberculosis Foundation, Netherlands |
| MDR-TB | multidrug-resistant TB |
| MSF | Médecins Sans Frontières |
| NPV | national pharmacovigilance system |
| NTP | national TB programme |
| PMDT | programmatic management of drug-resistant TB |
| SAE | serious adverse event |
| SGOT | serum glutamic-oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| TB | tuberculosis |
| TDR | Special Programme for Research and Training in Tropical Diseases |
| TSH | thyroid stimulating hormone |
| ULN | upper limit of normal |
| USAID | United States Agency for International Development |
| XDR-TB | extensively drug-resistant TB |
| γGT | gamma glutamyl transferase |

Background

Health programmes that systematically monitor patient safety are at an advantage to prevent and manage adverse drug reactions (ADRs), as well as improve health-related quality of life and treatment outcomes. National tuberculosis programmes (NTPs) that actively pursue drug-safety monitoring and management are also better prepared to introduce new tuberculosis (TB) drugs and novel regimens.

The prospect of new anti-TB drugs and use of novel regimens led WHO to release its first implementation manual for pharmacovigilance of anti-TB drugs in 2012 (1). Later in 2012, WHO provided interim advice that the use of shorter regimens for multidrug-resistant TB (MDR-TB) be accompanied by the collection of drug-safety data within a framework of observational research (2). In 2013 and 2014, the WHO interim policies on bedaquiline and delamanid recommended active pharmacovigilance as one of the five conditions to be met when using these drugs to treat MDR-TB patients (3,4).

NTPs and other stakeholders are now starting to introduce new anti-TB drugs and novel MDR-TB regimens according to WHO recommendations. A number of programmes managing MDR-TB patients have also introduced active pharmacovigilance to monitor drug-safety and take early action to avert treatment interruption and other unfavourable patient outcomes (5–7).

The application of pharmacovigilance methods (such as cohort event monitoring) described in the 2012 implementation manual for pharmacovigilance of anti-TB drugs in 2012 (1), was largely based on experience with the use of drugs for malaria, human immunodeficiency virus (HIV) and noncommunicable diseases. This however led to practical questions related to the implementation of drug-safety monitoring alongside other components of programmatic management of drug-resistant TB (PMDT).

The lack of familiarity of many TB practitioners with the principles of drug-safety monitoring and the limited capacity of national drug-safety authorities in some countries to provide the necessary support, generated a demand for more explicit guidance. A recent survey conducted by Médecins Sans Frontières (MSF) and the Stop TB Partnership Global Drug Facility (GDF) in the 27 high MDR-TB burden countries, showed concerns about ADRs being one of the main barriers to the introduction of bedaquiline and delamanid (MSF/GDF, unpublished information).

Several stakeholders expressed concern that the introduction of new anti-TB drugs may be slowed down or even prevented due to a lack of capacity for countries to mount active pharmacovigilance. In response, the WHO Global TB Programme (WHO/MTB) convened key technical and funding agencies to a meeting in Geneva, Switzerland on 28–29 July 2015

to discuss essential requirements for the implementation of active pharmacovigilance and proper management of ADRs when introducing new anti-TB medicines or novel MDR-TB regimens. This document reflects the consensus achieved during this meeting and in subsequent discussions involving NTP managers of selected countries and the WHO Essential Medicines and Health Products Department (see list of contributors in [Annex 1](#)).

Other WHO documents – particularly the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant TB* (henceforth termed “PMDT Handbook” in this document) (8), *Policy implementation package for new TB drug introduction* (9), and the current WHO/MTB website on TB drug safety as well as the associated frequently asked questions (10) – will be updated accordingly.

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